Cancer and Hematological Research 2021

Cancer Services,
Hamad Medical Corporation

مؤسسة حمد الطبية
Hamad Medical Corporation
HEALTH • EDUCATION • RESEARCH
صحة • تعليم • بحوث

Cancer and Hematological Research 2021

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Preface

Dr. Mohammed Salem,

Medical Director, National Centre for Cancer Care and Research,
Chairman, Cancer Services
Hamad Medical Corporation

Dear Colleagues,

I am delighted to share with you our annual publication of Cancer and Hematological Research for 2021.

Cancer research over the past decade has diversified enormously, and substantial advances have been made globally in the understanding of this complex disease. As we are now emerging from the COVID 19 pandemic, we look forward to the future and how we can improve patient care through cancer research and its findings.

Through synergizing medicine and science we provide the most comprehensive level of cancer care to our patients. However, as populations in general are now living longer we must continuously strive to find more innovative ways of managing and treating this disease. Through our international collaborations, Hamad Medical Corporation has participated in multi-center cancer research and clinical trials and as we go forward into 2023 I look forward to seeing more research and publications in high impact journals, and more collaborations with international cancer institutes.

With best wishes

Introduction

Dr. Mohammed Ussama Al Homsi,

Deputy Medical director and clinical research and education Center for Cancer Care and Research Hamad Medical Corporation

It gives me great pleasure to present the annual catalogue of Cancer and Hematology Research for 2021.

Despite the challenges from the COVD-19 pandemic we have continued to improve the quality and quantity of our research and research outputs throughout 2021 as demonstrated by the steady increase in the Impact Factor (IF) of our publications and the increase in the citations index of our individual researchers.

This year we have added a brief introductory synopsis regarding the span and scope of our research which includes our research priorities and research capability within the Cancer Translational Research Faculty.

Another key achievement in 2021 was that for the first time the Best of ASCO (American Society of Clinical Oncology) 2021 conference was held in Qatar.

The Best of Asco allowed selected presentations for the annual meeting to be delivered in Qatar by local experts.

I wish to extend my thanks to the entire team of clinical, research and support professionals who have contribute to these impressive achievements.

With best wishes

Cancer Research at Hamad Medical Corporation

The 1st National Cancer Strategy – A Pathway to Excellence was published in 2012 and was a five-year plan to transform Cancer Care in Qatar. The Qatar National Cancer Research Strategy published in 2013 was a companion document.

The current strategy is the National Cancer Framework, next steps on the Pathway to Excellence 2017-2022 integrated the research component into the main strategy.

The strategy delivered the establishment of clear standardized rapid referral pathways for suspected cancer, National Clinical Management Guidelines for each cancer and National Breast and Bowel screening programs. New roles such as Multi Discipline Team Coordinators, Patient Pathway Coordinators and Clinical Nurse Specialists were also introduced.

Cancer Services at Hamad Medical Corporation (HMC)

Hamad Medical Corporation is the only provider of secondary and tertiary cancer services in Qatar, and they are delivered across the HMC campus.

Cancer is diagnosed and treated in multiple facilities across the HMC campus including Surgical Specialty Center, Hamad General Hospital, Rumaila Hospital, Women's Wellness and Research Centre, Ambulatory Care Centre, Qatar Rehabilitation Centre and National Centre for Cancer Care and Research (NCCCR).

NCCCR provides Medical Oncology, Radiation Oncology, Hematology and Hemopoietic Stem Cell Therapies as well as hosting PET CT, Nuclear Medicine, Interventional Radiology and Cancer Genetics Services. It is accredited as an ESMO Designated Centre of Integrated Oncology and Palliative Care.

Cancer Clinical Research Priorities at Hamad Medical Corporation

- Cancer Epidemiology, Cancer Services and Cancer Outcomes Research
- Clinical Research and Real-World Evidence Research.
- New Diagnostics with advanced imaging and molecular pathology
- New Treatment Technologies in Radiotherapy and Surgical Oncology
- Special patient cohorts with familial and hereditary cancers patterns or disease clusters

Cancer Clinical Trials

A Cancer Clinical Trials and Research Team supports both Pharmaceutical Sponsored and Investigator Initiated cancer clinical trials as well as other types of clinical research. There are policies and protocols for investigational drugs and the Pharmacy Department provides an investigational drugs service through well-established standard operating procedures.

Cancer Genetics Clinical and Translational Research

Carrying out clinical, translational, and basic science genetics research projects with local institutes as well as with prestigious international centres with the mission to further understand and explore the genetic components of sporadic, familial and inherited cancers in Qatar, its genotype-phenotype correlations and identifying sporadic and founder effects contributing to the disease incidence and prevalence in Qatar through considering inter- and intra-tumor genetic variability, tumor environment, and individual's lifestyle and morbidities. In addition, optimizing precision medicine research to improve cancer treatment, Our research aims to enhance the understanding of familial

cancers and identifying common mutations targets which can guide early and personalized treatment and prevention modalities for patients in addition to their asymptomatic family members thus benefiting from risk reducing strategies and reducing mortality and morbidity relating to hereditary cancers.

Cancer Translational Research Facility

The Cancer Translational Research Facility (CTRF) opened in 2014 and has been developing capability and capacity ever since. Senior Scientists, Postdoctoral Scientists, Research Associates and Assistants undertake Basic, Pre-Clinical and Translational Cancer Research and there is access to the TRI Core Facilities.It also supports the development of the next generation scientists by hosting Biomedical Science PhD and MSc students as well as providing internships and work experience opportunities.

Cancer Translational Research Priorities

The CTRF seeks to develop new and more precise ways to detect, diagnose, treat, and monitor cancer in patients through:

- Developing new diagnostics with Molecular Pathology and Precision Medicine
- Cancer Immunotherapy development and monitoring
- Better ways to monitor treatment efficacy before clinically apparent (Dynamic Biomarkers)
- Omics Research: proteomics, genomics, immunomics, metabolomics, microbiomics
- Stem Cell Therapy and Cellular Therapies Research.

Translational Cancer Research Facility Technological Capabilities

Technology	Function
CliniMACS Prodigy	automated GMP-compliant manufacturing of cell therapy products (CAR-T cells, CAR-NK cells)
Flow Cytometry	Wide Range of Services including Immune Phenotyping of Cell Population
Jess™ system	Characterization detection of targeted proteins and antibodies
AutoMACS® Pro Separator	Magnetic isolation of any cell type (dendritic cells, T cells, NK cell, etc.) from PBMCs or whole blood
Ella™ system	Quantification of cytokines /chemokines in patients' serum or plasma samples
RS 2000 Rad Source irradiator	X-ray iirradiation of small animals and human cells to generate feeder cells for functional assays
Mantra System	Identification of specific tumor bio markers
Mabtech IRIS™ ELISpot and FluoroSpot reader	Capture analytes/cytokines secreted by immune cells immediately throughout the stimulation process
4-D Nucleofector system	Transfection of primary and established cells in several formats
xCELLigence Real Time Cell Analyzer- DP	Real time measurement of cell proliferation, invasiveness and migration

Collaborative Cancer Research Partners

National Academic Collaborative Partners include Qatar University, Hamad bin Khalifa University, Qatar Biomedical Research Institute, Sidra Medicine, Weill Cornell Medicine Qatar, and Texas A&M Qatar. There are also a range of collaborative research projects with international partners.

Summary

Table 1- Research Publications in 2016, 2017, 2018, 2019, 2020, 2021						
Publications	2016	2017	2018	2019	2020	2021
Original Research Articles	26(51%)	33(24%)	21(15%)	32(21%)	44 (23%)	25 (19%)
Case Reports/ Series	8(10%)	15(10%)	16(11%)	28(19%)	64 (34%)	52 (41%)
Review/Book Chapters	5(6%)	13(12%)	13(9%)	16(11%)	35(18%)	22(18%)
Abstracts	-	-	-	13(9%)	10(5%)	14 (11%)
Conference Presentations	40(33%)	63(54%)	92(64%)	60(40%)	37(20%)	14 (11%)
Dissertations and Thesis Papers	-	-	1(1%)	-	-	-
Total	79	124	143	149	190	127

Research Projects

There were 84 active research projects in 2021.

Research Output: Publications

A total of 127 research communications have been published or presented in national, regional, international journals or conferences during 2021. Of these 25 original research articles, 52 case reports/series, 22 review articles, 14 Abstracts and 14 conference presentations.

Figure 1 Publications in 2021 in different categories

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A total of 127 research communications have been published or presented in national, regional, international journals or conferences during 2021. Of these 25 original research articles, 52 case reports/series, 22 review articles, 14 Abstracts and 14 conference presentations.

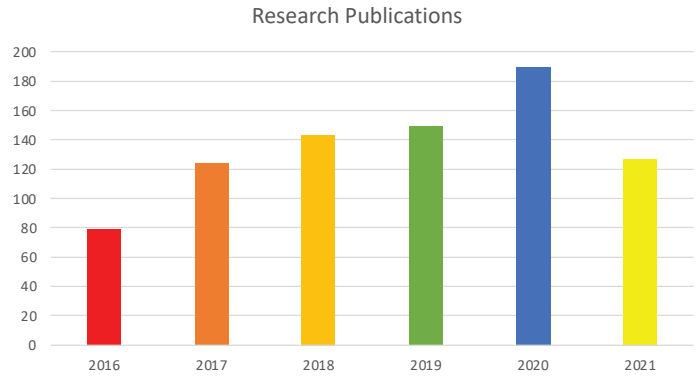


Figure 2 Research publications in 2016, 2017, 2018, 2019, 2020, 2021

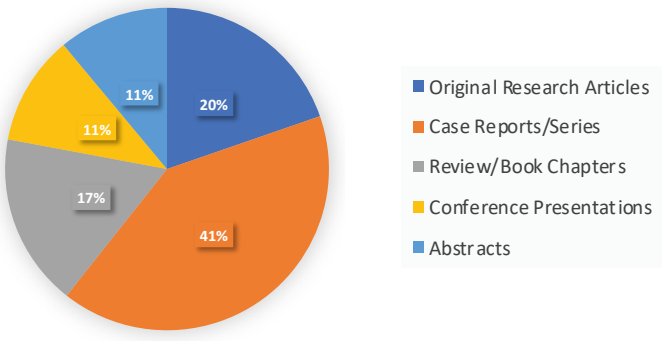
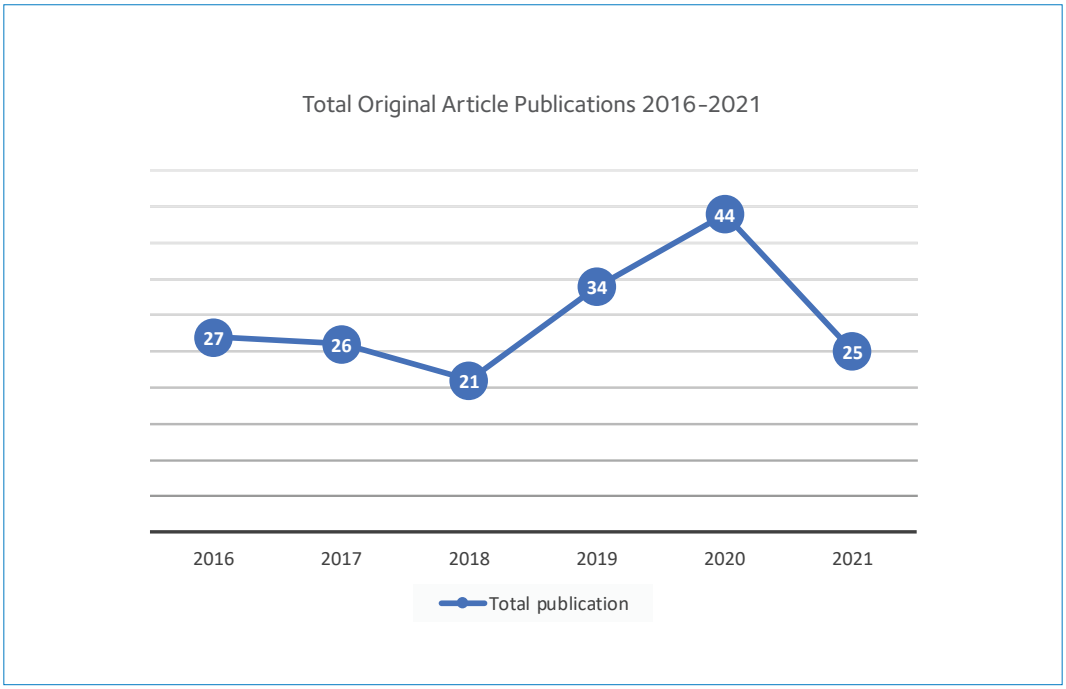


Figure 3 research publications in 2021 in different categories

Table 2 - Original Articles Impact Factors 2016- 2021						
Impact Factor	2016	2017	2018	2019	2020	2021
0-1	6	13	6	1	3	1
1-2	6	2	2	3	6	2
2-3	3	6	6	7	7	4
3-4	3	1	2	1	1	6
4-5	5	2	1	12	7	3
5-6	2	-	1	2	4	1
6-7	2	1	1	1	6	4
7-8	-	1	-	1	-	3
8-9	-	-	-	2	-	-
9-10	-	-	-	2	-	-
>10	-	-	2	2	10	1
Total	27	26	21	34	44	25



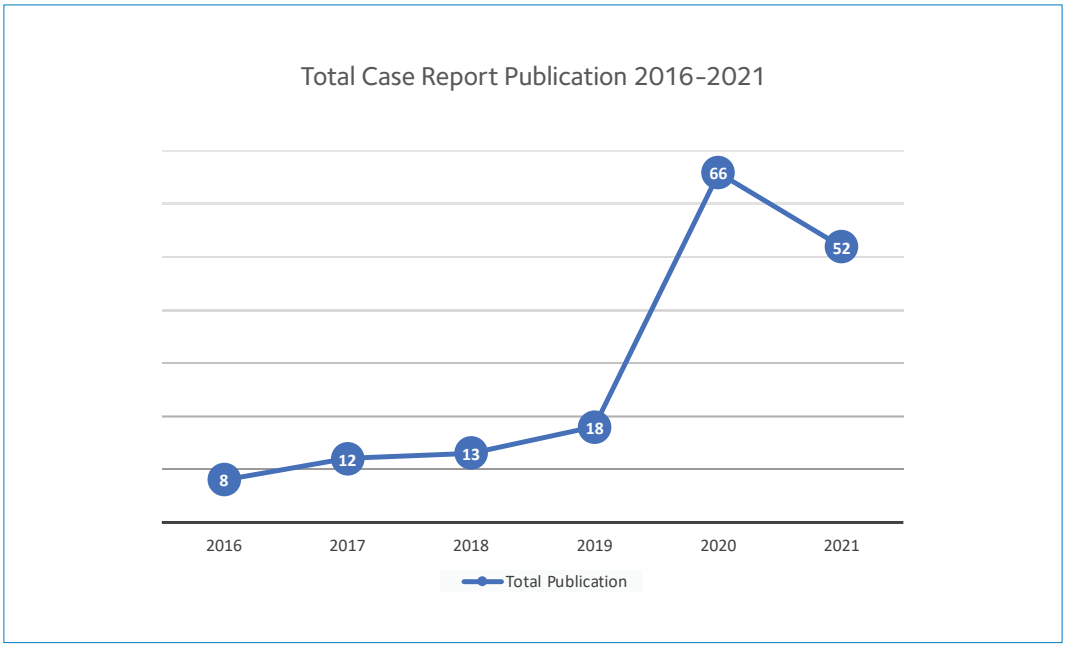


Table 4 - Case Reports Impact Factors 2016 – 2021

Impact Factor	2016	2017	2018	2019	2020	2021
0-1	5	9	10	8	52	24
1-2	1	1	2	3	8	10
2-3	-	2	-	4	-	4
3-4	-	-	-	2	1	3
4-5	1	-	-	1	-	2
5-6	-	-	1		-	1
6-7	1	-	-		-	3
7-8	-	-	-		-	5
8-9	-	-	-		-	-
9-10	-	-	-		-	-
>10	-	-	-		1	-
Total	8	12	13	18	64	52

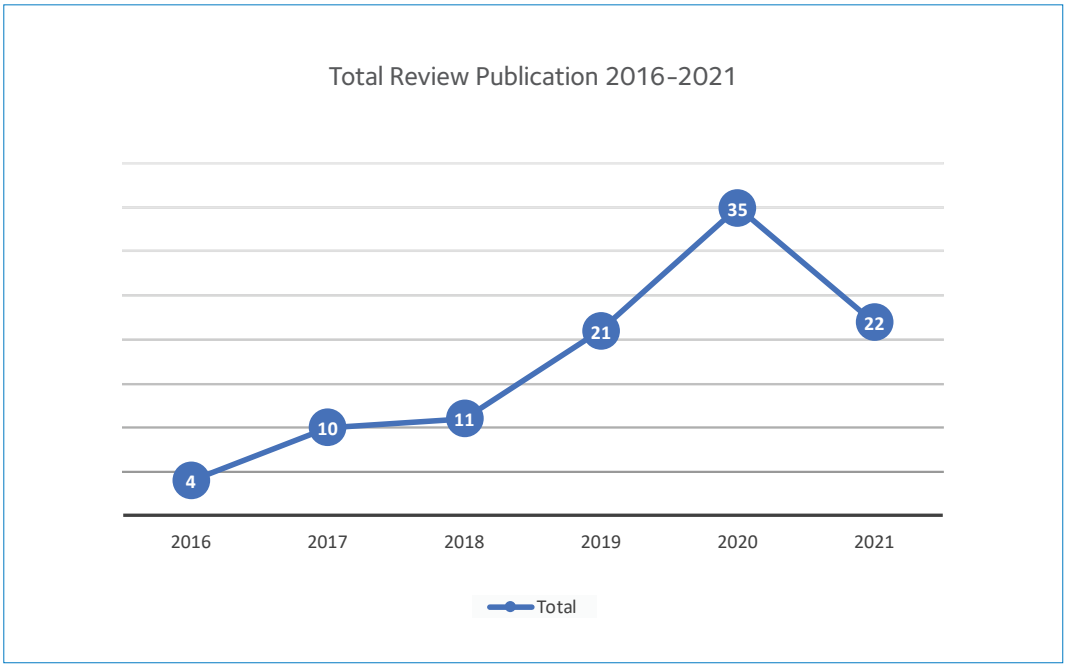


Table 3– Reviews Impact Factors 2016- 2021

Impact Factor	2016	2017	2018	2019	2020	2021
0-1	1	4	3	1	6	-
1-2	-	-	1	3	5	5
2-3	1	1	1	2	4	4
3-4	-	3	1	6	2	5
4-5	1	-	1	-	5	1
5-6	-	1	1	1	4	-
6-7	1	-	1	2	2	3
7-8	-	1	1	-	4	-
8-9	-	-	-	-	-	1
9-10	-	-	-	-	2	-
>10	-	-	1	6	1	3
Total	4	10	11	21	35	22

ACTIVE RESEARCH PROJECTS

Active Research Projects

Study Number	Study Title	Study Principal Investigator	Funding Organization
IRGC-04-SI-17-137	Modulatory Effects of KIR Surface Repertoire on the Effector Functions mediated by Chimeric Antigen Receptor-Engineered Natural Killer Cells	Dr. Maysaloun Merhi	Hamad Medical Corporation (HMC)
IRGC-04-SI-17-142	Investigation of immuno-regulatory mechanisms and biomarkers involved in anti-NY-ESO-1 immune responses in colorectal cancer patients	Dr. Said Dermime	Hamad Medical Corporation (HMC)
IRGC-05-JI-18-367	Identification of genes predisposing to BRCA1/2- negative hereditary breast and ovarian cancers (HBOC) in Qatar- Towards precision treatment and prevention	Dr. Fatemeh Abbaszadeh	Hamad Medical Corporation (HMC)
IRGC-06-SI-19-190	Integrated Genomics- Proposal for an Institutional Diagnostic Sample Repository for Blood Cancers for Precision Medicine	Dr. Susanna Jane Lawson El-Akiki	Hamad Medical Corporation (HMC)
MRC-01-17-172	Arabic modified version of palliative outcome scale (POS): Cross? cultural adaptation and validation	Ms. Asma Mohammad Younus	Hamad Medical Corporation (HMC)
MRC-01-18-080	The role of immunoscore in solid tumors: a prognostic and predictive impact on patient outcomes	Mr. Mahmoud Gasim Mahmoud Mohd	Hamad Medical Corporation (HMC)
MRC-01-18-352	Mental Adjustment to Cancer and Effectiveness of CBT in Anxiety, Depression and Health Related Quality of Life of Patients Diagnosed with Cancer	Ms. Hafisa P Hassan	Hamad Medical Corporation (HMC)
MRC-01-18-401	HLA-Haploidentical Hematopoietic Stem Cell Transplantation for Hematological Diseases: A Prospective Observational Study.	Dr. Javid Gaziev	Hamad Medical Corporation (HMC)

MRC-01-19-034	Molecular Biomarkers in Hematologic Malignancies	Dr. Dina Sameh Abdelrahman Soliman	Hamad Medical Corporation (HMC)
MRC-01-19-044	A Randomized, Multicenter, Open-Label Cross-Over Study to Evaluate Patient Preference and Satisfaction of Subcutaneous Administration Of The Fixed-Dose Combination Of Pertuzumab And Trastuzumab In Patients With Her2-Positive Early Breast Cancer	Dr. Salha Mohd. Bu Jassoum	Roche Pharmaceuticals, Switzerland
MRC-01-19-245	KAP among healthcare workers towards Palliative care in HMC	Dr. Hisham Elmorsi Ali Elmorsi	Hamad Medical Corporation (HMC)
MRC-01-19-359	Predictive Model to diagnose pleural tuberculosis in exudative pleural effusion cases in Qatar	Dr. Mousa Shaher Mousa Hussein	Hamad Medical Corporation (HMC)
MRC-01-19-423	Relationship between Communication and Health-Related Quality of Life in Cancer Patients in Qatar	Ms. Sahar Saadani A Maksoud	Hamad Medical Corporation (HMC)
MRC-01-19-466	Primary Myelofibrosis: Clinical, pathological and genetic profiling, NCCCR Experience	Dr. Sarah Abdelghany Abdelghany Elkourashy	Hamad Medical Corporation (HMC)
MRC-01-19-510	The effect of bariatric surgery on hematological and nutritional parameters among patients with obesity in Qatar: A Retrospective Study	Dr. Turki Faris S.M. Al-Ahbabi	Not funded
MRC-01-19-522	Reliability of QoL questionnaires in Cancer patients and determining the genetic relevance in regard to QoL	Dr. Hisham Elmorsi Ali Elmorsi	Hamad Medical Corporation (HMC)
MRC-01-20-058	Immune regulation in CML: mechanisms associated with response to treatment & progression	Dr. Susanna Jane Lawson El-Akiki	Hamad Medical Corporation (HMC)

MRC-01-20-084	Screening of NY-ESO-1antibody at the National Center for Cancer Care and Research, HMC to determine its prevalence and utility as a potential predictive biomarker of cancer	Ms. Afsheen Raza	Hamad Medical Corporation (HMC)
MRC-01-20-1016	Characterization of the immune response in cancer patients recovered from COVID-19	Dr. Mai Mostafa Hisham Ali Mostafa	Hamad Medical Corporation (HMC)
MRC-01-20-1033	Epidemiology of COVID-19 infection in patients with Haematological Malignancies: A European Haematology Association Survey (EPICOVIDEHA Study)	Dr. Ali Senosi Omrani	Not funded
MRC-01-20-106	Molecular and clinic-pathological Differences between Screen-Detected and Symptomatic Breast cancers and their impact on disease prognosis and survival in state of Qatar	Dr. Hind Hassan Ahmed Habish	Hamad Medical Corporation (HMC)
MRC-01-20-108	Pregnancy associated breast cancer-Prognosis and Outcome.	Dr. Hind Hassan Ahmed Habish	Hamad Medical Corporation (HMC)
MRC-01-20-1089	Nocardiosis characteristics, management, and outcomes in Qatar? a retrospective cohort study	Dr. Abeer Sharif Bajwa	Hamad Medical Corporation (HMC)
MRC-01-20-1148	Clinical application of precision medicine utilizing unselected adult biobank participants for BRCA1/2 screening as prevention and early detection of breast and ovarian cancer high risk population in the state of Qatar	Dr. Hind Hassan Ahmed Habish	Hamad Medical Corporation (HMC)
MRC-01-20-1149	Colo-rectal cancer 2-year disease free survival in the State of Qatar by race and stage and pathology	Dr. Mai Mostafa Hisham Ali Mostafa	Hamad Medical Corporation (HMC)
MRC-01-20-179	Characteristics of rare factors deficiencies in Qatar: a retrospective observational study	Dr. Shehab Fareed A. Mohamed	Not funded

MRC-01-20-180	Gene Mutation Linked to Leukopenia Among Arabs in Qatar: A prospective Study	Dr. Shehab Fareed A. Mohamed	Not funded
MRC-01-20-213	The economic impact of antimicrobial stewardship programs at Hamad Medical Corporation in Qatar	Ms. Dina H. F. Abushanab	Hamad Medical Corporation (HMC)
MRC-01-20-267	Breast Cancer Survivorship Program: Benefits & Outcomes Study	Dr. Salha Mohd. Bu Jassoum	Hamad Medical Corporation (HMC)
MRC-01-20-392	Quality of Life of Nurses Treating Patients with Coronavirus Disease 2019 (COVID-19) in Qatar (PROTECTOR Study) MRC-05-114	Mr. Abdulqadir Jeprel Japer Nashwan	Hamad Medical Corporation (HMC)
MRC-01-20-397	Towards MR-Only Radiotherapy: GPU Implementation Of Multi-Scale And Dual Contrast Patch Based Method	Ms. Souha Aoudi	Hamad Medical Corporation (HMC)
MRC-01-20-418	The impact of Tyrosine Kinase inhibitors on fatherhood in patients with chronic myeloid leukemia	Dr. Mohammad Abdullah Moh'd Abu-Tineh	Not funded
MRC-01-20-500	Change In Numbers And Reasons For Emergency Department Visits At H.M.C. Before And After Covid-19 Pandemic - MRC-05-060	Mr. Elli Gabriel Lustre Concepcion	Hamad Medical Corporation (HMC)
MRC-01-20-507	Soluble predictive biomarkers of response in Non-Small Cell lung cancer patients treated with immunotherapy in National Center for Cancer Care and Research, HMC	Ms. Afsheen Raza	Hamad Medical Corporation (HMC)
MRC-01-20-541	Predictive biomarkers of response and adverse events in Hepatocellular carcinoma patients treated with Sorefinib or Levnatinib and/or Immunotherapy in National Center for Cancer Care and Research, HMC	Ms. Afsheen Raza	Hamad Medical Corporation (HMC)
MRC-01-20-545	Reinterpretation of breast cancer gene variants of uncertain significance from the Qatari high-risk genetic screening program	Dr. Borbala Mifsud	Not funded, It is a part of master's study at HBKU

MRC-01-20-726	Effect Of COVID-19 Pandemic Upon Reasons For Hospitalization - MRC-05-034	Mr. Elli Gabriel Lustre Concepcion	Not in Abhath
MRC-01-20-765	Cost Effectiveness of Using Different Treatment Modalities for The Treatment of ITP	Dr. Mohd. Abdeldaem Mohd. Yassin	Hamad Medical Corporation (HMC)
MRC-01-20-799	Impact of Co-morbidity on Breast Cancer Systemic Treatment	Dr. Faroug Salih Hamed Ali	Hamad Medical Corporation (HMC)
MRC-01-20-800	Changes in microbiome expression and signatures after neoadjuvant therapy in colorectal cancers	Dr. Mai Mostafa Hisham Ali Mostafa	Hamad Medical Corporation (HMC)
MRC-01-20-812	The outcome of fatherhood in patients with Philadelphia negative myeloproliverative neoplasms	Dr. Elrazi Awadelkarim Hamid Awadelkarim Ali	Not funded
MRC-01-20-932	Effects of Life style and Diet on Recurrence of Colorectal Cancer in a tertiary cancer center-Qatar	Dr. Faroug Salih Hamed Ali	Hamad Medical Corporation (HMC)
MRC-01-20-958	Clinical presentation, management and outcomes of gastrointestinal stromal tumors (2012-2020)	Dr. Hassan Ali Saoud Al Thani	Hamad Medical Corporation (HMC)
MRC-01-20-973	A Comparative Analysis of Efficacy and Safety of Enoxaparin and Direct Oral Anticoagulants (DOACs): amongst cancer patients in Qatar. A Retrospective Cohort Study	Ms. Radoa Abdulla E M Abdulla Al-Ansari	Hamad Medical Corporation (HMC)
MRC-01-21-067	Assessment of Radiation Anxiety and Radiation Protective Behaviors among nurses at NCCCR	Ms. Anite Philip	Not funded
MRC-01-21-1019	Clinical manifestations and outcome of MPN patients with calreticulin gene mutations	Dr. Mohammad Abdullah Moh'd Abu-Tineh	Not funded
MRC-01-21-110	InterNaTional rEgistry oN Sars-cov-2 posItiVe nEuroendocrine neoplasm patients (INTENSIVE) - MRC-05-226	Dr. Kakil Ibrahim Rasul	Not funded

MRC-01-21-111	A pilot study of the immune response to the COVID-19 vaccine in cancer patients in Qatar	Dr. Maysaloun Merhi	Hamad Medical Corporation (HMC)
MRC-01-21-117	Automatic segmentation for MRI guided gynecological Brachytherapy using a multiplane Residual Convolutional Neural Network	Mr. Yoganathan Sullimullur Arunachalam	Not funded
MRC-01-21-119	Generating synthetic CT from daily Cone Beam CT using a patch-based 3D deep learning neural network	Mr. Yoganathan Sullimullur Arunachalam	Not in Abhath
MRC-01-21-247	outcome of gastric signet ring cells carcinoma in the State of Qatar	Dr. Dr. Alaaeldin Shablak	Hamad Medical Corporation (HMC)
MRC-01-21-260	Long-term Evaluation of Health Outcomes and Cost- Effectiveness of Qatar's National Bowel Cancer Screening Program: A Population-based Colorectal Cancer Screening	Mr. Ahmad Mohammad Adel El Sayed	Hamad Medical Corporation (HMC)
MRC-01-21-267	Depressive, anxiety, and PTSD symptoms in patients with cancer	Dr. Mahmoud K.M. Alshawwaf	Not funded
MRC-01-21-413	Artificial intelligence-based model for automatic MR Quality Control	Mr. Tarraf Torfeh	Not funded
MRC-01-21-517	Effect of immunotherapy, chemotherapy and target therapy on COVID -19 infection among cancer patients- Qatar Experience	Dr. Mai Mostafa Hisham Ali Mostafa	Not funded
MRC-01-21-519	Incidence of hyperprogression in cancer patients receiving immunotherapy. Qatar experience	Dr. Mai Mostafa Hisham Ali Mostafa	Not funded
MRC-01-21-567	Determining Oncology Nurses' Knowledge, Perceptions, and Needs about Palliative and Spiritual Care at HMC - MRC-05-202	Dr. Azza Adel Ibrahim Hassan	Not funded. It is a part of Msc/ PHD University of Colorado Anschutz campus Colorado USA

MRC-01-21-693	Real-World Efficacy and Safety of Off-Label Use of Immune Checkpoint Inhibitors (ICI) in Cancer: A Retrospective Cohort Study in Qatar.	Mr. Mr. Seif Ashraf Sharief Abaza	Hamad Medical Corporation (HMC)
MRC-01-21-697	Assessment of Organs Motion Impact on Brachytherapy Treatment Planning	Ms. Souha Aoudi	Hamad Medical Corporation (HMC)
MRC-01-21-719	Nasopharyngeal carcinoma: 5-Year experience in Qatar	Dr. Shaza Ahmed Hamed Mohamed Bek	Hamad Medical Corporation (HMC)
MRC-01-21-740	Ten-year outcomes of preoperative chemo radiation for rectal carcinoma in Qatar: single institutional experience experience	Dr. Saju Raveendran Divakar	Not funded
MRC-01-21-830	Image-guided Machine Learning Enhanced Brain Tissue and Tumor Segmentation for Radiation Oncology Planning	Mr. Tarraf Torfeh	Not funded, submitted by Inselspital University hospital of Bern, Switzerland
MRC-01-21-935	The impact of COVID19 on Compassion fatigue and quality of life of oncologists and other health care providers at the NCCCR in Qatar	Mr. Abdelhamid Afana	Not funded
MRC-01-21-963	The role of radiotherapy in the management of extremity soft tissue sarcomas- a tertiary institution's experience.	Dr. Dr. Venkada Manickam Gurusamy	Not funded
MRC-01-21-974	Clinical and epidemiological features and management outcome of avascular necrosis in sickle cell patients.	Dr. Awni A. A. Alshurafa	Not funded
MRC-01-21-986	The Clinicopathological Profile Of Multiple Myeloma In Qatar between 2017-2021	Dr. Hesham Mahmoud A Elsabah	Not funded
MRC-02-18-054	Triple Negative Breast Cancer Prospective Registry in Middle East, and Africa	Dr. Salha Mohd. Bu Jassoum	Merck Sharp & Dohme (MSD), UK

MRC-02-18-145	Young Adults with ASD: Health Needs Assessment and Pathways to Care	Dr. Sanaa Taha Alharahsheh	Qatar Foundation (QF), Qatar
MRC-02-20-1226	A Multicountry, Multicentre, Non-interventional, Prospective Study to.D5161R00028 EARLY-EGFR Study Determine the Prevalence of EGFR Mutations in Patients With Early-stage, Surgically Resected, Non-squamous, Non-small Cell Lung CancerDetermine the Prevalence of EGFR Mutations in Patients With EarlySurgically Resected, Non-squamous, Non-small Cell Lung Cancer	Dr. Reyad Hassan Mohsen	AstraZeneca Pharmaceutical Company, UK
MRC-02-20-289	UBR5, E3 Ubiquitin ligase, in triple negative breast cancers; potential Role in Anti-Tumor Immunity and cancer metabolism	Prof. Lotfi Chouchane	Qatar National Research Fund (QNRF), Qatar
MRC-02-20-655	Genetic determinants of high-risk non-BRCA1/2 familial breast cancer in Qatar.	Dr. Julie Decock	Qatar Biomedical Research Institute (QBRI), Qatar
MRC-02-21-015	CEFtolozane-Tazobactam for the Empiric Anti-bacterial Treatment of Neutropenic Fever in Hematology Patients; a Single-arm, Single-center, Open-label Clinical Trial (CEF-10 Study)	Dr. Ali Senosi Omrani	Merck Sharp & Dohme (MSD), UK
MRC-02-21-264	Sickle Cell disease Cost of Illness Study in GCC	Dr. Mohd. Abdeldaem Mohd. Yassin	Not funded, Sponsored by Novartis Pharmaceutical Company, Switzerland
MRC-02-21-462	Prospective, observational study in Sickle Cell Disease patients on Crizanlizumab treatment in Middle East countries and India (SPOTLIGHT)	Dr. Mohd. Abdeldaem Mohd. Yassin	Novartis Pharmaceutical Company, Switzerland

MRC-02-21-562	A Cross-sectional, Noninterventional, Multicentre Study to Determine the Prevalence of Homologous Recombination Deficiency Among Women with Newly Diagnosed, High-grade, Serous or Endometrioid Ovarian, Primary Peritoneal, and/or Fallopian Tube Cancer	Dr. Hind Hassan Ahmed Habish	AstraZeneca Pharmaceutical Company, UK
MRC-02-21-725	Acquired Thrombotic Thrombocytopenic Purpura Landscaping in Gulf Countries	Dr. Ruba Yasin Ibrahim Taha	Sanofi Pharmaceutical Company, France
MRC-02-21-878	Exploring Drug Resistance Mechanisms in Triple Negative Breast Cancers: From Patient Derived Organoids towards Precision Medicine	Prof. Lotfi Chouchane	Qatar Foundation (QF), Qatar
MRC-02-21-890	Quality of life and mental health of women who experienced breast cancer in Qatar	Dr. Suhad Nashif	Qatar University (QU), Qatar
MRC-03-17-150	Mapping Genotype to Phenotype for Colorectal Cancer Stem Cells: Implications and Perspectives In Cancer Therapy	Dr. Cristina Maccalli	Qatar National Research Fund (QNRF), Qatar
MRC-03-19-043	Comprehensive integration of mutanome as a true personalized immunotherapy modality in colorectal cancer patients	Dr. Said Dermime	Qatar National Research Fund (QNRF), Qatar
MRC-03-20-580	Towards personalized cancer medicine: Immunoscore and immunogenomic score in primary and metastatic colorectal cancer patients from Europe and Qatar	Dr. Davide Bedognetti	Qatar National Research Fund (QNRF), Qatar
MRC-03-21-400	Pre-implementation of a smartphone application to support the delivery of antimicrobial prescribing policy	Dr. Ziad Nasr	Not funded
IRGC-07-SI-20-716	Cloning of B cells secreting anti-SARS-CoV-2 neutralizing antibodies and large-scale production of coronavirus-specific monoclonal antibodies from participants vaccinated with mRNA SARS-CoV-2 vaccine	Dr. Said Dermime	Hamad Medical Corporation (HMC)

MRC-01-19-273	The Effectiveness of Magic Mouthwash in Chemotherapy/Radiotherapy-induced Mucositis: A Prospective Observational Study	Ms. Taghrid Sahteh I Abou Hassan	Hamad Medical Corporation (HMC)
MRC-01-21-113	Characterization of the cellular and humoral immune responses to the COVID-19 vaccine in healthy population in Qatar	Dr. Maysaloun Merhi	Hamad Medical Corporation (HMC)

ONCOLOGY

Original Articles

Ancestry-associated transcriptomic profiles of breast cancer in patients of African, Arab, and European ancestry

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Abstract

Breast cancer largely dominates the global cancer burden statistics; however, there are striking disparities in mortality rates across countries. While socioeconomic factors contribute to population-based differences in mortality, they do not fully explain disparity

among women of African ancestry (AA) and Arab ancestry (ArA) compared to women of European ancestry (EA). In this study, we sought to identify molecular differences that could provide insight into the biology of ancestry-associated disparities in clinical

outcomes. We applied a unique approach that combines the use of curated survival data from The Cancer Genome Atlas (TCGA) Pan-Cancer clinical data resource, improved single-nucleotide polymorphism-based inferred ancestry assignment, and a novel breast cancer subtype classification to interrogate the TCGA and a local Arab breast cancer dataset. We observed an enrichment of BasalMyo tumors in AA patients (38 vs 16.5% in EA, p = 1.30E – 10), associated with a significant worse overall (hazard ratio (HR) =2.39, p = 0.02) and disease-specific survival (HR = 2.57, p = 0.03). Gene set enrichment analysis of BasalMyo AA and EA samples revealed differences in the abundance of T-regulatory and T-helper type 2 cells, and enrichment of cancer-related pathways with prognostic implications (AA: PI3K-Akt-mTOR and ErbB signaling; EA: EGF, estrogen-dependent and DNA repair signaling). Strikingly, AMPK signaling was associated with opposing prognostic connotation (AA: 10-year HR = 2.79, EA: 10-year HR = 0.34). Analysis of ArA patients suggests enrichment of BasalMyo tumors with a trend for differential enrichment of T-regulatory cells and AMPK signaling. Together, our findings suggest that the disparity in the clinical outcome of AA breast cancer patients is likely related to differences in cancer-related and microenvironmental features.

Citation: Roelands J, Mall R, Almeer H, Thomas R, Mohamed MG, Bedri S, Al-Bader SB, Junejo K, Ziv E, Sayaman RW, Kuppen PJK, Bedognetti D, Hendrickx W, Decock J. Ancestry-associated transcriptomic profiles of breast cancer in patients of African, Arab, and European ancestry. *NPJ Breast Cancer.* 2021 Feb 8;7(1):10.

Impact Factor: 7.519

Anti-cancer effects of Tranilast: An update

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Abstract

ranilast (TRN) or (N-3,4 -dimethoxy cinnamoyl]-anthranilic acid) is an analog of a tryptophan metabolite and is identified mainly as an anti-allergic agent with limited side effects. The anti-cancer effects of tranilast either alone or in combination with chemotherapeutic drugs have been evidenced in several pre-clinical studies. The main mechanism of action of tranilast includes targeting and modulation of various signaling and immune regulatory pathways including Transforming growth factor-beta (TGF-ß), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), phosphatidylinositol 3-kinase (PI3K), MAP-Kinase (MAPK), Protein kinase B (⇈Akt/PKB), c-Jun N-terminal kinase, modulation of cancer stem cells, etc. Most of these pathways are involved in tumor proliferation, invasion, and metastasis and it is postulated that tranilast, with its low toxicity profile and high anti-carcinogenic abilities, can serve as a potential anti-tumorigenic agent. The main aim of this review is to provide updated information on the anti-cancer effects of tranilast and its significance as a therapeutic agent.

Keywords: Tranilast Anti-carcinogenic drug Anti-inflammatory drug Combination therapy

Citation: Osman S, Raza A, Al-Zaidan L, Inchakalody VP, Merhi M, Prabhu KS, Abdelaziz N, Hydrose S, Uddin S, Dermime S. Anti-cancer effects of Tranilast: An update. *Biomed Pharmacother.* 2021 Sep;141:111844.

Impact Factor: 7.18

Sanguinarine mediated apoptosis in Non-Small Cell Lung Cancer via generation of reactive oxygen species and suppression of JAK/STAT pathway

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Abstract

Effective treatment of lung cancer remains a significant clinical challenge due to its multidrug resistance and side effects of the current treatment options. The high mortality associated with this malignancy indicates the need for new therapeutic interventions with fewer side effects. Natural compounds offer various benefits such as easy access, minimal side effects, and multi-molecular targets and thus, can prove useful in treating lung cancer. Sanguinarine (SNG), a natural compound, possesses favorable therapeutic potential against a variety of cancers. Here, we examined the underlying molecular mechanisms of SNG in Non-Small Cell Lung Cancer (NSCLC) cells. SNG

suppressed cell growth and induced apoptosis via downregulation of the constitutively active JAK/STAT pathway in all the NSCLC cell lines. siRNA silencing of STAT3 in NSCLC cells further confirmed the involvement of the JAK/STAT signaling cascade. SNG treatment increased Bax/Bcl-2 ratio, which contributed to a leaky mitochondrial membrane leading to cytochrome c release accompanied by caspase activation. In addition, we established the antitumor effects of SNG through reactive oxygen species (ROS) production, as inhibiting ROS production prevented the apoptosis-inducing potential of SNG. In vivo xenograft tumor model further validated our in vitro findings. Overall, our study investigated the molecular mechanisms by which SNG induces apoptosis in NSCLC, providing avenues for developing novel natural compound-based cancer therapies.

Keywords: Alkaloids; Antioxidants; Antiproliferative; Apoptosis; Cancer stem cells; ROS; STAT3; Sanguinarine.

Citation: Prabhu KS, Bhat AA, Siveen KS, Kuttikrishnan S, Raza SS, Raheed T, Jochebeth A, Khan AQ, Chawdhery MZ, Haris M, Kulinski M, Dermime S, Steinhoff M, Uddin S. Sanguinarine mediated apoptosis in Non-Small Cell Lung Cancer via generation of reactive oxygen species and suppression of JAK/STAT pathway. *Biomed Pharmacother.* 2021 Dec;144:112358

Impact factor: 7.18

Differential gene expression of tumor-infiltrating CD33+ myeloid cells in advanced- versus early-stage colorectal cancer

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Abstract

Colorectal cancer (CRC) has high mortality rates, especially in patients with advanced disease stages, who often do not respond to therapy. The cellular components of the tumor microenvironment are essentially responsible for dictating disease progression and response to therapy. Expansion of different myeloid cell subsets in CRC tumors has been reported previously. However, tumor-infiltrating myeloid cells have both pro- and anti-tumor roles in disease progression. In this study, we performed transcriptomic profiling of cells of myeloid lineage (CD33+) from bulk CRC tumors at varying disease stages. We identified differentially expressed genes and pathways between CRC patients with advanced stage and early stages. We found that pro-angiogenic and hypoxia-related genes were upregulated, while genes related to immune and inflammatory responses were downregulated in CD33+ myeloid cells from patients with advanced stages, implying that immune cell recruitment and activation could be compromised in advanced disease stages. Moreover, we identified a unique "poor prognosis CD33+ gene signature" by aligning top upregulated and downregulated genes in tumor-infiltrating myeloid cells from our analyses with data from The Cancer Genome Atlas. Our results showed that this gene signature is an independent prognostic indicator for disease-specific survival in CRC patients, potentially reflecting its clinical importance.

Keywords: Colorectal cancer; Myeloid cells; Transcriptomics; Tumor microenvironmen

Citation: Toor SM, Taha RZ, Sasidharan Nair V, Saleh R, Murshed K, Abu Nada M, Elkord E. Differential gene expression of tumor-infiltrating CD33+ myeloid cells in advanced- versus early-stage colorectal cancer. *Cancer Immunol Immunother.* 2021 Mar;70(3):803-815.

Impact Factor: 6.93

Transcriptome of CD8+ tumor-infiltrating T cells: a link between diabetes and colorectal cancer

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Abstract

There is an increased risk of colorectal cancer (CRC) development in patients with non-insulin-dependent type 2 diabetes. CD8+ T cells have been implicated in diabetes and are crucial for anti-tumor immunity. However, transcriptomic profiling for CD8+ T cells from CRC diabetic patients has not been explored. We performed RNA sequencing and compared transcriptomic profiles of CD8+ tumor-infiltrating T lymphocytes (CD8+ TILs) in CRC diabetic patients with CRC nondiabetic patients. We found that genes associated with ribogenesis, epigenetic regulations, oxidative phosphorylation and cell cycle arrest were upregulated in CD8+ TILs from diabetic patients, while genes associated with PI3K signaling pathway, cytokine response and response to lipids were downregulated. Among the significantly deregulated 1009 genes, 342 (186 upregulated and 156 downregulated) genes were selected based on their link to diabetes, and their associations with the presence of specific CRC pathological parameters were assessed using GDC TCGA colon database. The 186 upregulated genes were associated with the presence of colon polyps history ($P = 0.0007$) and lymphatic invasion ($P = 0.0025$). Moreover, CRC patients with high expression of the 186 genes were more likely to have poorer disease-specific survival (DSS) (Mantel–Cox log-rank $P = 0.024$) than those with low score. Our data provide novel insights into molecular pathways and biological functions, which could be altered in CD8+ TILs from CRC diabetic versus nondiabetic patients, and reveal candidate genes linked to diabetes, which could predict DSS and pathological parameters associated with CRC progression. However, further investigations using larger patient cohorts and functional studies are required to validate these findings.

Citation: Saleh, R., Sasidharan Nair, V., Murshed, K. et al. Transcriptome of CD8+ tumor-infiltrating T cells: a link between diabetes and colorectal cancer. *Cancer Immunol Immunother* 70, 2625–2638 (2021).

Impact Factor: 6.93

Regulation of Circular RNA CircNFATC3 in Cancer Cells Alters Proliferation, Migration, and Oxidative Phosphorylation

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Abstract

Circular RNAs were once considered artifacts of transcriptome sequencing but have recently been identified as functionally relevant in different types of cancer. Although there is still no clear main function of circRNAs, several studies have revealed that circRNAs are expressed in various eukaryotic organisms in a regulated manner often independent of their parental linear isoforms demonstrating conservation across species. circNFATC3, an abundant and uncharacterized circular RNA of exon 2 and 3 from *NFATC3*, was identified in transcriptomic data of solid tumors. Here we show that circNFATC3 gain- and loss-of-function experiments using RNAi-mediated circRNA silencing and circular mini vector-mediated overexpression of circularized constructs in breast and ovarian cancer cell lines affect molecular phenotypes. The knockdown of circNFATC3 induces a reduction in cell proliferation, invasion, migration, and oxidative phosphorylation. Gain-of-function of circNFATC3 in MDA-MB-231 and SK-OV-3 cells show a significant increase in cell proliferation, migration, and respiration. The above results suggest that circNFATC3 is a functionally relevant circular RNA in breast and ovarian cancer.

Keywords: RNA-seq; circRNA; circRNA mini vector; invasion; migration; oxidative phosphorylation; siRNA.

Citation: Karedath T, Al-Dasim FM, Ahmed I, Al-Qurashi A, Raza A, Andrews SS, Ahmed AA, Ali Mohamoud Y, Dermime S, Malek JA. Regulation of Circular RNA CircNFATC3 in Cancer Cells Alters Proliferation, Migration, and Oxidative Phosphorylation. *Front Cell Dev Biol.* 2021 Mar 19;9:595156.

Impact Factor: 6.081

Breast Cancer Screening Practices in a Tertiary Care Center in the State of Qatar: A Cross-Sectional Survey

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Abstract

Introduction: Breast cancer is the most common cancer in females. In Qatar, mortality related to breast cancer came in third after lung cancer and leukemia. In this study, we aim to comprehensively evaluate the rate of internal medicine residents and faculty compliance with breast cancer screening in Hamad Medical Corporation (Doha, Qatar), as well as to identify barriers and facilitators that could potentially augment changes to enhance physician-led cancer screening.

Methods: A cross-sectional web-based survey was distributed among internal medicine physicians between December 2018 and March 2019 at a tertiary medical centre. It focused on the knowledge, attitude, and practice of physicians regarding breast cancer screening guidelines and explored potential barriers and proposed solutions. Chi-square and *t*-test statistics were used to draw conclusions where appropriate.

Results: A total of 158 physicians responded to the survey, with a response rate of 61%. 75.9% were postgraduate trainees. Around three-quarters of the physicians mentioned that they would recommend breast cancer screening for their age-appropriate average-risk patients. There was a statistically significant difference between the trainees, consultants, and specialists regarding the modality of choice, where the majority of the trainees opted mammogram every 2 or 3 years while 44.4% of the consultants indicated yearly self-breast exam ($p<0.001$). The percentage of survey participants who rarely to never offer breast cancer screening in the outpatient settings was 37.8%. Unclear pathway (40%) and lack of time in clinic/ward rounds (26.5%) were the major reported barriers for cancer screening.

Conclusion: In the current era of personalized medicine, physicians should be more oriented to local guidelines to provide optimal care to their patients. While the attitude towards breast cancer screening is positive, the overall compliance with the national recommendations is sub-optimal. Further initiatives and intervention programs are required to promote the breast cancer screening in Qatar.

Keywords: Middle East; breast cancer; physicians; residency training program; screening.

Citation: Parambil JV, Najim M, Mahmoud M, Abubeker IY, Kartha A, Calaud F, Al-Mohamed A, Al-Mohannadi D, Chandra P, A Yassin M. Breast Cancer Screening Practices in a Tertiary Care Center in the State of Qatar: A Cross-Sectional Survey. *Breast Cancer (Dove Med Press).* 2021 Jan 8;13:21-30.

Impact Factor: 5.088

Transcriptome of Tumor-Infiltrating T Cells in Colorectal Cancer Patients Uncovered a Unique Gene Signature in CD4+ T Cells Associated with Poor Disease-Specific Survival

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Abstract

Colorectal cancer (CRC) is influenced by infiltration of immune cell populations in the tumor microenvironment. While elevated levels of cytotoxic T cells are associated with improved prognosis, limited studies have reported associations between CD4+ T cells and disease outcomes. We recently performed transcriptomic profiling and comparative analyses of sorted CD4+ and CD8+ tumor-infiltrating lymphocytes (TILs) from bulk tumors of CRC patients with varying disease stages. In this study, we compared the transcriptomes of CD4+ with CD8+ TILs. Functional annotation pathway analyses revealed the downregulation of inflammatory response-related genes, while T cell activation and angiogenesis-related genes were upregulated in CD4+ TILs. The top 200 deregulated genes in CD4+ TILs were aligned with the cancer genome atlas (TCGA) CRC dataset to identify a unique gene signature associated with poor prognosis. Moreover, 69 upregulated and 20 downregulated genes showed similar trends of up/downregulation in the TCGA dataset and were used to calculate "poor prognosis score" (ppScore), which was significantly associated with disease-specific survival. High ppScore patients showed lower expression of Treg-, Th1-, and Th17-related genes, and higher expression of Th2-related genes. Our data highlight the significance of T cells within the TME and identify a unique candidate prognostic gene signature for CD4+ TILs in CRC patients.

Keywords: T cells; colorectal cancer; transcriptomics; tumor microenvironment.

Citation: Toor SM, Sasidharan Nair V, Saleh R, Taha RZ, Murshed K, Al-Dhaheri M, Khawar M, Ahmed AA, Kurer MA, Abu Nada M, Elkord E. Transcriptome of Tumor-Infiltrating T Cells in Colorectal Cancer Patients Uncovered a Unique Gene Signature in $CD4^+$ T Cells Associated with Poor Disease-Specific Survival. *Vaccines (Basel).* 2021 Apr 1;9(4):334.

Impact Factor: 4.82

Tumor-Infiltrating Lymphoid Cells in Colorectal Cancer Patients with Varying Disease Stages and Microsatellite Instability-High/Stable Tumors

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Abstract

Immune checkpoint inhibition is an effective anti-cancer therapeutic approach but has shown limited efficacy in treating colorectal cancer (CRC) patients. Importantly, immune constituents of the tumor microenvironment (TME) can influence therapy response and cancer progression. We investigated the expression of immune checkpoints (ICs) on lymphoid populations within the CRC TME and compared with cells from normal colon tissues using samples from 50 patients with varying disease stages. We found that the levels of B cells, T cells, and NK cells were similar, IC-expressing CD4+ and CD4+CD8+ double positive T cells were higher, while CD8+ T cells and CD4-CD8- double negative T cells were significantly lower in CRC tumors. Notably, patients with mismatch-repair deficiency/microsatellite instability-high tumors had higher levels of IC-expressing CD4+ and CD8+ T cells than patients with proficient MMR and microsatellite stable tumors. Lastly, The Cancer Genome Atlas Colon Adenocarcinoma datasets showed associations between low expression of selective genes and poorer progression-free interval. Our findings highlight differential expression of ICs on lymphoid cells in CRC tumors in the era of cancer immunotherapy, which at present is solely approved for anti-PD-1 therapy in patients with dMMR/MSI-H tumors. Further investigations into their functionality have potentials for deciphering resistance mechanisms to IC inhibition.

Keywords: B cells; MSI-H; MSS; NK cells; T cells; colorectal cancer; dMMR; immune checkpoints.

Citation: Toor SM, Sasidharan Nair V, Murshed K, Abu Nada M, Elkord E. Tumor-Infiltrating Lymphoid Cells in Colorectal Cancer Patients with Varying Disease Stages and Microsatellite Instability-High/Stable Tumors. *Vaccines (Basel).* 2021 Jan 19;9(1):64.

Impact Factor: 4.82

Quality of Life, Sleep Quality, Depression, Anxiety, Stress, Eating Habits, and Social Bounds in Nurses during the Coronavirus Disease 2019 Pandemic in Qatar (The PROTECTOR Study): A Cross-Sectional, Comparative Study

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Abstract

There have been numerous concerns regarding the physical and mental health of nurses during the COVID-19 pandemic. Stress, sleep deprivation, anxiety, and depression potentiated nurses' vulnerability to poor eating habits.

Aims and objectives: The purpose of this study was to explore the differences between nurses' characteristics with COVID-19 facility designation, and sleep quality, depression, anxiety, stress, eating habits, social bonds, and quality of life.

Design: A cross-sectional, comparative study.

Methods: An online survey was sent using the corporation's email to nurses working in three hospitals in Qatar from September to December 2020. One of them is a designated COVID-19 facility. The sleep quality, depression, eating habits, social bonds, and quality of life were measured using The Insomnia Severity Index (ISI), Depression Anxiety and Stress Scale 21 (DASS-21), Emotional Eater Questionnaire (EEQ), Oslo Social Support Scale (OSSS-3), and the World Health Organization Quality of Life (WHOQOL-BREF), respectively.

Results: A total of 200 nurses participated in the study (RR: 13.3%). No statistically significant association was found between designated facility (COVID-19 vs. not COVID-19) or nurses' characteristics and ISI categories (OR 1.15; 95% CI 0.54, 2.44). Nurses working in COVID-19 facilities had increased odds of having higher EEQ categories by 2.62 times (95% CI 1.18, 5.83). Similarly, no statistically significant associations were found between any of the nurses' characteristics and OSSS-3 categories. On the other hand, no statistically significant associations were found between any of the nurses' characteristics and QOL domains except for the gender and social relationships' domain.

Conclusion: Overall, the quality of life of nurses in Qatar is on a positive level whether they are assigned to a COVID-19 facility or not. Although no significant difference was found with regard to the sleep quality, stress, anxiety, depression, and eating habits between nurses in a COVID-19 facility and in a non-COVID-19 facility, special interventions to diminish stressors need to be implemented and maintained.

Keywords: Coronavirus Disease 2019 (COVID-19); eating habits; nurses; quality of life; social support.

Citation: Nashwan AJ, Villar RC, Al-Qudimat AR, Kader N, Alabdulla M, Abujaber AA, Al-Jabry MM, Harkous M, Philip A, Ali R, Chandra P, Yassin MA, Shraim M, Singh K. Quality of Life, Sleep Quality, Depression, Anxiety, Stress, Eating Habits, and Social Bounds in Nurses during the Coronavirus Disease 2019 Pandemic in Qatar (The PROTECTOR Study): A Cross-Sectional, Comparative Study. *J Pers Med.* 2021 Sep 15;11(9):918.

Impact Factor: 3.37

IMPORTANCE trial: a provisional study-design of a single-center, phase II, double-blinded, placebo-controlled, randomized, 4-week study to compare the efficacy and safety of intranasal esketamine in chronic opioid refractory pain

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Abstract

Background: Cancer is the second leading cause of death globally. Up to 86% of advanced cancer patients experience significant pain, while 10-20% live in chronic pain. Besides, increasing prescription of opioids resulted in 33,000 deaths in the US in 2015. Both reduce patients' functional status and quality of life. While cancer survival rates are increasing, therapeutic options for chronic opioid refractory pain are still limited. Esketamine is the s-enantiomer of ketamine, with superior analgesic effect and less psychotomimetic side effects. Intranasal esketamine was approved by the FDA for treatmentresistant depression. However, its use in chronic cancer pain has never been tested. Therefore, we propose a phase II, randomized, placebo-controlled trial to evaluate the efficacy and safety of intranasal esketamine in chronic opioid refractory cancer pain.

Methods and analysis: We will recruit 120 subjects with chronic opioid refractory pain, defined as pain lasting more than 3 months despite optimal therapy with high dose opioids (>60 mg morphine equivalent dose/day) and optimal adjuvant therapy. Subjects will be randomized into two groups: intranasal esketamine (56mg) and placebo. Treatment will be administered twice a week for four consecutive weeks. The primary outcome is defined as reduction in the Numeric Pain Rating Scale (NPRS) after first application. Secondary outcomes include NPRS reduction after four weeks, the number of daily morphine rescue doses, functional status and satisfaction, and depression.

Conclusion: This study may extend therapeutic options in patients with chronic pain, thus improving their quality of life and reducing opioid use.

Keywords: Cancer pain, Esketamine, Pain measurement, Opioid refractory

Citation: Fernandes M, Schelotto M, Doldi PM, Milani G, Ariza Manzano AA, Perera Valdivia D, Winter Matos AM, Hamdy Abdelrahim Y, Hamad Bek SA, Benitez BK, Romanelli Tavares VL, Basendwah AM, Albuquerque Sousa LH, Xavier NF, Zertuche Maldonado T, Toyomi de Oliveira S,

Chaker M, Menon Miyake M, Uygur Kucukseymen E, Waqar K, Alkhozondar OMJ, Bernardo da Silva R, Droppelmann G, Vaz de Macedo A, Nakamura R, Fregni F. IMPORTANCE trial: a provisional study-design of a single-center, phase II, double-blinded, placebo-controlled, randomized, 4-week study to compare the efficacy and safety of intranasal esketamine in chronic opioid refractory pain. *F1000Res.* 2021 Jan 22;10:42.

Impact Factor: 3.23

Venous Thromboembolism in Hospitalized Melanoma Patients: Analysis from the National Inpatient Sample Database

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Abstract

Introduction: The association between cancer and hyper-coagulability is well known. However, the association between melanoma and venous thromboembolism (VTE) has not been identified.

Methods: We studied the national inpatient sample (NIS) which compromise 20% of US hospitalization to better characterize melanoma and VTE. We analyzed the data between 2010 and 2014 using ICD-9 codes.

Results: Melanoma patients were grouped into presence/absence of VTE. Multiple logistic regression was used to obtain the odds ratio (OR) to compare the mortality of the inpatient, total charges, length of stay (LOS), and disability at discharge. A total of 61,812 melanoma patients were identified, of which 5.2% were hospitalized for VTE. The presence of VTE was associated with a remarkable higher rate of discharge with a moderate to severe disability (57.5% vs 41.4%, P<0.001), in-hospital stroke (7.6% vs 4.9%, P<0.001), and in-hospital mortality (8.8% vs 5.1%, P<0.001). Costs of hospitalization (64,720$ vs 46,606, P<0.001) and LOS (5 vs 3 days, P<0.001) were significantly higher as well in the VTE group. After adjusting for common confounder, VTE was found to be an independent predictor of mortality (OR = 1.596, 95% CI [1.399-1.821], P<0.001).

Conclusion: In summary, melanoma patients with VTE had higher inpatient mortality, LOS, higher hospital cost, and a higher degree of disability upon discharge.

Keywords: VTE; coagulation; melanoma; venous thromboembolism.

Citation : Alhasson H, Al-Banaa K, Abu-Tineh M, Alhasson B, Zhao Y, Yassin MA. Venous Thromboembolism in Hospitalized Melanoma Patients: Analysis from the National Inpatient Sample Database. *Int J Gen Med.* 2021 Nov 9;14:7855-7860

Impact Factor: 2.445

Design and construction of a customizable phantom for the characterization of the three-dimensional magnetic resonance imaging geometric distortion

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Abstract

One of the main challenges to using magnetic resonance imaging (MRI) in radiotherapy is the existence of system-related geometric inaccuracies caused mainly by the inhomogeneity in the main magnetic field and the nonlinearities of the gradient coils. Several physical phantoms, with fixed configuration, have been developed and commercialized for the assessment of the MRI geometric distortion. In this study, we propose a new design of a customizable phantom that can fit any type of radio frequency (RF) coil. It is composed of 3D printed plastic blocks containing holes that can hold glass tubes which can be filled with any liquid. The blocks can be assembled to construct phantoms with any dimension. The feasibility of this design has been demonstrated by assembling four phantoms with high robustness allowing the assessment of the geometric distortion for the GE split head coil, the head and neck array coil, the anterior array coil, and the body coil. Phantom reproducibility was evaluated by analyzing the geometric distortion on CT acquisition of five independent assemblages of the phantom. This solution meets all expectations in terms of having a robust, lightweight, modular, and practical tool for measuring distortion in three dimensions. Mean error in the position of the tubes was less than 0.2 mm. For the geometric distortion, our results showed that for all typical MRI sequences used for radiotherapy, the mean geometric distortion was less than 1 mm and less than 2.5 mm over radial distances of 150 mm and 250 mm, respectively. These tools will be part of a quality assurance program aimed at monitoring the image quality of MRI scanners used to guide radiation therapy.

Keywords: 3D geometric distortion; MR-guided radiation therapy; MRI; customizable phantom.

Citation: Torfeh T, Hammoud R, Paloor S, Arunachalam Y, Aouadi S, Al-Hammadi N. Design and construction of a customizable phantom for the characterization of the three-dimensional magnetic resonance imaging geometric distortion. *J Appl Clin Med Phys.* 2021 Dec;22(12):149-157.

Impact factor: 2.17

Caring for patients with cancer in Qatar: the impact on the mental health of voluntary caregivers

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Abstract

Background: Cancer is a disease where both patients and caregivers receive and provide care, respectively, for extended periods of time, and often amidst challenging personal conditions. In Qatar, with cancer as the third largest cause of death, cancer care has become a national healthcare priority. However, the needs of informal caregivers who are experiencing various psychological issues such as anxiety, depression, and stress are overlooked due to the demanding and time-consuming nature of the care of patients with cancer. Aim: The aim of this research is to identify the prevalence of psychological issues (anxiety, depression, and stress) among informal Arabicspeaking caregivers of patients with cancer. Methodology: The research utilized the Arabic version of Depression Anxiety Stress Scales (DASS21) test to measure the anxiety, depression and stress among caregivers of patients with cancer. A total of 128 participants participated in the study. Results: According to DASS 21, the results revealed that the overall prevalence of depression, anxiety, and stress in this study was found to be 57%, 52%, and 50%, respectively. Conclusion: The research concluded that voluntary care givers of patients with cancer were found to experience high levels of depression, anxiety and stress.

Citation: Idris, Z., Yassin, K., Ali, N., Zada, H., & Ghazouani, H. (2021). Caring for patients with cancer in Qatar: the impact on the mental health of voluntary caregivers. *Middle East Journal of Family Medicine,* 7(10).

Impact Factor: 1.3

Featuring Trends in the Epidemiology of Lung Cancer Following the Publication of the National Cancer Strategy in Qatar

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Abstract

Objectives: Qatar has witnessed significant reforms in its health care system, including the care of cancer patients. In 2011, the National Cancer Strategy was released with the aim to deliver a high standard of care to cancer patients across the country. We sought to investigate the featuring trends in the epidemiological and clinical characteristics of lung cancer in Qatar following the publication of the National Cancer Strategy.

Methods: We conducted a retrospective cohort study documenting the epidemiological and clinical characteristics of primary lung cancer cases in Qatar diagnosed from 1 January 2011 to 31 December 2018.

Results: The overall age-standardized incidence rate was 8.7 per 100 000 persons (11.6 per 100 000 and 5.4 per 100 000 persons for males and females, respectively). The one, three, and five-year overall survival rates were 67.0%, 48.0%, and 28.0%, respectively. The three-year overall survival rates for stages I, II, III, and IV were 97.0%, 78.0%, 52.0%, and 31.0%, respectively. The three-year survival rates for males and females were 43.0% and 64.0%, respectively ($p = 0.029$), for Qatari and non-Qatari nationals were 42.0% and 49.0%, respectively ($p = 0.252$), and for smokers and non-smokers were 39.0% and 69.0%, respectively ($p \leq 0.001$). The overall age-standardized mortality rate was 5.5 per 100 000 persons. Adenocarcinoma was the most common histologic type.

Conclusions: Despite the low overall lung cancer incidence rate in Qatar, there is a rise in the incidence among females when compared to previous studies. Qatar has favorable five-year lung cancer

survival rates compared to many developed and neighboring countries. Policymakers in the country should consider the changing patterns in lung cancer incidence when planning future preventive strategies.

Keywords: Lung Neoplasms, Incidence, Survival Rate, Retrospective Studies, Delivery of Health Care, Qatar

Citation: Ibrahim WH, Shariff K, El Mistiri M, Alhomsi U, Alshurafa A, Farooqui K, Faris ME, Aboujabal KA, Aboujabal KA, Ghazouani H, Akbar RA, Waheed MA, Mohsen RH, Eledrisi M. Featuring Trends in the Epidemiology of Lung Cancer Following the Publication of the National Cancer Strategy in Qatar. *Oman Med J.* 2021 May 31;36(3):e276. doi: 10.5001/omj.2021.71. PMID: 34239716; PMCID: PMC8237402.

Impact Factor: 1.265

Assessment of Deep Vein Thrombosis (DVT) incidence among ambulatory cancer patients in Qatar: A retrospective cohort study

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Abstract

Background: Thromboprophylaxis of ambulatory cancer patients is considered controversial. However, some guidelines suggest conducting VTE risk assessment using the Khorana risk assessment scoring model. This study aims to assess the incidence of Deep Vein Thrombosis (DVT) and related cancer types, focusing on the incidence of DVT in ambulatory patients actively on chemotherapy, with Khorana risk score (KRS). Methods: The Doppler ultrasound reports over 12-month period were reviewed. A total of 205 patients were included in the study. Patients with DVT were screened for the relevant biomarkers in KRS model and any other additional risk factors. Furthermore, a comparison between ambulatory patients who developed DVT and those who did not, was carried on determining the KRS association with incidence. Results: The incidence of DVT in ambulatory cancer patients was higher than the inpatient setting (23% vs. 8%). Breast cancer was the most common malignancy associated with DVT (30%) followed by colon cancer (17%). Chemotherapy increased the incidence of DVT in ambulatory patients (29% vs. 13%). Patients with KRS of ≥2 were more likely to develop DVT (37.5%). Conclusion: This study highlights the importance of conducting a thorough DVT risk assessment for ambulatory cancer patients on chemotherapy and the need to look for KRS to reconsider additional risk factors.

Keywords: VTE; DVT; Ambulatory care; Cancer; Chemotherapy; Prophylaxis

Citation: Abdelwahab R, Hamad A, Negm R, Al Tarawneh N, Elazzazy S .Assessment of Deep Vein Thrombosis (DVT) Incidence among Ambulatory Cancer Patients in Qatar: A Retrospective Cohort Study" *GSC Biological and Pharmaceutical Sciences*, 2021, 16(03), 049–058. September 2021.

Impact Factor: 0.3

ONCOLOGY

Case Reports

Tuberculosis following programmed cell death receptor-1 (PD-1) inhibitor in a patient with non-small cell lung cancer. Case report and literature review

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Abstract

Immune checkpoint inhibitors (ICIs)—anti-programmed death-1 (PD-1) and their ligands (PD-L1 and PD-L2) have become widely used in the treatment of several malignancies. Many immune-related adverse events (irAEs) have been linked to these agents. Nonetheless, tuberculosis (TB) reactivation during their use is increasingly recognized and reported. Herein, we present a 58-year-old lady with advanced non-small cell lung cancer (NSCLC) ALK-negative, EGFR wild, and PD-L1 immune histochemistry (IHC) strongly positive in 95% of tumor cells, on ongoing treatment with Pembrolizumab as a frstline monotherapy. Our patient presented with 1-week history of productive cough and high-grade fever. Further workup yielded the diagnosis of pulmonary tuberculosis after her Pembrolizumab sixth cycle with positive AFB smear and TB PCR from BAL (rifampin resistance not detected), with negative HIV status. Hence, immunotherapy was held, and patient was commenced on anti-TB regimen. History revealed contact with active TB patient over the past decade, without previous documentation of latent TB or previous TB infection. Her sputum AFB smear remained persistently positive 4 weeks through anti-TB regimen course. Later, the patient was discharged after her sputum was cleared from AFB (two negative sets). In light of pembrolizumab mechanism

of action as an immune checkpoint inhibitor, we suspected its implication on reactivating latent TB which was observed in our patient demonstrating features of pulmonary tuberculosis. She was not re-challenged with Pembrolizumab following TB diagnosis.

Keywords: Tuberculosis · NSCLC · PD-1 inhibitor · Pembrolizumab · Immune related adverse events · Case report

Citation: Suliman AM, Bek SA, Elkhatim MS, Husain AA, Mismar AY, Eldean MZ, Lengyel Z, Elazzazy S, Rasul KI, Omar NE. Tuberculosis following programmed cell death receptor-1 (PD-1) inhibitor in a patient with non-small cell lung cancer. Case report and literature review. *Cancer Immunology, Immunotherapy.* 2021 Apr;70(4):935-44.

Impact Factor: 6.693

Hyperosmolar Hyperglycaemic State and Diabetic Ketoacidosis in Nivolumab-Induced Insulin-Dependent Diabetes Mellitus

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Abstract

Nivolumab is a monoclonal antibody directed against programmed cell death-1 receptor. It has an increasing application in the treatment of various advanced metastatic cancers. The incidence of autoimmune side effects associated with such agents is expected to increase. New-onset autoimmune diabetes mellitus associated with immune checkpoint inhibitor treatment is rare, occurring in less than 1% of patients. Nivolumab-induced diabetes often presents as diabetic ketoacidosis, which could be life-threatening if not recognized and treated promptly. We present the case of a patient who developed severe diabetic ketoacidosis concomitant with hyperosmolar hyperglycaemic state (HHS) after receiving nivolumab for metastatic testicular lymphoma. Pre-nivolumab blood glucose levels were normal, apart from transient hyperglycaemia related to steroids as part of the chemotherapy protocol. The diagnosis was confirmed with extremely low C-peptide in the clinic.

Learning points: Checkpoint inhibitor-associated diabetes can present abruptly with life-threatening complications.Most patients require multiple daily injections of insulin upon discharge.Cessation of checkpoint inhibitor therapy does not revert diabetes.

Keywords: DKA; HHS; checkpoint inhibitors; diabetes mellitus; nivolumab.

Citation: Saleh AO, Taha R, Mohamed SFA, Bashir M. Hyperosmolar Hyperglycaemic State and Diabetic Ketoacidosis in Nivolumab-Induced Insulin-Dependent Diabetes Mellitus. *Eur J Case Rep Intern Med.* 2021 Aug 13;8(8):002756. doi: 10.12890/2021_002756. PMID: 34527623; PMCID: PMC8436836.

Impact Factor: 3.40

Primary mediastinal choriocarcinoma presenting as cutaneous metastasis with resistance to chemotherapy: case report and literature review

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Abstract

Cutaneous metastases of choriocarcinoma are rare. They may indicate poor prognosis and resistance to chemotherapy. In this report, we present a case of a 25-year-old man who presented with central pleuritic chest pain and right upper arm mass for about a week. The patient also had significant weight loss during the last 5 months along with an episode of generalized seizure. Chest computed tomography scan revealed an 8 cm anterior mediastinal mass. A skin punch biopsy from the right upper arm mass revealed a malignant neoplasm with morphology consistent with metastatic choriocarcinoma. Further work-up revealed multiple lung and brain lesions. Ultrasound of the testes revealed no abnormalities. Several chemotherapy regimens were tried; however, there was no response and the disease showed progression. The patient died 6 months after initial presentation.

Keywords: chemotherapy; choriocarcinoma; cutaneous; mediastinum; metastasis.

Citation: Murshed KA, Kanbour A, Akhtar M, Al Hyassat S. Primary mediastinal choriocarcinoma presenting as cutaneous metastasis with resistance to chemotherapy: case report and literature review. *J Cutan Pathol.* 2021 Jan;48(1):81-85

Impact Factor: 1.32

Late Cystic Metastasis of an Ovarian Granulosa Cell Tumor to the Liver

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Abstract

Granulosa cell tumor (GCT) is a unique form of sex cord tumor that is mostly unilateral and of low-grade malignancy. Most GCT recurrence is with pelvic or peritoneal dissemination. Liver metastasis is rarely reported. This study reports a rare case of GCT with liver metastasis nine years post initial presentation. We also discuss surgical intervention, radiological findings, histology, treatment approaches, and review of similar reported cases.

Keywords: sex cord stromal tumors, granulosa cell tumor, liver metastasis, late recurrence, partial hepatectomy

Citation: Aleter A, Mahajan P S, Petkar M A, et al. (September 17, 2021) Late Cystic Metastasis of an Ovarian Granulosa Cell Tumor to the Liver. *Cureus13*(9): e18051.

Impact Factor: 1.1

Ciliated Cell Variant of Endometrial Carcinoma in an Adenomyoma in Uterus

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Abstract

Ciliated cell variant of endometrioid adenocarcinoma (CCVEA) is an extremely rare tumor that has been seldom reported in the literature as low-grade endometrioid carcinoma with a favorable prognosis. CCVEA is characterized by neoplastic glands composed predominantly of ciliated cells with relatively little nuclear atypia. Recognition of the ciliated component is the key to the diagnosis of CCVEA but it can lead to diagnostic confusion with tubal metaplasia especially on endometrial biopsies. Herein, we report the case of a 56-year-old woman who presented with post-menopausal vaginal bleeding. Endometrial biopsy revealed extensive atypical complex endometrial hyperplasia composed predominantly of ciliated cells. The patient subsequently had a hysterectomy and bilateral salpingo-oophorectomy that revealed a large adenomyoma, adherent to the right ovary. The adenomyoma was extensively involved by CCVEA with some extension to the endometrial cavity. To the best of our knowledge, this is the first report of CCVEA that appears to arise in an adenomyoma.

Keywords: ciliated cell variant of endometrioid adenocarcinoma, low grade endometrial carcinoma, tubal metaplasia, cilia, endometrial carcinoma

Citation: Rashid S, Akhtar M (July 03, 2021) Ciliated Cell Variant of Endometrial Carcinoma in an Adenomyoma in Uterus. *Cureus 13*(7): e16148. DOI 10.7759/cureus.16148

Impact Factor: 1.1

Pleural Effusion Revealing a Diagnosis of Ewing Sarcoma

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Abstract

Pleural effusion can rarely present as an initial manifestation of Ewing sarcoma. We illustrate a case of a young male adult who was admitted with pleural effusion that led to the diagnosis of Ewing sarcoma.

Keywords: pathology, pulmonology, bone tumors, pleural fluid (pf), ewing sarcoma (es)

Citation: Ali K, Habib M, Taha N M, et al. (December 15, 2021) Pleural Effusion Revealing a Diagnosis of Ewing Sarcoma. *Cureus 13*(12): e20439.

Impact Factor: 1.1

Glottic Malignant Fibrous Histiocytoma: A Case Report and Literature Review

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Abstract

Pleomorphic sarcoma of the larynx is a rare variant of laryngeal cancer. We present the case of a 59-year-old male patient who has been smoking for 40 years. He presented with signs and symptoms of an obstructive glottic mass. The diagnostic workup pointed to a malignant pathology; the histopathology report confirmed the diagnosis of glottic undifferentiated pleomorphic sarcoma (malignant fibrous histiocytoma).

Keywords: Laryngeal cancer, Sarcoma, Laryngectomy, Undifferentiated pleomorphic sarcoma, Malignant fibrous histiocytoma

Citation: Aljariri AA, Alsaleh AR, Al-Enazi HA, Haider HA, Petkar M, Rahman W, Nashwan AJ. Glottic Malignant Fibrous Histiocytoma: A Case Report and Literature Review. *Case Rep Oncol.* 2021 Mar 31;14(1):641-646.

Impact Factor: 0.97

Metastatic angiosarcoma of the scalp presented as posttraumatic subgaleal hematoma: The many faces of a diagnostic challenge

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Abstract

Angiosarcomas represent highly-aggressive malignant lesions of the endothelial cells of blood vessels, affecting mostly the elderly population, and usually located in the scalp or face. As cutaneous angiosarcomas often metastasize to the lung, they can manifest in var- ious forms. We report a case of a 77-year-old male who presented after a posttraumatic blunt scalp lump that was initially diagnosed as infected subgaleal hematoma. This was later found to be an angiosarcoma. Further workup revealed that the tumor was invad- ing the dura, with a rare pattern of mixed concomitant cystic and solid lung metastasis with ground-glass infiltrates. The patient underwent soft tissue reconstruction with splitthickness skin graft for the scalp lesion and palliative chemotherapy. We are discussing the common manifestations of scalp angiosarcomas and their potential pulmonary metastatic patterns. Also, a review of the differential diagnoses that may mimic cutaneous scalp angiosarcoma will be demonstrated.

Keywords: Angiosarcoma Head and neck Lung metastases Diagnostic radiology

Citation: Aker L, Petkar MA, Quazi SJ, Adam RI. Metastatic angiosarcoma of the scalp presented as posttraumatic subgaleal hematoma: The many faces of a diagnostic challenge. *Radiol Case Rep.* 2021 Jul 23;16(9):2812-2816.

Impact Factor: 0.83

First case of huge classic papillary thyroid cancer rupturing spontaneously leading to ischemic necrosis, perforation and inflammation of overlying skin: Case report and review of the literature

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Abstract

Introduction: Papillary thyroid cancer (PTC) is the commonest form of well-differentiated endocrine carcinoma. It is categorized into indolent and aggressive, where the indolent subtypes (classic, follicular) rarely demonstrate aggressive behavior. We present a classic PTC presenting with a rapidly growing huge anterior neck mass that subsequently spontaneously ruptured subcutaneously resulting in ischemia, necrosis, and perforation of overlying skin leading to inflammation. Presentation of case: A 37-year-old female with no comorbidities presented to our emergency department with a neck swelling of 2 years duration that rapidly enlarged one week prior to presentation. Though the mass initially appeared of inflammatory nature, the tumor was a PTC, and she underwent total thyroidectomy with selective right side neck dissection and debridement of necrotic skin. The gross specimen revealed a fragmented non-intact right thyroid lobe mass causing pressure ischemia, necrosis and perforation of the skin. Histopathology showed a 9 × 9 × 5 cm classic PTC staged as pT3b N1b. Postoperative course was uneventful, she was discharged by the eighth postoperative day, and then she received a high dose of radioactive iodine ablation (RAI). Discussion: Classic PTC is usually of a smaller size and a relatively benign course compared to other PTC subtypes and thyroid cancers. It is indolent with favorable prognosis. Although it is associated with increased risk of lymph node metastases at the time of diagnosis, it is slow growing with high survival rates approaching 95%. Conclusion: Despite that classic PTC progresses slowly, it should still be suspected in neck swellings presenting with rapid and aggressive behavior. Prompt and systematic assessment is required with surgical intervention and radioactive iodine ablation therapy.

Keywords: Thyroid cancer Papillary thyroid cancer Lymphocytic thyroiditis Ischemic necrosis Case report

Citation: Abusabeib A, El Ansari W, Al Hassan MS, Petkar M, Mohamed S. First case of huge classic papillary thyroid cancer rupturing spontaneously leading to ischemic necrosis, perforation and inflammation of overlying skin: Case report and review of the literature. *Int J Surg Case Rep.* 2021 Aug;85:106136.

Impact Factor: 0.63

Nasal-alar invasive cutaneous aspergillosis in a patient with anaplastic astrocytoma: A case report

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Abstract

Invasive aspergillosis is commonly encountered in immunosuppressed patients either primarily through direct inoculation or secondary from blood dissemination.

This report describes a case of 53 years old immunocompromised female patient who was diagnosed with frontotemporal anaplastic astrocytoma and developed nasal skin lesion turned to be invasive cutaneous aspergillosis.

Keywords: ala, anaplastic astrocytoma, Aspergillus, invasive cutaneous aspergillosis

Citataion: Aljariri AA, Shaikh A,Nashwan AJ, Petkar MA, Ganesan S. Nasal-alar invasive cutaneous aspergillosis in a patient with anaplastic astrocytoma: A case report. *Clin Case Rep.*2021;9:2295–2299.

Impact Factor: 0.532

Pseudomyogenic hemangioendothelioma of bone with rare *WWTR1-FOSB* fusion gene: Case report and literature review

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Abstract

Pseudomyogenic hemangioendothelioma rarely arises in bone. *WWTR1-FOSB* fusion gene is rarely reported in PMHE of bone. Currently, fusion genes can be used as diagnostic markers in PMHE; however, their prognostic and therapeutic significance is unclear.

Keywords: FOSB; WWTR1; bone; pseudomyogenic hemangioendothelioma.

Citation: Murshed KA, Torres-Mora J, ElSayed AM, Ammar A, Al-Bozom I. Pseudomyogenic hemangioendothelioma of bone with rare *WWTR1-FOSB* fusion gene: Case report and literature review. *Clin Case Rep.* 2021 Jan 19;9(3):1494-1499.

Impact Factor: 0.532

Invasive ductal breast carcinoma preceded by CALR-positive essential thrombocythemia

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Abstract

Persistent thrombocytosis in patients with cancer needs workup because it can be linked to essential thrombocytosis. The management should be individualized to start treatment for low-risk essential thrombocytosis due to the combined risk of thrombosis.

Keywords: breast cancer, calreticulin, essential thrombocythemia, invasive ductal carcinoma, thrombocythemia

Citation: Ali EA, Elmalik H, Omar NE, Yassin MA. Invasive ductal breast carcinoma preceded by CALR-positive essential thrombocythemia. *Clinical Case Reports.* 2021 Mar;9(3):1732-6.

Impact Factor: 0.532

Schistosoma gallbladder polyp masquerading as a neoplasm: Rare case report and literature review

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Abstract

Schistosomiasis affecting the gastrointestinal tract is common in tropical and subtropical areas but associated polyps presenting as gallbladder pathology are rare clinical entities necessitating high clinical suspicion.

Keywords: gallbladder polyps, Praziquantel, Schistosomiasis

Citation: Ali, G. A., Goravey, W., Al Maslamani, M. A., & Hadi, H. A. (2021). Schistosoma gallbladder polyp masquerading as a neoplasm: Rare case report and literature review. *Clinical Case Reports, 9*(7).

Impact Factor: 0.532

Primary bladder amyloidosis mimicking bladder cancer complicated by bladder rupture: A case report

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Abstract

Amyloidosis is related to the extracellular deposition of abnormal protein fibrils in various tissues. It can be either localized to an organ or generalized, affecting multiple systems. Amyloidosis of the urinary bladder is a rare histopathological finding. It is clinically interesting that such cases' clinical, radiological, and even endoscopic presentation mimic urothelial carcinoma to a great extent. Here, we discuss a case of a 49-year-old gentleman who presented with frank painless hematuria. The patient was diagnosed with a bladder mass suspicious of malignancy depending on the clinical presentation aided by the cystoscopic and radiological evaluation. Histopathologic samples of the transurethral resection of the mass proved to be primary bladder amyloidosis. This case is of unique clinical interest in that it is the first case reported of bladder amyloidosis that is complicated by extraperitoneal bladder rupture post-operatively. However, no immediate intraoperative perforation to the bladder wall during resection was evidenced.

Keywords: amyloidosis; bladder cancer; hematuria; transurethral resection.

Citation: Sibira RM, Albakar A, Younes N, Albozom IA, Al Rumaihi K. Primary bladder amyloidosis mimicking bladder cancer complicated by bladder rupture: A case report. *Clin Case Rep.* 2021 Nov 22;9(11):e05140.

Impact Factor: 0.532

Mitotically active cellular fibroma of the ovary diagnosis and treatment

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Abstract

Mitotically active cellular fibroma (MACF) of the ovary is a relatively newly recognized histological disease entity which explains its scarce reporting in literature and unknown prognosis [1]. In this tumor type, high mitotic activity is noticed without severe atypia. These tumors are categorized as benign ovarian tumors with late recurrence, if any. However, we herein report an unusual case of an ovarian mitotically active atypical fibrous tumor case which presented as recurrence within six months of being operated thereby raising suspicion of an element of malignancy. On presentation, the patient suffered from abdominal pain and abdomino-pelvic mass. After imaging confirmed an ovarian neoplastic lesion patient underwent bilateral salpingo-oophorectomy and hysterectomy. Histopathology defined the lesion as "ovarian mitotically active atypical fibrous tumor". Six months later, abdominal pain recurred for which imagining was done and confirmed a newly developed well defined irregular complex solid cystic mass causing intestinal obstruction giving an impression of a malignant neoplasm, probably ovarian carcinoma. However, histopathology for the new lesion remained the same as was for the previous mass, i.e. mitotically active ovarian fibroma, but with lung and mesenteric lymph nodes metastases. Patient couldn't be operated on due to her co-morbid conditions, and the mass was vascular. She was given supportive care with consideration to start hormonal therapy and during this period died due to sepsis. This case highlights the importance of having a high suspicion of the possibility of malignancy when mitotically active cellular fibroma manifests as a recurrence of mass as this tumor may tend to have an uncertain malignant potential. Thereby, stressing the importance of long term follow up even after the primary tumor is surgically treated without any surgical difficulty or tumor rupture [2]. Such tumors need to be followed and reported more often to help understanding the way they behave and their management.

Keywords: Fibroma; Ovarian tumors; Fibrosarcoma; Ovarian neoplasm

Citation: Dawoud R., El-Malik H., Fatima H., Faris M., Brich S., Al Rashid A, and Elazzazy S. Mitotically active cellular fibroma of the ovary diagnosis and treatment. *GSC Biological and Pharmaceutical Sciences,* 2021, 17(02), 160–166.

Impact Factor: 0.3

IMPORTANCE trial: a provisional study-design of a single-center, phase II, double-blinded, placebo-controlled, randomized, 4-week study to compare the efficacy and safety of intranasal esketamine in chronic opioid refractory pain

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Abstract

Background: Cancer is the second leading cause of death globally. Up to 86% of advanced cancer patients experience significant pain, while 10-20% live in chronic pain. Besides, increasing prescription of opioids resulted in 33,000 deaths in the US in 2015. Both reduce patients' functional status and quality of life. While cancer survival rates are increasing, therapeutic options for chronic opioid refractory pain are still limited. Esketamine is the s-enantiomer of ketamine, with superior analgesic effect and less psychotomimetic side effects. Intranasal esketamine was approved by the FDA for treatmentresistant depression. However, its use in chronic cancer pain has never been tested. Therefore, we propose a phase II, randomized, placebo-controlled trial to evaluate the efficacy and safety of intranasal esketamine in chronic opioid refractory cancer pain.

Methods and analysis: We will recruit 120 subjects with chronic opioid refractory pain, defined as pain lasting more than 3 months despite optimal therapy with high dose opioids (>60 mg morphine equivalent dose/day) and optimal adjuvant therapy. Subjects will be randomized into two groups: intranasal esketamine (56mg) and placebo. Treatment will be administered twice a week for four consecutive weeks. The primary outcome is defined as reduction in the Numeric Pain Rating Scale (NPRS) after first application. Secondary outcomes include NPRS reduction after four weeks, the number of daily morphine rescue doses, functional status and satisfaction, and depression.

Conclusion: This study may extend therapeutic options in patients with chronic pain, thus improving their quality of life and reducing opioid use.

Keywords: Cancer pain, Esketamine, Pain measurement, Opioid refractory

Citation: Fernandes M, Schelotto M, Doldi PM, Milani G, Ariza Manzano AA, Perera Valdivia D, Winter Matos AM, Hamdy Abdelrahim Y, Hamad Bek SA, Benitez BK, Romanelli Tavares VL, Basendwah AM, Albuquerque Sousa LH, Xavier NF, Zertuche Maldonado T, Toyomi de Oliveira S, Chaker M, Menon Miyake M, Uygur Kucukseymen E, Waqar K, Alkhozondar OMJ, Bernardo da Silva R, Droppelmann G, Vaz de Macedo A, Nakamura R, Fregni F. IMPORTANCE trial: a provisional study-design of a single-center, phase II, double-blinded, placebo-controlled, randomized, 4-week study to

compare the efficacy and safety of intranasal esketamine in chronic opioid refractory pain. *F1000Res.* 2021 Jan 22;10:42.

Impact Factor: 3.23

ONCOLOGY

Review Articles

Serum immune checkpoint biomarkers as predictors of response to anti-PD-1/PD-L1 treatment in non-small cell lung cancer (NSCLC) patients

Raza, R. Mohsin, A. Kanbour, S. Vijayakar, A. Philip, M.A. Tauro, S. Sherif, M. Merhi, V. Inchakalody, A.R. Zar Gul, M.U. Al Homsi, S. Dermime

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Abstract

Background: There is limited data on the predictive biomarkers of response to immune checkpoint blockade (ICB) treatment of non-small cell lung cancer (NSCLC) patients. The main aim of this prospective study is to understand the utility of pretreatment soluble immune checkpoint and tumor markers as early predictors of response in locally advanced/metastatic NSCLC patients treated with ICBs. Methods: The study was conducted at the National Center for Cancer Care and Research (NCCCR), HMC, Qatar. A total of 26 patients on anti-PD-1/PDL-1 treatment were enrolled, and pre-treatment blood samples were collected. Multiplex Magnetic Bead Panel kits were utilized to measure concentrations of soluble immune checkpoint and tumor markers including BTLA, GITR, HVEM, IDO, LAG-3, PD-1, PDL-1, PDL2, TIM-3, CD28, CD80, 4-1BB, CD27, CTLA-4, ICOS Ligand, CD276, VISTA, B7-H6; CD47 (IAP), BLAST-1, Galectin-9, TIMD-4; OX40, S100A8/A9, E-cadherin, MICB, Nectin 2, NTSE, PVR, Singlec 7, Singlec 9,CEA, CA-19-9, CA-125 CYFRA21-1 and CA-15-3. MannWhitney test was used to evaluate difference in medians in responders and nonresponders. Response to treatment was assessed 4 months after initiation of treatment via PET CT imaging data. Results: Clinical response to ICB treatment was determined based on RECIST criteria and PET CT imaging data. 12/26 (46%) patients showed clinical response to the treatment while 14/26 (54%) were identified as non-responders. Interestingly, in clinically responding patients, significant upregulation of the immune inhibitory soluble programmed death-ligand 1 (sPD-L1) molecule (<0.002**) and the immune stimulatory biomarkers glucocorticoid-induced TNFR-related protein (GITR) (<0.0005***), and Herpes virus entry mediator (HVEM) (<0.006**) were recorded. However, non-responding patients showed significant upregulation of 3 important immune suppressive biomarkers; T-cell immunoglobulin and mucin domain containing 4 (TIMD-4) ($p<0.0361$*), Nectin 2 ($p<0.0310$*) and the carcinoembryonic antigen (CEA) tumor marker ($p<0.0484$*).

Conclusions: The study shows that soluble immune suppressive/stimulatory biomarkers can serve as plausible early biomarkers of response to ICB treatment.

Citation: A. Raza, R. Mohsin, A. Kanbour, S. Vijayakar, A. Philip, M.A. Tauro, S. Sherif, M. Merhi, V. Inchakalody, A.R. Zar Gul, M.U. Al Homsi, S. Dermime. Serum immune checkpoint biomarkers as predictors of response to anti-PD-1/PD-L1 treatment in non-small cell lung cancer (NSCLC) patients. *Annals of Oncology*, 2021. 32 (Suppl. 7), S1380. DOI:

Impact Factor 32.976

17 Predictive soluble biomarkers of immune response to checkpoint blockade in non-small cell lung cancer (NSCLC) patients

Afsheen Raza, Reyad Mohsen, Aladdin Kanbour, Abdul Rehman Zar Gul, Anite Philip, Suma Vijayakumar, Shereena Hydrose, Maysaloun Merhi, Varghese Inchakalody, Shahab Uddin, Mohammed Ussama Al Homsi, Said Dermime

Hamad Medical Corporation, Doha, Qatar

Abstract

Background There is limited data on the predictive biomarkers of response to immune checkpoint blockade (ICB) treatment of non-small cell lung cancer (NSCLC) patients. The main aim of this prospective study was to understand the utility of pre-treatment soluble immune checkpoint markers as surrogate markers for tissue PD-L1 and as predictors of response in locally advanced/metastatic NSCLC patients treated with ICBs.

Methods The study was conducted at the National Center for Cancer Care and Research (NCCCR), HMC, Qatar. A total of 30 patients on Pembrolizumab/Nivolumab were enrolled and blood samples were collected before treatment. 17 Healthy controls were also included in the study. Multiplex Magnetic Bead Panel kits for soluble immune checkpoint markers was utilized to measure the concentrations of 24 soluble markers including BTLA, GITR, HVEM, IDO, LAG-3, PD-1, PDL-1, PDL-2, TIM-3, CD28, CD80, 4-1BB, CD27, CTLA-4, ICOS Ligand, CD276, VISTA, B7-H6; CD47 (IAP), BLAST-1, Galectin-9, TIMD-4; OX40 and S100A8/A9. Mann-Whitney test was used to evaluate a) the difference in median values between healthy controls and pre-treatment samples b) compare soluble markers with tissue PD-L1 status and c) response to treatment 4 months after treatment via PET CT imaging data.

Results The results showed significant changes in the pre-treatment plasma concentrations of soluble markers in the NSCLC patients compared to healthy controls. Significant upregulation was observed in the immune suppression markers: S100A8/A9 (<0.0001****), PDL-2 (<0.006**), LAG-3 (<0.006**), PD-1 (<0.008*), TIM-3 (<0.002*), CD80 (<0.001*) and Galactin 9 (<0.023*). Significant upregulation was observed for the immune stimulatory markers: TIMD4 (<0.0001****), CD137/4-1BB (<0.007*), CD134/OX40 (<0.006**) in NSCLC patients compared to healthy controls. When soluble markers were compared with tissue PD-L1, significant upregulation of CD276/B7-

H3 (<0.039*) and VISTA (<0.034*) was observed in patients expressing >50% of PD-L1 in their tissues.We then corelated the pre-treatment soluble markers expression with the clinical response of the patients to Pembrolizumab/Nivolumab using imaging (PET CT) data obtained 4 months after treatment. Interestingly, significant upregulation of GITR (<0.0005***), PD-L1 (<0.002**) and HVEM (<0.006**) was observed in responding patients.

Conclusions The study demonstrates that 10 markers show differences in NSCLC patients as compared to healthy controls; 2 markers as surrogates for tissue PDL-1 and 3 markers as predictive biomarkers of response to ICB treatment.

Citation: Raza A, Mohsen R, Kanbour A, *et al* 17 Predictive soluble biomarkers of immune response to checkpoint blockade in non-small cell lung cancer (NSCLC) patients *Journal for ImmunoTherapy of Cancer* 2021;9

Impact Factor: 12.4

Emerging dynamics pathways of response and resistance to PD-1 and CTLA-4 blockade: tackling uncertainty by confronting complexity

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Abstract

Immune checkpoint inhibitors provide considerable therapeutic benefit in a range of solid cancers as well as in a subgroup of hematological malignancies. Response rates are however suboptimal, and despite considerable efforts, predicting response to immune checkpoint inhibitors ahead of their administration in a given patient remains elusive. The study of the dynamics of the immune system and of the tumor under immune checkpoint blockade brought insight into the mechanisms of action of these therapeutic agents. Equally relevant are the mechanisms of adaptive resistance to immune checkpoint inhibitors that have been uncovered through this approach. In this review, we discuss the dynamics of the immune system and of the tumor under immune checkpoint blockade emanating from recent studies on animal models and humans. We will focus on mechanisms of action and of resistance conveying information predictive of therapeutic response.

Keywords: CTLA-4; Dynamics biomarkers; Immune checkpoint inhibitors; MDSCs; PD-1; Tregs.

Citation: Relecom A, Merhi M, Inchakalody V, Uddin S, Rinchai D, Bedognetti D, Dermime S. Emerging dynamics pathways of response and resistance to PD-1 and CTLA-4 blockade: tackling uncertainty by confronting complexity. *J Exp Clin Cancer Res.* 2021 Feb 18;40(1):74.

Impact Factor: 11.378

Carcinomas of the Uterine Cervix: Comprehensive Review with An Update on Pathogenesis, Nomenclature of Precursor and Invasive Lesions, and Differential Diagnostic Considerations

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Abstract

Most cervical carcinomas and their related lesions are attributed to an infection by human papillomavirus (HPV). The infection usually starts in the basal cells at the squamocolumnar junction. It causes cell proliferation and maturation abnormalities along with nuclear abnormalities resulting in low-grade squamous intraepithelial lesions. An overwhelming majority of these lesions spontaneously disappear, and the infection is cleared. In a small subset of high-risk HPV infection cases, the lesions may persist and progress to high-grade squamous intraepithelial lesions. These are associated with the incorporation of the viral genome into the human genome. Some of the high-grade squamous intraepithelial lesions, over several years, progress to invasive carcinoma. Carcinomas of the cervix are usually squamous cell carcinomas (SCCs), but 20% to 25% of the cases may manifest as adenocarcinomas. Similar to SCC, adenocarcinomas may initially manifest as adenocarcinomas in situ and may progress to invasive carcinomas after a variable period of time. In the recently published World Health Organization classification of female genital tumors, SCCs, and adenocarcinomas of the cervix are divided into HPV-associated and HPV-independent tumors. This review draws on the latest terminology and the several morphologic subtypes recognized for each category.

Keywords: adenocarcinoma in situ, endocervical adenocarcinoma, female genital tumors, FIGO staging, human papillomavirus, squamous cell carcinoma, squamous intraepithelial lesion, WHO classification

Citation: Arafah M, Rashid S, Tulbah A, Akhtar M. Carcinomas of the Uterine Cervix: Comprehensive Review with An Update on Pathogenesis, Nomenclature of Precursor and Invasive Lesions, and Differential Diagnostic Considerations. *Adv Anat Pathol.* 2021 May 1;28(3):150-170.

Impact factor: 4.72

The role of PAK4 in the immune system and its potential implication in cancer immunotherapy

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Abstract

The p21 activated kinases (PAKs) are known to play a role in the regulation of cell morphology and functions. Among the various members of PAKs family, only the PAK4 protein has been shown to be overexpressed in cancer cells and its upregulation was associated with tumor development. Indeed, several studies have shown that PAK4 overexpression is implicated in carcinogenesis by different mechanisms including promotion of cell proliferation, invasion and migration, protection of cells from apoptosis, stimulation of the tumor-specific anchorage-independent cell growth and regulation of the cytoskeletal organisation and adhesion. Moreover, high PAK4 protein levels have been observed in several solid tumors and have been shown able to enhance cancer cell resistance to many treatments especially chemotherapy. Interestingly, it has been recently demonstrated that PAK4 downregulation can inhibit the PD-1/PD-L1 immune regulatory pathway. Taken together, these findings not only

implicate PAK4 in oncogenic transformation and in prediction of tumor response to treatment but also suggest its role as an attractive target for immunotherapy. In the current review we will summarize the different mechanisms of PAK4 implication in tumor development, describe its role as a regulator of the immune response and as a potential novel target for cancer immunotherapy.

Keywords: PAK4 Tumorigenesis PD-1 Immunotherapy

Citation: Naïja A, Merhi M, Inchakalody V, Fernandes Q, Mestiri S, Prabhu KS, Uddin S, Dermime S. The role of PAK4 in the immune system and its potential implication in cancer immunotherapy. *Cell Immunol.* 2021 Sep;367:104408

Impact Factor: 3.90

Cancer and severe mental illness in low- and middle-income countries: The challenges and outlook for the future

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Abstract

Objective: Patients with severe mental illness (SMI) face health inequalities that lead to under treatment of diseases such as cancer and result in increased mortality. There is literature addressing this issue for SMI patients in high-income countries but few for those in low- and middle-income countries. This review aims to draw attention to the health inequalities and the compounding factors faced by SMI patients in low- and middle-income countries. The relevance of integration of psycho-oncology in the care of SMI patients with cancer is integral to reduce disparities and address varied contributory factors.

Methods: The literature review was conducted by searching through two databases which includes PubMed and Google Scholar. We searched for articles using keyword search terms: severe mental illness, SMI, schizophrenia, bipolar disorder, cancer, low- middle-income countries, low- and middle-income countries, psycho-oncology, HPV vaccine, cancer incidence, cancer mortality, cancer control, cancer screening, cancer treatment and palliative care.

Results: A total of 80 research articles were included in our literature review. We found that there was an increased requirement for adapting to the changing disease landscape in low- and middle-income countries. An improvement on aspects such as vaccination, screening and prevention is necessary, and also efforts to change social stance towards SMI is crucial.

Conclusion: There is an increase incidence of cancer in low- and middle-income countries, and the number of patients with SMI in low- and middle-income countries is also rising. This is due to social, psychological, economical and healthcare factors. Low- and middle-income countries must consider improving these aspects in order to adapt to the changing landscape.

Keywords: cancer; high-income countries; low- middle-income countries; mental health; oncology; psycho-oncology; schizophrenia; screening; severe mental illness.

Citation: Park SJ, Wai A, Pavithran K, Kunheri B, Valsraj K. Cancer and severe mental illness in low- and middle-income countries: The challenges and outlook for the future. *Psychooncology.* 2021 Dec;30(12):2002-2011.

Impact factor: 3.894

Sclerosing epithelioid fibrosarcoma: in-depth review of a genetically heterogeneous tumor

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Abstract

First described in 1995 by Meis-Kindbloom et al. as a variant of fibrosarcoma simulating carcinoma, sclerosing epithelioid fibrosarcoma (SEF) is a malignant soft tissue sarcoma characterized by epithelioid cells in dense sclerotic stroma, frequent immunoreactivity for MUC4 and heterogeneous genetic profile with recurrent EWSR1 gene rearrangement. It typically affects middle-age adults with a predilection for the lower extremity. It is believed that SEF is closely related to low-grade fibromyxoid sarcoma (LGFMS), both tumors show overlapping features in morphology, immunophenotype, and molecular profile. In this review, we discuss the clinical, morphologic, and immunohistochemical features of SEF with particular emphasis on its molecular diversity and relation to LGFMS.

Keywords: EWSR1; MUC4; Sclerosing epithelioid fibrosarcoma; low-grade fibromyxoid sarcoma; soft tissue.

Citation: Murshed KA, Al-Bozom I, Ammar A. Sclerosing epithelioid fibrosarcoma: in-depth review of a genetically heterogeneous tumor. *APMIS.* 2021 Aug;129(8):455-460.

Impact factor: 3.428

PD-L1 immunostaining: what pathologists need to know

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Abstract

Background: Immune checkpoint proteins, especially PD-L1 and PD-1, play a crucial role in controlling the intensity and duration of the immune response, thus preventing the development of autoimmunity. These proteins play a vital role in enabling cancer cells to escape immunity, proliferate and progress.

Methods: This brief review highlights essential points related to testing for immune checkpoint therapy that histopathologists need to know.

Results: In recent years, several inhibitors of these proteins have been used to reactivate the immune system to fight cancer. Selection of patients for such therapy requires demonstration of PD-L1 activation on the tumor cells, best done by immunohistochemical staining of the tumor and immune cells using various antibodies with predetermined thresholds.

Conclusions: Immune checkpoint therapy appears to be promising and is rapidly expanding to include a large variety of cancers.

Keywords: Activation; Cancer; Immune cells; Immune checkpoint; Immunohistochemistry; Inhibition; Inhibitors; PD-1; PD-L1; T-cells.

Citation: Akhtar M, Rashid S, Al-Bozom IA. PD-L1 immunostaining: what pathologists need to know. Diagn Pathol. 2021 Oct 25;16(1):94. doi: 10.1186/s13000-021-01151-x. Erratum in: *Diagn Pathol.* 2022 Jun 11;17(1):50.

Impact Factor: 2.92

ONCOLOGY

Abstracts

Non-invasive grading of cervix cancer using diffusion weighted imaging

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Abstract

Purpose or Objective: To implement a non-invasive workflow based on radiomics for the prediction of the grade of cervix cancer (CC) using DWI.

Material and Methods: 39 patients with CC were collected from the medical records of our institution. For each patient, pretreatment DWI (with 3 b-values 0, 100, and 1000), manual delineation of the GTV and grade classification (17 with grade 2, 22 with grade 3) were available. Apparent Diffusion Coefficient maps ADC_{100} and ADC_{1000} corresponding to b-values 100 and 1000 respectively were generated using the mono-exponential model. The dataset was randomized and divided into training set (30 patients) and validation set (9 patients).

Radiomic features were extracted from DWI (b-value = 0, 100, 1000) and ADC maps (ADC_{100} and ADC_{1000}). 42 radiomic features were extracted from GTV's volume of interest for each image volume. They were composed of 3 shape, 8 first order, and 31 texture features. Shape features describe the 3D geometric properties of the tumor. The first order features describe tumor intensity distribution. Texture features, which describe the intra-tumor heterogeneity, were extracted from the gray level co-occurrence (6), neighborhood grey-level different (3), grey-level run length (11), and grey-level zone length (11) matrices.

Machine learning models (MLM) were composed of three blocs: preprocessing, selection and classification. Features preprocessing methods were TR_GAUSS (mapping data to have normal distribution), MINMAX_SC (linear scaling to [0, 1]), or ROBUST_SC (scaling to the interquartile range), STD_SC (removing the mean and scaling to unit variance), TR_UNIF (mapping to uniform distribution), L2_NORM (scaling samples to have unit norm). The selection methods of the most representative features were based on univariate statistical tests (Anova-F score (AF) or mutual information (MI)), or Support Vector Machine (SVM) model which performs class separation by hyperplanes. Binary classification, into grade 2 or 3, was by sparse linear model with elastic net regularization.

MLM was assessed by the computation of the ROC curve, the area under the ROC curve (AUC) (measure of separability between classes for any threshold) and the accuracy (the fraction of correct predictions) for each grade.

Results: Table 1 shows AUC and accuracy on the training (AUC_t, ACC_t) and validation (AUC_v, ACC_v) sets obtained for each MLM. MLM with features processed by TR_GAUSS and selected with SVM gave the best results; (AUC_t = 1, ACC_t=1) and (AUC_v = 0.81, ACC_v=0.8) were obtained respectively for training and validation sets. Figure 1 shows the roc curve obtained for the MLM (TR_GAUSS, SVM, elastic-net linear classifier).

Conclusion: In this paper, we demonstrated that MLM models trained on the radiomics, extracted from DWI and corresponding ADC maps, could potentially predict the grade of CC tumors. Future work will consist on consolidating our results on more patient datasets.

Citation: S. Aouadi, S.Chandramouli, T. Torfeh, R. Hammoud, and N. Al-Hammadi, " Non-invasive grading of cervix cancer using diffusion weighted imaging "*Radiotherapy and Oncology* 161:S1547-S1548, DOI: 10.1016/S0167-8140(21)08269-4

Generation of synthetic CT with 3D deep convolutional neural networks for brain MR-only radiotherapy

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Abstract

Purpose/Objective: To create a synthetic CT (sCT) from T2-weighted brain MRI using 3D convolutional neural networks (CNN) algorithm and to assess the resulting image quality in comparison to reference CT.

Material/Methods: Conventional T2-weighted MRI (1.5T GE MRI, PROPELLER, TR = 6144.9 ms, TE = 89.82 ms, FA = 160º) and CT datasets from 13 patients who underwent brain radiotherapy were included in this retrospective study. CT and MRI were coregistered and resampled to resolution of 1x1x1mm3. The mask of the background was extracted from MRI using the levelsets algorithm.

A high-resolution, compact 3D convolutional network was used for the generation of sCT. It used a stack of residual dilated convolutions with increasingly large dilation factors which incorporated large volumetric context. The root mean square error was used as the loss function between sCT and CT. The algorithm is available in the open source NiftyNet library as «highresnet».

Geometric assessment of the sCT was performed for all patients using leave one out cross-validation. Voxel-wise Mean Absolute Error (MAE) and Mean Errors (ME) were computed to assess sCT intensities. Bone, soft-tissues and air cavities geometry were quantified by dice (DI), sensitivity(SE) and specificity (SP) indices. MAE Water Equivalent Path Length (MAE_WEPL) was computed for a multitude of spokes starting from the center point of the brain and crossing the whole skull to evaluate the radiologic path length. A comparison with the multiscale and dual contrast patch based method (MDPBM) that was previously published was performed.

Results : Figure 1 gives the visual assessment of the generated sCT using CNN and shows the average MAE in bins of 20 HU. Mean MAE, ME and MAE_WEPL values for sCT evaluation, using CNN, were 121.92 (σ=21.13), -24.28 (σ=33.73), and 2.18(σ=0.46), respectively. Mean MAE, ME and MAE_WEPL values for sCT evaluation, using MDPBM, were 99.69 (σ=11.07), 2.01 (σ=11.18), and 1.72(σ=0.54), respectively. Table 1 shows DI, SE and SP indices for bone, soft-tissues and air cavities using CNN and MDPBM. MDPM demonstrated better performance than CNN in our dataset.

Conclusion: A promising study on the generation and validation of CT-substitute from standard clinical T2 MRI is presented. The algorithm is based on convolutional neural networks. A dosimetric evaluation of the sCT for radiotherapy treatment planning is to be done. Also, further work will be done to assess and improve the method on more patients and different clinical sites

Citation: S. Aouadi, R. W. Hammoud, T. Torfeh, S. Paloor, N. Al-Hammadi, " Generation of synthetic CT with 3D deep convolutional neural networks for brain MR-only radiotherapy", *Radiotherapy and Oncology* 161:S1377-S1378, DOI: 10.1016/S0167-8140(21)08108-1

Characterization of the geometric distortion and the quality of MR images used for spine SBRT

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Abstract

Introduction: High-quality MR imaging represents a key element for spinal stereotactic body radiation therapy (SBRT) to improve target volume delineation and reduce radiation dose to normal tissues.

MR geometric accuracy and image quality are essentials to determine the accuracy of the treatment planning.

The aim of this study is to investigate the geometric distortion and the image quality of for the typical sequences used in spinal SBRT and over a clinically relevant Field of View (FOV).

Methods Image quality and geometric distortions on a 1.5T GE MRI-SIM commissioned for RT planning are assessed using the anterior array coil along with the table coil.

In-plane and through-plane distortions are characterized using a phantom that covers a large field of view of 200mm and consists of layers of foam embedded with a matrix of ellipsoidal markers.

Image quality in terms of SNR and uniformity was assessed using the ACR phantom.

The assessment of geometric distortion and image quality was performed for typical pulse sequences used in RT planning (2D T1, 2D T2 and 3D cube).

An in-house software module which automatically locates features and performs an automatic image quality control was developed.

Results: The table below shows the geometric distortion for all the sequences. Up to a radial distance of 150 mm, the mean distortion was 0.6 mm for the Axial T1, 0.5 mm for the axial Cube T2, 0.8 mm for the sagittal T1 and 0.7 mm for the sagittal T2.

Table 2 shows the image quality assessment results. The highest SNR was recorded for the axial cube T2 sequence while the lowest SNR was recorded for the sagittal T2 sequence. No significant difference in uniformity has been recorded between the sequences.

Conclusion: This study aimed at investigating the 3D geometric distortion and the quality of MR images used for spinal SBRT.

Results showed that the geometric distortion are within the tolerances. Further investigation on the dosimetric impact of the MR distortion will be performed for various DVH parameters.

Citation: T. Torfeh, R. Hammoud, S. Aouadi, Y. Arunachalam, S. Paloor, N. Al-Hammadi "Characterization of the geometric distortion and the quality of MR images used for spine SBRT" *Radiotherapy and Oncology*, 161, S1395 - S1396

MALIGNANT HEMATOLOGY

Original Articles

Characterization of complete lncRNAs transcriptome reveals the functional and clinical impact of lncRNAs in multiple myeloma

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Abstract

Multiple myeloma (MM) is an incurable disease, whose clinical heterogeneity makes its management challenging, highlighting the need for biological features to guide improved therapies. Deregulation of

specific long non-coding RNAs (lncRNAs) has been shown in MM, nevertheless, the complete lncRNA transcriptome has not yet been elucidated. In this work, we identified 40,511 novel lncRNAs in MM samples. lncRNAs accounted for 82% of the MM transcriptome and were more heterogeneously expressed than coding genes. A total of 10,351 overexpressed and 9,535 downregulated lncRNAs were identified in MM patients when compared with normal bone-marrow plasma cells. Transcriptional dynamics study of lncRNAs in the context of normal B-cell maturation revealed 989 lncRNAs with exclusive expression in MM, among which 89 showed de novo epigenomic activation. Knockdown studies on one of these lncRNAs, SMILO (specific myeloma intergenic long non-coding RNA), resulted in reduced proliferation and induction of apoptosis of MM cells, and activation of the interferon pathway. We also showed that the expression of lncRNAs, together with clinical and genetic risk alterations, stratified MM patients into several progression-free survival and overall survival groups. In summary, our global analysis of the lncRNAs transcriptome reveals the presence of specific lncRNAs associated with the biological and clinical behavior of the disease.

Citation: Carrasco-Leon A, Ezponda T, Meydan C, Valcárcel LV, Ordoñez R, Kulis M, Garate L, Miranda E, Segura V, Guruceaga E, Vilas-Zornoza A, Alignani D, Pascual M, Amundarain A, Castro-Labrador L, Martín-Uriz PS, El-Omri H, Taha RY, Calasanz MJ, Planes FJ, Paiva B, Mason CE, San Miguel JF, Martin-Subero JI, Melnick A, Prosper F, Agirre X. Characterization of complete lncRNAs transcriptome reveals the functional and clinical impact of lncRNAs in multiple myeloma. *Leukemia*. 2021 May;35(5):1438-1450.

Impact Factor: 11.528

Postmarketing safety of anaplastic lymphoma kinase (ALK) inhibitors: an analysis of the FDA Adverse Event Reporting System (FAERS)

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Abstract

Background: Inhibitors of the anaplastic lymphoma kinase (ALK) gene mutation are highly effective treatments for ALK-positive lung cancer. We conducted this pharmacovigilance analysis using the Food and Drug Administration Adverse Event Reporting System (FAERS).

Patients and methods: FAERS files from 2012 to 2020 were used. Reports for crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib were filtered. We used the Medical Dictionary for Regulatory Activities (MedDRA version 22.1). Further, we searched for adverse events on the preferred term (PT) level based on case reports in the literature. After filtering duplicate reports, disproportionality analysis was used to detect safety signals by calculating proportional reporting ratios (PRRs), reporting odds ratios (RORs), empirical Bayesian geometric mean, and information component. Reports were considered statistically significant if the 95% confidence interval did not contain the null value.

Results: Within the system organ classes, significant safety signals were found, including those for crizotinib [eye disorders (PRR 2.09, ROR 2.12)], ceritinib [gastrointestinal disorders (PRR 2.19, ROR 2.41), hepatobiliary disorders (PRR 4.4, ROR 4.52), respiratory disorders (PRR 1.96, ROR 2.08)], alectinib [hepatobiliary disorders (PRR 2.60, ROR 2.63)], brigatinib [respiratory disorders (PRR 2.15, ROR 2.31)], and lorlatinib [metabolism disorders (PRR 3.34, ROR 3.53)]. For adverse events on the PT level, we found several significant signals, including pneumothorax with crizotinib (PRR 3.29, ROR 3.29), ceritinib (PRR 3.13, ROR 3.13), and alectinib (PRR 4.88, ROR 4.89); myasthenia gravis with

lorlatinib (PRR 6.05, ROR 6.05); photosensitivity reactions with crizotinib (PRR 2.20, ROR 2.20), ceritinib (PRR 4.30, ROR 4.31), alectinib (PRR 20.43, ROR 20.51), and brigatinib (PRR 20.97, ROR 21.05); pulmonary arterial hypertension with brigatinib (PRR 2.92, ROR 2.92) and lorlatinib (PRR 9.2, ROR 9.24); and rectal perforation with crizotinib (PRR 7.83, ROR 7.83). All the detected safety signals were confirmed using Bayesian methods.

Conclusion: ALK inhibitors differed in their safety profile reports. We found several significant safety signals that matched previously published case reports, including pulmonary arterial hypertension, rectal perforation, myasthenia gravis, and photosensitivity. These signals require further regulatory investigation to determine their significance and potentially update the product labels to inform patients and clinicians.

Keywords: ALK inhibitors; adverse events; lung cancer; pharmacoepidemiology; pharmacovigilance; post-marketing surveillance.

Citation: Omar NE, Fahmy Soliman AI, Eshra M, Saeed T, Hamad A, Abou-Ali A. Postmarketing safety of anaplastic lymphoma kinase (ALK) inhibitors: an analysis of the FDA Adverse Event Reporting System (FAERS). *ESMO Open*. 2021 Dec;6(6):100315.

Impact Factor: 6.883

Predictive value of tyrosine phosphatase receptor gamma for the response to treatment tyrosine kinase inhibitors in chronic myeloid leukemia patients

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Abstract

Protein tyrosine phosphatase receptor gamma (PTPRG) is a member of the receptor-like family protein tyrosine phosphatases and acts as a tumor suppressor gene in different neoplasms. Recent

studies reported the down-regulation of PTPRG expression levels in Chronic Myeloid Leukemia disease (CML). In addition, the BCR-ABL1 transcript level is currently a key predictive biomarker of CML response to treatment with Tyrosine Kinase Inhibitors (TKIs). The aim of this study was to employ flow cytometry to monitor the changes in the expression level of PTPRG in the white blood cells (WBCs) of CML patients at the time of diagnosis and following treatment with TKIs. WBCs from peripheral blood of 21 CML patients were extracted at diagnosis and during follow up along with seven healthy individuals. The PTPRG expression level was determined at protein and mRNA levels by both flow cytometry with monoclonal antibody (TPγ B9-2) and RT-qPCR, and BCR-ABL1 transcript by RT-qPCR, respectively. PTPRG expression was found to be lower in the neutrophils and monocytes of CML patients at time of diagnosis compared to healthy individuals. Treatment with TKIs nilotinib and Imatinib Mesylate restored the expression of PTPRG in the WBCs of CML patients to levels observed in healthy controls. Moreover, restoration levels were greatest in optimal responders and occurred earlier with nilotinib compared to imatinib. Our results support the measurement of PTPRG expression level in the WBCs of CML patients by flow cytometry as a monitoring tool for the response to treatment with TKIs in CML patients.

Citation: Ismail MA, Vezzalini M, Morsi H, Abujaber A, Al Sayab A, Siveen K, Yassin MA, Monne M, Samara M, Cook R, Sorio C, Modjtahedi H, Al-Dewik NI. Predictive value of tyrosine phosphatase receptor gamma for the response to treatment tyrosine kinase inhibitors in chronic myeloid leukemia patients. *Sci Rep.* 2021 Apr 23;11(1):8833

Impact Factor: 4.996

Effects of Intermittent Fasting on Response to Tyrosine Kinase Inhibitors (TKIs) in Patients with Chronic Myeloid Leukemia: An Outcome of European LeukemiaNet Project

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Abstract

The overall survival of patients with Chronic Myeloid Leukemia (CML) treated by using tyrosine kinase inhibitors (TKIs) is very close to that of the healthy population. However, little is known about the effect of specific measures such as intermittent fasting, especially during Ramadan period. A 3-year retrospective study was conducted to evaluate the effect of fasting on patients with CML receiving TKIs by evaluating certain clinical, hematological, and molecular parameters. A total of 49 patients were eligible, with a median age of 46 years (range: 22-86), of these 36 (73.5%) were males and 13 (26.5%) were females. Twenty-seven (55%) patients are Middle Eastern, while 16 (32.7%) from the Indian subcontinent, and 6 (12.3%) Africans. Imatinib was the most common TKI; used in 25 patients (51%). The mean White blood cells (WBCs), neutrophils, and BCR-ABL were found to be reduced after fasting compared to before and during with statistical difference. The use of TKIs while fasting did not result in significant changes in hematological nor BCR-ABL levels in our study. Patients who wish to practice intermittent fasting may be reassured in this regard, yet physicians can adopt the safe trial approach, where they allow the patients to fast, but with instructions such as when to break fasting.

Keywords: chronic myeloid leukemia (CML); fasting; intermittent fasting; tyrosine kinase inhibitors (TKIs).

Citation: Yassin, M. A., Ghasoub, R. S., Aldapt, M. B., Abdulla, M. A., Chandra, P., Shwaylia, H. M., Nashwan, A. J., Kassem, N. A., & Akiki, S. J. Effects of Intermittent Fasting on Response to Tyrosine Kinase Inhibitors (TKIs) in Patients With Chronic Myeloid Leukemia: An Outcome of European LeukemiaNet Project. *Cancer Control.* 2021;28:107327482110092.

Impact Factor: 3.67

Assessment of Dasatinib Versus Nilotinib as Upfront Therapy for Chronic Phase of Chronic Myeloid Leukemia in Qatar: A Cost-Effectiveness Analysis

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Abstract

Background: The economic outcome research of approved tyrosine kinase inhibitors for treating the chronic phase of chronic myeloid leukemia in developing is scarce. The aim of this study was to assess the cost-effectiveness of dasatinib and nilotinib for newly diagnosed chronic myeloid leukemia patients.

Methods: A decision tree model was developed linking clinical effectiveness (defined as major molecular response) and/or complete cytogenetic response, utility, and cost data over a 12-month period. Patients are recruited from Qatar Cancer Registry. The probability of primary clinical outcome is calculated from DASISION (dasatinib) and ENESTnd (nilotinib) trials. Direct healthcare costs were derived from the national healthcare payer system, whereas adverse effects data were derived from local incident reporting system.

Results: In the first-line treatments of chronic myeloid leukemia patients, nilotinib has greater major molecular response (39% nilotinib vs 12% dasatinib) and complete cytogenetic response (24% nilotinib vs 16% dastinib) response outcomes, and more adverse effects than dasatinib (13.3% vs 4%). Moreover, nilotinib is more cost-effective with annual costs (USD63,589.59) and after 12 months of follow-up. Despite the lower acquisition annual cost of dasatinib (USD59,486.30), the incremental cost-effectiveness ratio of nilotinib (vs dasatinib) per major molecular response/complete cytogenetic response achieved was USD15,481.10 per year. There were no cases in both arms that progressed to accelerated or blast phase. At a threshold of 3 times gross domestic product per capita of Qatar and

according to World Health Organization recommendation, the nilotinib use is still cost-effective.

Conclusion: Upfront therapy of chronic myeloid leukemia-chronic phase patients by nilotinib plan appears to be more cost-effective than dasatinib.

Keywords: cancer; chronic myeloid leukemia; dasatinib; leukemia; nilotinib; tyrosine kinase inhibitors.

Citation: Adel A, Abushanab D, Hamad A, Abdulla M, Izham M, Yassin M. Assessment of Dasatinib Versus Nilotinib as Upfront Therapy for Chronic Phase of Chronic Myeloid Leukemia in Qatar: A Cost-Effectiveness Analysis. *Cancer Control*. 2021 Jan-Dec;28:10732748211001796.

Impact Factor: 2.339

Downregulation of Lymphoid enhancer-binding factor 1 (LEF-1) expression (by immunohistochemistry and/ flow cytometry) in chronic Lymphocytic Leukemia with atypical immunophenotypic and cytologic features

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Abstract

Introduction: Lymphoid enhancer-binding factor 1 (LEF-1) overexpression has been recently remarkably reported in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and has shown utility in distinguishing CLL/SLL from other B-cell lymphomas. CLL has a well-defined immunophenotype, yet, some cases of CLL demonstrate atypical morphology/ phenotype reflected by low Matutes score (atypical CLL). Till date, LEF1 expression has not been systematically studied in cases of CLL with atypical features. Methods: In this study, LEF-1 expression was assessed by two different techniques, (immunohistochemistry and flow cytometry), to investigate the expression profile of LEF-1 in cases of CLL/SLL, in comparison with other low-grade B-lymphomas and CLL with atypical features, including atypical immunophenotype and CLL with increased prolymphocytes

or morphologically atypical cells. Results: We found that LEF-1 expression is downregulated in CLL with atypical immunophenotype/features compared to classic CLL; Chi-Square P < .0001. The ratio for LEF-1 expression in malignant B-cells/NK (by flow cytometry) in CLL/SLL with classic immunophenotype was higher than atypical CLL and is significantly higher in other small B-cell lymphomas (P < .01). Absence of LEF-1 expression in CLL/SLL is correlated (P < .05) with downregulation of CD5, CD23, CD200, expression of FMC7, brighter expression of CD79b, brighter expression of surface light chain, increased prolymphocytes and lower Matutes score. Conclusion: As downregulation of LEF-1 expression is well correlated with atypical CLL, we suggest adding LEF-1 to Matutes score as a beneficial marker to differentiate classic from atypical CLL LEF-1 could also serve as a potential prognostic indicator for CLL clinical course.

Keywords: atypical CLL, Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), Flow cytometry, Immunohistochemistry, Lymphoid enhancer-binding factor 1 (LEF-1)

Citation: Soliman DS, Al-Kuwari E, Siveen KS, Al-Abdulla R, Chandra P, Yassin M, Nashwan A, Hilmi FA, Taha RY, Nawaz Z, El-Omri H, Mateo JM, Al-Sabbagh A. Downregulation of Lymphoid enhancer-binding factor 1 (LEF-1) expression (by immunohistochemistry and/ flow cytometry) in chronic Lymphocytic Leukemia with atypical immunophenotypic and cytologic features. *Int J Lab Hematol.* 2021 Jun;43(3):515-525.

Impact Factor: 2.30

MALIGNANT HEMATOLOGY

Case Reports

Aberrant Acquisition of T-cell Associated Markers in Plasma Cell Neoplasms: An Aggressive Disease with Extramedullary Involvement and Very Short Survival

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Abstract

Background: Plasma cell neoplasms can show aberrant expression of different lineage-related antigens; however, co-expression of T-cell-associated markers on malignant plasma cells is extremely rare.

Material and methods: This report describes clinicopathologic characteristics of three myeloma patients with emergent plasmablastic morphology and aberrant acquisition of T-cell-associated markers diagnosed in our center. An extensive literature search for similar cases was conducted, and the relevant pathologic, clinical, and prognostic characteristics were summarized.

Results: A total of 22 cases of plasma cell neoplasm (including the three cases reported here) showed aberrant co-expression of T-cell markers. We found an evident association between aberrant expression of T-cell markers on malignant plasma cells and extramedullary involvement, aggressive morphologic features, high proliferative index ki67 >90%, aggressive clinical course, an adverse outcome, and short survival.

Discussion & Conclusion: Due to the rarity of this aberrant phenotype and scarcity of the published data, the precise causative mechanism and its clinical implications have not yet been elucidated.

Keywords: Aberrant T-cell markers, Plasma cell myeloma, Plasma cell neoplasm, Aggressive myeloma

Citation: Soliman DSA, El Sabah H, Ganwo I, Amer A, Taha RY, Szabados L, Eldean MS, Al-Sabbagh A, Ibrahim F. Aberrant Acquisition of T-cell Associated Markers in Plasma Cell Neoplasms: An Aggressive Disease with Extramedullary Involvement and Very Short Survival. *Mediterr J Hematol Infect Dis.* 2021 Jul 1;13(1):e2021043.

Impact Factor: 3.112

Dasatinib-induced chylothorax: An unusual presentation of a common adverse event—A case report with literature review

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Abstract

Tyrosine kinase inhibitors (TKIs) are the key agents for treating CML and BCR–ABL+ B-ALL. Dasatinib is a potent second-generation TKI. Here, we have discussed the case of a 51-year-old gentleman diagnosed with B-myeloid mixed-phenotype acute leukemia with t(9;22)(q34.1;q11.2); BCR–ABL1p210, in complete hematological, cytogenetic, and molecular remission, who developed chylothorax. Though pleural effusion is a commonly observed adverse effect of dasatinib therapy, chylothorax is rare. The ability of Dasatinib to inhibit multiple families of tyrosine kinases could be considered the etiology. Discontinuation of the drug resolved the symptom, but pleural effusion recurred once Dasatinib was resumed. Chylothorax induced by Dasatinib is a differential to be kept in mind, owing to the limited number of cases being reported.

Citation: Paul T, Ellahie AY, Almohtasib YS, Sinha U, El Omri H. Dasatinib-induced chylothorax: An unusual presentation of a common adverse event-A case report with literature review. *EJHaem.* 2021 May 18;2(3):545-550.

Impact Factor: 2.997

Pruritus as a Presenting Symptom of *FIP1L1-PDGFRA*-Positive Chronic Eosinophilic Leukemia

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Abstract

Eosinophilia can be found in a variety of benign and malignant conditions, and a persistent eosinophilic count of more than 1500/mm^3 necessitates additional investigation. Patients with FIP1L1-PDGFRA-positive chronic eosinophilic leukemia might present as asymptomatic or in a catastrophic state with multi-organ involvement. We present the case of a young male patient who was diagnosed with FIP1L1-PDGFRA chronic eosinophilic leukemia after a long history of recurrent cutaneous symptoms with no systemic signs.

Keywords: FIP1L1-PDGFRA; chronic eosinophilic leukemia; eosinophilia; imatinib.

Citation: Abu-Tineh M, Aljaloudi E, Yassin MA. Pruritus as a Presenting Symptom of *FIP1L1-PDGFRA*-Positive Chronic Eosinophilic Leukemia. *J Blood Med.* 2021 Dec 29;12:1061-1063.

Impact Factor: 2.2

Ruxolitinib (a JAK2 inhibitor) as an emerging therapy for refractory pruritis in a patient with low-risk polycythemia vera: A case report

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Abstract

Introduction: Polycythemia vera (PV) is a Philadelphia-negative myeloproliferative neoplasm (MPN) characterized by the overproduction of red blood cells. The presence of JAK2 mutation is detected in up to 99% of patients with PV. Pruritis is commonly encountered in patients with PV and is considered the most troublesome symptom. Multiple treatment modalities are used for treatment; however, their efficacy is variable. Sometimes, pruritis will not improve even by the use of combined therapies. Recently, Ruxolitinib (a JAK2 inhibitor) has been shown to be very effective, especially in patients with refractory pruritis in the setting of other treatment modalities failure.

Patient concern: We describe a 55-year-old male with history of low risk PV presented with severe itching despite using different therapies, including phlebotomy and hydroxyurea. His laboratory results on presentation were significant for red blood cells (RBC) of 8.2 × 106/uL (normal = 4.5-5.5), hematocrit (Hct) of 52.8% (normal = 40-50%), platelet count of 519 × 103/uL (normal = 150-400), white blood cells count of 12.3 × 103/uL (normal = 4-10), and basophils count of 0.22 × 103/uL (normal < 0.1).

Diagnosis: PV related refractory pruritis.

Intervention: Pruritis improved dramatically after starting Ruxolitinib therapy with an improvement of hematological parameters (both hematocrit and platelet count).

Conclusion: Different treatment modalities have shown to be beneficial in treating PV-related pruritis, but the clinical outcomes are highly variable. This case report aims to shed light on Ruxolitinib as an emerging therapy for the treatment of refractory cases of PV-related pruritis.

Citation: Al-Mashdali AF, Kashgary WR, Yassin MA. Ruxolitinib (a JAK2 inhibitor) as an emerging therapy for refractory pruritis in a patient with low-risk polycythemia vera: A case report. *Medicine (Baltimore).* 2021 Nov 5;100(44):e27722.

Impact Factor: 1.15

Interferon-Alpha 2-a and Its Dual Effect in Treating Two Diseases (Hepatitis C and Polycythemia Vera)

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Abstract

Hepatitis C and polycythemia vera (PV) co-existence is not rare; it has been reported in the literature. Treatment with interferon (IFN) has been used to treat both conditions; however, the use of IFN in concomitant hepatitis C infection with PV and its outcome are rarely described in the literature. Here, we report a 56-years-old male patient with hepatitis C virus infection and PV, who was treated with IFN for his chronic hepatitis C, which resulted in significant improvement of HB as well as normalization of his bone marrow and eradication of the clone (*Jak2* V617F).

Keywords: Hepatitis; Hepatitis C; Interferon; Polycythemia vera

Citation: Shwaylia H, Ali E, Yassin MA. Interferon-Alpha 2-a and Its Dual Effect in Treating Two Diseases (Hepatitis C and Polycythemia Vera). *Case Rep Oncol.* 2021 Jun 11;14(2):851-854. doi: 10.1159/000515782.

Impact Factor: 1.143

Coexistence of Prefibrotic Myelofibrosis with Monoclonal Gammopathy of Undetermined Significance: A Case Report

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Abstract

The coexistence of dual hematological neoplasms is an unusual and challenging presentation due to the different combination of etiopathology. The presentation of synchronous dual hematological malignancies can be one of the 3 types: myeloid + lymphoid or dual lymphoid or dual myeloid. Here, we are reporting a case of a 53-year-old male with simultaneous presence of JAK*2 V617F*-positive myeloproliferative neoplasm with features favoring prefibrotic phase of primary myelofibrosis (pre-PMF) in combination with monoclonal gammopathy of undetermined significance (MGUS). In such cases of simultaneous existence of dual hematological neoplasm management, it is recommended to treat the more aggressive one. Currently, our management plan is focusing on treating the pre-PMF and observation of MGUS with regular monitoring for transformation to MM.

Keywords: Coexistence; Monoclonal gammopathy of undetermined significance; Myeloproliferative neoplasm; Prefibrotic phase of primary myelofibrosis; Second malignancies.

Citation: Ismail OM, Amer A, Ibrahim FA, Abu-Tineh M, Yassin MA. Coexistence of Prefibrotic Myelofibrosis with Monoclonal Gammopathy of Undetermined Significance: A Case Report. *Case Rep Oncol.* 2021 Oct 14;14(3):1435-1440.

Impact Factor: 1.143

Neurolymphomatosis of the median nerve, optic nerve, L4 spinal nerve root and cauda equina in patients with B-cell malignancies: a case series

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Abstract

Background: Neurolymphomatosis is rare. Neoplastic lymphocytes are seen to invade nerves (cranial or peripheral), nerve roots or other related structures in patients with hematological malignancy. It is a separate entity from central nervous system lymphoma. Neurolymphomatosis has most commonly been described in association with B-cell non-Hodgkin lymphoma. Neurolymphomatosis in the context of Burkitt lymphoma and the post-renal transplant setting has not been described before.

Case reports: We report for the first time in the Arabian Gulf countries and nearby Arab states four cases of neurolymphomatosis (one Asian, and the other 3 are from Arabic nationals) occurring between 2012 and 2017 involving the median nerve, optic nerve, nerve root and cauda equina in patients with Burkitt lymphoma, Philadelphia chromosome-positive B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma.

Conclusions: Neurolymphomatosis is rare and can be difficult to diagnose by biopsy but reliably confirmed by a combined imaging approach. Prior treatment with high-dose dexamethasone might suppress 18F-fluorodeoxyglucose (FDG) activity and decrease the sensitivity of positron emission tomography/computed tomography (PET/CT). The prognosis is generally poor but using high-dose methotrexate as well as high-dose chemotherapy and autologous stem cell transplantation may be an effective way to treat neurolymphomatosis.

Keywords: B cell-acute lymphoblastic leukemia (b-ALL); Burkitt lymphoma; Cauda equina syndrome; Diffuse large B-cell lymphoma; L4 spinal nerve root; Median nerve palsy; Neurolymphomatosis; Optic nerve lesion; Post-transplant lymphoproliferative disorder (PTLD); Renal transplant.

Citation: Alazawi S, Elomri H, Taha R, Bakr M, Abdelhamid MT, Szabados L, Yassin M, Sabah HE, Aboudi K, Ellahie A, Fadul A, Gameil A, Al Battah A, Fernyhough LJ. Neurolymphomatosis of the median nerve, optic nerve, L4 spinal nerve root and cauda equina in patients with B-cell malignancies: a case series. *J Med Case Rep.* 2021 Mar 26;15(1):133.

Impact factor: 1.07

Hyperosmolar Hyperglycaemic State and Diabetic Ketoacidosis in Nivolumab-Induced Insulin-Dependent Diabetes Mellitus

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Abstract

Nivolumab is a monoclonal antibody directed against programmed cell death-1 receptor. It has an increasing application in the treatment of various advanced metastatic cancers. The incidence of autoimmune side effects associated with such agents is expected to increase. New-onset autoimmune diabetes mellitus associated with immune checkpoint inhibitor treatment is rare, occurring in less than 1% of patients. Nivolumab-induced diabetes often presents as diabetic ketoacidosis, which could be life-threatening if not recognized and treated promptly. We present the case of a patient who developed severe diabetic ketoacidosis concomitant with hyperosmolar hyperglycaemic state (HHS) after receiving nivolumab for metastatic testicular lymphoma. Pre-nivolumab blood glucose levels were normal, apart from transient hyperglycaemia related to steroids as part of the chemotherapy protocol. The diagnosis was confirmed with extremely low C-peptide in the clinic.

Learning points: Checkpoint inhibitor-associated diabetes can present abruptly with life-threatening complications.Most patients require multiple daily injections of insulin upon discharge. Cessation of checkpoint inhibitor therapy does not revert diabetes.

Keywords: DKA; HHS; checkpoint inhibitors; diabetes mellitus; nivolumab.

Citation: Saleh AO, Taha R, Mohamed SFA, Bashir M. Hyperosmolar Hyperglycaemic State and Diabetic Ketoacidosis in Nivolumab-Induced Insulin-Dependent Diabetes Mellitus. *Eur J Case Rep Intern Med*. 2021 Aug 13;8(8):002756. doi: 10.12890/2021_002756.

Impact factor: 1.0

Dasatinib-Induced Colitis with Rectal Sparing in a Patient with Chronic Myeloid Leukemia (Chronic Phase) on Dasatinib as an Upfront Therapy: Case Report

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Abstract

Dasatinib is a BCR-ABL tyrosine kinase inhibitor which was approved in 2006 for the treatment of adults diagnosed with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP) and accelerated (myeloid or lymphoid blast) phase and CML with resistance or intolerance to prior therapy including imatinib and in adults with Ph+ acute lymphoblastic leukemia. Common adverse reactions (>15%) in patients diagnosed with CP-CML include myelosuppression, fluid retention, and diarrhea. We report a 34-year-old Filipino female patient who received dasatinib as upfront therapy for the treatment of CP-CML who experienced chronic diarrhea for 2 months, which progressed to colitis.

Keywords: Chronic myeloid leukemia; Colitis; Dasatinib.

Citation: Maat Z, Mushtaq K, Yassin MA. Dasatinib-Induced Colitis with Rectal Sparing in a Patient with Chronic Myeloid Leukemia (Chronic Phase) on Dasatinib as an Upfront Therapy: Case Report. *Case Rep Oncol.* 2021 Oct 18;14(3):1441-1446.

Impact Factor: 0.97

Chronic Myeloid Leukemia in a Patient with Hepatitis B Virus Infection: A Case Report

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Abstract

Chronic myeloid leukemia (CML) is a myeloproliferative disorder diagnosed by demonstrating the Philadelphia chromosome (Ph) or the BCR-ABL fusion gene. Tyrosine kinase inhibitors (TKIs) are the standard of therapy. There are increasing reports of hepatitis B virus reactivation (HBVr) in patients on this treatment. We report a case of a 46-year-old male patient diagnosed to have CML in the chronic phase and resolved hepatitis B infection. He was treated with imatinib as upfront therapy for CML and with lamivudine as prophylaxis against HBVr. The patient tolerated both treatments well with no adverse effects. The aim is to address the deficiencies in the literature in regard to managing these patients, prevention, and follow-up.

Keywords: Chronic myeloid leukemia; Hepatitis B; Hepatitis B virus reactivation; Imatinib; Tyrosine kinase inhibitor

Citation: Ali Hailan YM, Mudawi D, Yassin MA. Chronic Myeloid Leukemia in a Patient with Hepatitis B Virus Infection: A Case Report. *Case Rep Oncol.* 2021 Jun 24;14(2):1004-1009.

Impact factor: 0.97

P190$^{BCR-ABL1}$ in a Patient with Philadelphia Chromosome Positive T-Cell Acute Lymphoblastic Leukemia: A Rare Case Report and Review of Literature

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Abstract

T-acute lymphoblastic leukemia/lymphoblastic lymphoma (T-ALL/LBL) is rare and aggressive leukemia. Philadelphia chromosome positive (Ph+) is the most common cytogenetic abnormality in chronic myeloid leukemia (CML) and B-acute lymphoblastic leukemia (B-ALL). Ph+ T-ALL is exceeding rare and has a therapeutic and prognostic significance. The incidence and outcome of Ph+ T-ALL are unknown. Differentiation between Ph+ T-ALL/LBL and T-cell lymphoblastic crises of CML may be difficult. We report a rare case of adult de novo T-ALL with significant monocytosis, having Ph+ with (P190 *BCR-ABL1*) as a cytogenetic abnormality. He was treated with ALL induction chemotherapy and imatinib and achieved complete remission, then relapsed twice and expired shortly after the last CNS relapse.

Keywords: T-cell-acute lymphoblastic leukemiaPhiladelphia positive acute leukemiaAcute leukemiaT-blastic phase of CMLDe novo T-ALLP190$^{BCR-ABL1}$ positive acute leukemia

Citation: Kohla S, EL Kourashy S, Nawaz Z, Youssef R, Al-Sabbagh A, Ibrahim F, A: P190BCR-ABL1 in a Patient with Philadelphia Chromosome Positive T-Cell Acute Lymphoblastic Leukemia: A Rare Case Report and Review of Literature. *Case Rep Oncol* 2021;14:1040-1050.

Impact Factor: 0.97

Budd-Chiari syndrome on background of JAK2V617F mutation with no hematologic abnormalities

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Abstract

Whenever considering idiopathic Budd-Chiari syndrome, consider the possibility of JAK2 mutation even if clinical parameters are within normal range.

Keywords: Bud-Chiari syndrome; JAK 2 mutation; hepatic vein thrombosis; myeloproliferative disease.

Citation: Bint I Bilal A, Ata F, Abdelrazek M, Yassin MA. Budd-Chiari syndrome on background of JAK2V617F mutation with no hematologic abnormalities. *Clin Case Rep.* 2021 Sep 13;9(9):e04668.

Impact Factor: 0.532

Acute appendicitis revealing a diagnosis of chronic myelogenous leukemia

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Abstract

Gastrointestinal manifestations of leukemias have been well recognized. Typically, acute leukemias cause typhlitis or appendicitis more commonly than chronic leukemias.

Our case points to appendicitis as possible manifestation of chronic myelogenous leukemia.

Keywords: appendicitis, typhlitis, chronic myelogenous leukemia, leukemia, chronic myelogenous leukemia, hematologic malignancies

Citation: Ahmad R, Ali E, Okar L, et al. Acute appendicitis revealing a diagnosis of chronic myelogenous leukemia. *Clin Case Rep.* 2021;9:1913–1916.

Impact Factor: 0.532

A Case Report of *BCR-ABL-JAK2*-Positive Chronic Myeloid Leukemia with Complete Hematological and Major Molecular Response to Dasatinib

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Abstract

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm (MPN) that harbors the Philadelphia chromosomal translocation resulting in the uncontrolled production of mature granulocytes. Commonly, patients are diagnosed with CML during blood work for other reasons or enlarged spleen. The diagnosis is based on WHO criteria that require the demonstration of Philadelphia chromosome. Typically, *JAK2* mutation is not found in *BCR-ABL1*-positive MPN (CML). Most patients with CML are *JAK2* negative. It is rare for CML Philadelphia-positive patients to have a coexisting *JAK2* mutation. Little is known regarding the effect of *JAK2* mutation on the disease course of CML, the complications, and the response to treatment. We report the case of a 57-year-old man with no previous medical illness who presented with elevated white blood cell count on perioperative assessment for hernial repair; on further workup, he was diagnosed with Philadelphia-positive CML. He was found to have *JAK2* mutation and was started on treatment with dasatinib and achieved hematological and cytogenetic remission with loss of the *JAK2* mutation. Patients with *JAK2*-positive *BCR-ABL*-positive CML had a good hematological and cytogenetic response to dasatinib. In such rare coexistence of *JAK* and *BCR-ABL*, dasatinib is a good option due to multi-kinase activity.

Citation: Ali EAH, Al-Akiki S, Yassin MA. A Case Report of *BCR-ABL-JAK2*-Positive Chronic Myeloid Leukemia with Complete Hematological and Major Molecular Response to Dasatinib. *Case Rep Oncol.* 2021 Apr 15;14(1):690-694. doi: 10.1159/000514632.

Impact Factor: 0.532

Pseudomyogenic hemangioendothelioma of bone with rare *WWTR1-FOSB* fusion gene: Case report and literature review

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Abstract

Pseudomyogenic hemangioendothelioma rarely arises in bone. *WWTR1-FOSB* fusion gene is rarely reported in PMHE of bone. Currently, fusion genes can be used as diagnostic markers in PMHE; however, their prognostic and therapeutic significance is unclear.

Keywords: FOSB; WWTR1; bone; pseudomyogenic hemangioendothelioma.

Citation: Murshed KA, Torres-Mora J, ElSayed AM, Ammar A, Al-Bozom I. Pseudomyogenic hemangioendothelioma of bone with rare *WWTR1-FOSB* fusion gene: Case report and literature review. *Clin Case Rep.* 2021 Jan 19;9(3):1494-1499.

Impact Factor: 0.532

MALIGNANT HEMATOLOGY

Review Articles

Ophthalmologic manifestations as the initial presentation of chronic myeloid leukemia: A review

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Abstract

The presentation of chronic myeloid leukemia (CML) can be variable and related to the phase of the disease. It can manifest a wide range of symptoms and signs; ocular involvement is reported in patients with leukemia at the time of diagnosis. We describe ophthalmic manifestations as an initial presentation in patients with CML. We identified 38 publications between 1971 and 2020 describing ocular manifestations in CML. Ophthalmic problems occur either from direct or indirect infiltration of neoplastic cells or from secondary causes. Although nearly all ocular structures may be affected, leukemic retinopathy is the most frequent clinical manifestation. Others include iris infiltration, anterior uveitis, hypopyon, exudative/serous retinal detachment, and optic nerve infiltration.

Keywords: CML; Leukemia; Leukemic retinopathy; Ophthalmic Manifestations; Retinal detachment.

Citation: Yassin MA, Ata F, Mohamed SF, Alkhateeb A, Naeem U, Al-Qatami AI, Nashwan AJ, Fernyhough LJ. Ophthalmologic manifestations as the initial presentation of chronic myeloid leukemia: A review. *Surv Ophthalmol.* 2022 Mar-Apr;67(2):530-543.

Impact factor: 6.048

Leukemia Cutis as an Early Presentation or Relapsing Manifestation of Chronic Lymphocytic Leukemia (CLL)

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Abstract

Background and objective: Cutaneous infiltration by Chronic Lymphocytic Leukemia (CLL) is a rare complication. The clinical presentation, impact of it on disease prognosis, and the proper treatment choice are not clear. Here in our review, we try to answer these questions. Acquisition of evidences: A systematic search of PubMed, and Google Scholar for English language articles published from Jan 2000 to June 2019. Synthesis of evidences: A total of 56 cases were identified, with a median age of 66 years. Of these cases 43 were males and 12 were females, and one missing data, with a ratio of 3,6:1. Head and neck were most commonly involved. The commonest clinical presentation was papulonodular lesions, and the majority were diagnosed at an early stage. CLL skin involvement at the site of old herpetic lesions was common. Because of the rarity of the disease, treatment modalities varied widely, and there are no consensus on treatment. The majority were treated with chemotherapy. In general, 35 (77.8% - of the non-missing data) patients responded to treatment (25 patients had a complete remission and 10 a partial remission). All patients ≤60 years had an early-stage disease, on the other hand, all patients with advanced-stage were >60 years.

Conclusion: Patients with early-stage and localized leukemia cutis can benefit from observation alone strategy, while intervention in young patients with advanced disease is warranted. Skin infiltration by CLL does not affect prognosis, as most patients attained complete or partial remission with a very low progression rate.

Citation: Aldapt MB, Yassin M. Leukemia Cutis as an Early Presentation or Relapsing Manifestation of Chronic Lymphocytic Leukemia (CLL). *Acta Biomed.* 2021 May 12;92(2):e2021192.

Impact Factor: 3.79

Association of tuberculosis in patients with chronic myeloid leukemia: a treatment proposal based on literature review

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Abstract

Introduction: Chronic Myeloid leukemia (CML) is one of the first hematological malignancy linked with genetic alterations and have a targeted therapy with Tyrosine Kinase Inhibitors. However, there are certain unanswered questions and many unmet needs which limit its treatment. Concurrent Mycobacterium Tuberculosis (Mtb) infection is one of those significant factors. Tuberculosis (TB) is a highly prevalent disease in association with diabetes mellitus, malignancy, poor socioeconomic environment, HIV, and other immunosuppressive conditions in developed and developing countries. Anti-TB medications can affect other drug's pharmacokinetics by altering liver enzymes metabolism and poses treatment challenge with CML medications. Areas covered: The authors performed a rigorous literature review between 2000 and 2020 using PubMed and Google Scholar, with the main focus on all articles addressing the topic of TB in CML. Authors highlighted the need to improve clinical diagnosis and to define management strategy for this dilemma. Expert opinion: In the current era, there are no clear guidelines or recommendations in the literature that address this problem. The aim of this review was to collect and carefully analyze the literature to highlight the need for comprehensive guidelines and propose an algorithm for better management of TB in patients with CML.

Keywords: Chronic myeloid leukemia (CML); anti- TB medications; mycobacterium tuberculosis; treatment; tuberculosis (TB); tyrosine kinase inhibitors (TKI).

Citation: Iqbal P, Soliman A, De Sanctis V, Yassin MA. Association of tuberculosis in patients with chronic myeloid leukemia: a treatment proposal based on literature review. *Expert Rev Hematol.* 2021 Feb;14(2):211-217.

Impact Factor: 2.929

MPN-246: General Characteristics and Outcome of Renal Extramedullary Hematopoiesis in Patients with Myeloproliferative Neoplasms: A Literature Review

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Abstract

Kidneys are a rare but serious site for extramedullary hematopoiesis (EMH) with myeloproliferative neoplasms (MPNs).

Objective:To review cases of EMH affecting the kidneys, focusing on demographics, clinical manifestations, treatment, and outcomes.Design and Setting:We reviewed the literature for studies, case series, and case reports that reported on renal EMH with a primary or background diagnosis of MPN from 1990 to 2020.Results:Forty-three patients (79% males) were retrieved. The mean age of the cohort was 65 years (range 49–87 years). Most of the cohort was white Caucasian (91%). The type of MPN was mostly MF, seen in 35 patients (81.4%), while PV was seen in 5 patients (11.6%), and ET and CML were seen in 2 patients (4.7%) and 1 (2.3%) patient, respectively. The most common renal manifestations were renal failure and nephrotic syndrome in 39.5% of the cases, followed by renal failure alone (37.2%) and nephrotic syndrome in 9.3%. Interestingly, a renal mass was found in 9%. The average time to EMH development from the time of diagnosis was 7.8 years (range 0–20 years). Four patients developed EMH post-transplant, 3 of them allogenic while one was autologous. The JAK mutation was reported in 7 patients, and CALR mutation in one patient. Patients were treated with different medications, including diuretics, anti-hypertensives (mainly ACE inhibitors), and steroids. However, for MPNs, 25% received HU, 14% received thalidomide or a thalidomide analog, while 16% received JAK inhibitors, such as ruxolitinib. The CML case was treated with imatinib. The average duration of follow-up was 19 months, with a 42.5% death rate by the end of follow-up. Kidney function improved in 31% of patients, with ruxolitinib administration correlating with improved kidney function and survival (6 out of 7 patients).

Conclusions: An unexplained increase in renal function, proteinuria, or kidney mass in a setting of MPN should raise the suspicion of this diagnosis. There is currently no consensus or guidelines on the management of such cases. Ruxolitinib, with the limitations of small numbers treated, may offer some benefit; however, further studies and exploration of this drug and others in well-constructed prospective studies are needed.

Citation: Mohamed, S., Alkhateeb, M., Abdalhadi, A., Nashwan, A., Obeidat, K., Imam, Y., & Yassin, M. (2021). MPN-246: General Characteristics and Outcome of Renal Extramedullary Hematopoiesis in Patients with Myeloproliferative Neoplasms: A Literature Review. *Clinical Lymphoma Myeloma and Leukemia,* 21, S359. https://doi.org/10.1016/S2152-2650(21)01827-9

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Environmental Factors, Lifestyle Risk Factors, and Host Characteristics Associated with Philadelphia Negative Myeloproliferative Neoplasm: A Systematic Review

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Abstract

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders characterized by the overproduction of mature myeloid cells and are often associated with an acquired genetic mutation of *Janus Kinase2V617F*. Various epidemiological studies have indicated associations between environmental factors, lifestyle factors, and host characteristics with developing MPNs. This review aims to collect and summarize the existing information on these risk factors and establish their association with pathogenesis MPNs. Medline, Embase, PubMed, and grey literature were systematically searched using key terms for MPNs, and epidemiological study designs, that is, cross-sectional studies, case-control, and cohort, that investigated the risk factors for MPNs published were identified. Out of the 4621 articles identified, 20 met the selection criteria and were included in this review. Heterogeneity, study reliability, and bias were assessed. A significant association was found between smoking and the development of MPNs. This relationship has been explained by the substantial increase in several proinflammatory mediators and systematic oxidative stress causing hyperstimulation of myeloid compartments leading to the development of MPNs. Obesity was modestly linked with an increased risk of MPNs. The underlying mechanisms have been linked to changes in endocrine, metabolic, and inflammatory systems. No strong association was found between exposure to hazardous substances, that is, benzene and MPNs, but further investigation on the effects of increased levels and duration of exposure on hematopoietic stem cells will be beneficial. Unique individual and host variations have been determined as a modifier of disease pathogenesis and phenotype variations. There is a higher incidence rate of females developing MPNs, specifically ET, than males with higher PV incidence. Therefore, gender contributes to the heterogeneity in

myeloproliferative neoplasm. Studies identified as part of this review are very diverse. Thus, further in-depth assessment to explore the role of these etiological factors associated with MPNs is warranted.

Keywords: benzene; environmental; essential thrombocythemia; gender; host characteristics; lifestyle; myeloproliferative disease; myeloproliferative neoplasm; obesity; polycythemia vera; primary myelofibrosis; risk factor; smoking

Citation: Allahverdi N, Yassin M, Ibrahim M. Environmental Factors, Lifestyle Risk Factors, and Host Characteristics Associated With Philadelphia Negative Myeloproliferative Neoplasm: A Systematic Review. *Cancer Control.* 2021 Jan-Dec;28:10732748211046802.

Impact factor: 2.339

Strategic priorities for hematopoietic stem cell transplantation in the EMRO region

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Abstract

The World Health Organization-designated Eastern Mediterranean region (EMRO) consists of 22 countries in North Africa and Western Asia with a collective population of over 679 million. The area comprises some of the wealthiest countries per capita income and some of the poorest. The population structure is also unique and contrasts with western countries, with a much younger population. The region sits in the heart of the thalassemia belt. Many countries have a significant prevalence of sickle cell disease, and cancer is on the rise in the region. Therefore, the strategic priorities for the growth and development of hematopoietic stem cell transplantation (HSCT) differ from country to country based on resources, healthcare challenges, and prevalent infrastructure. Thirty-one reporting teams to the Eastern Mediterranean Blood and Marrow Transplantation Group have active HSCT programs in 12 countries; allogeneic transplants outnumber autologous transplants, and the proportion of allotransplants for non-malignant conditions is higher in the EMRO region than in Western Europe and North America. The vast majority (99%) of allotransplants are from matched related donors. Matched unrelated donors and other alternate donor transplants are underutilized. The chance of finding a matched related donor for allografts is higher, with a significant chance of finding matched donors among non-sibling related donors. Reasons for relatively lower rates of transplants compared with other countries are multifactorial. Capacity building, development of newer centers, innovative funding, and better utilization of information technology are required to make transplantation as an accessible modality to more patients. Cost-effectiveness and cost-containment, regulation, and ensuring quality will all be priorities in planning HSCT development in the region.

Keywords: EMRO; Eastern Mediterranean; HSCT; Hematopoietic cell; Strategic priorities; Transplantation program; WBMT.

Citation: Ahmed SO, El Fakih R, Elhaddad A, Hamidieh AA, Altbakhi A, Chaudhry QU, Bazarbachi A, Adil S, Al-Khabori M, Ben Othman T, Gaziev J, Khalaf M, Alshammeri S, Alotaibi S, Alshahrani M, Bekadja MA, Ibrahim A, Al-Wahadneh AM, Altarshi M, Alsaeed A, Madani A, Abboud M, Abujazar H, Bakr M, Abosoudah I, El Cheikh J, Almasari A, Alfraih F, Baldomero H, Elsolh H, Niederwieser D, Chaudhri N, Aljurf M. Strategic priorities for hematopoietic stem cell transplantation in the EMRO region. *Hematol Oncol Stem Cell Ther.* 2021 Oct 18:S1658-3876(21)00090-X.

Impact Factor: 1.659

Priapism in lymphoproliferative disorders: A systematic review

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Abstract

Priapism is defined as a persistent penile erection lasting more than 4 h. We searched the literature for reviews, case reports, and series for patients with lymphoproliferative disorders who developed priapism. The search involved all the lymphoproliferative disorders included in the revised 2016 World Health Organization classification of lymphoid neoplasms including chronic lymphocytic leukemia, multiple myeloma, Waldenström macroglobulinemia, and lymphomas. A total of 16 articles were found. The search included cases up to 4th January 2021. Priapism was seen most commonly as the first manifestation of lymphoproliferative disorders, rarely seen after treatment or after diagnosis.

Keywords: Leukemia; Lymphoma; Lymphoproliferative disorders; Male fertility; Multiple myeloma; Priapism.

Citation : Ali EA, Sardar S, Yassin MA. Priapism in lymphoproliferative disorders: A systematic review. *Hematol Oncol Stem Cell Ther.* 2021 Jun 10:S1658-3876(21)00054-6.

Impact Factor: 1.659

Priapism in Patients with Chronic Myeloid Leukemia (CML): A Systematic Review

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Abstract

Background: Priapism is defined as a penile erection that persists four or more hours and is unrelated to sexual stimulation. Priapism resulting from hematologic malignancy is most likely caused by venous obstruction from microemboli/thrombi and hyperviscosity caused by the increased number of circulating leukocytes in mature and immature forms. In patients with leukemia, 50% of cases of priapism are due to Chronic Myeloid Leukemia (CML). We present a systematic review of priapism in CML. Acquisition of evidence: An extensive literature research was carried out in PubMed, Google Scholar, SCOPUS, and Science Citation Index databases... The search included cases up to 4th August 2020. Synthesis of evidence: A total of 68 articles were found and included in our review, including 3 reviews from three different centers. We found 68 articles (102 patients; figure 1) and several case reports on priapism in CML. Priapism was noticed in some patients at the first presentation of CML. However, it was infrequently reported during the start of treatment, following the stop of medication and post-splenectomy. The mean age at presentation was 27.4 years, and the mean time from onset of priapism to the time to get medical attention (presentation) was 78.2 hours. The mean white blood cell count associated with priapism was 321.29x109/L, and the mean platelet count was 569 x10 9/L. The chronic phase of CML was the most common phase where priapism occurred. Most patients were Asian (>50%). Nearly a quarter of patients (27.4%) developed permanent erectile dysfunction.

Conclusions: Priapism is a urological emergency requiring urgent multidisciplinary management to prevent erectile dysfunction. Because of the relatively rare occurrence of priapism in CML patients, there is no standard treatment protocol.

Citation: Ali E, Soliman A, De Sanctis V, Nussbaumer D, Yassin M. Priapism in Patients with Chronic Myeloid Leukemia (CML): A Systematic Review. *Acta Biomed.* 2021 Jul 1;92(3):e2021193.

Impact Factor: 1.352

MALIGNANT HEMATOLOGY

Abstracts

Epidemiologic and Clinical Patterns of Lymphoma in Qatar 2013-2017: A Population-Based Cohort Study

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Abstract

Background: Lymphoma: either most common non-Hodgkin (NHL) or less common Hodgkin (HL), are well-known hematological malignancies. With advancement in treatment modalities, the survival in both lymphomas especially the "poor prognosis" non-Hodgkin lymphoma has evolved in the last decades. Hence, patient's outcome may be diverse and quite complicated; with some need extended time for observation, and others having multiple chemotherapy treatments. In this review, we will focus on the clinic-epidemiological patterns of various malignant lymphoma subtypes in Qatar in recent years (2013-2017)

Objective: The primary aim is to investigate and compare the overall survival (OS) for both types of lymphoma; HL and NHL at 1, 3 and 5-years of follow up in adult lymphoma patients in Qatar between January 2013 - December 2017. Other objectives include comparing between the most frequent histological varieties, clinical and epidemiological characteristics of HL and NHL lymphoma in Qatar. The secondary objectives included clinical characteristics, treatments used, treatment response, disease-free survival and overall survival.

Methods: A retrospective, descriptive study of consecutive cases was carried out at NCCCR, Qatar between 2013-2017. Inclusion criteria included: ≥ 18 years of age, male or female, any clinical stage at diagnosis, who had received any chemotherapy regimen, with a known outcome. Descriptive statistics was performed for all variables, and survival was assessed using Kaplan-Meier curves. Data was abstracted by Qatar National Cancer Registry and the 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid tumors is used as reference for disease staging and pathological classification. We used STATA version 13.0 (StataCorp., College Station, TX) for exploratory data analysis and descriptive statistics.

Results: During the period 2013-2017, 414 men and women were diagnosed with lymphoma in the state of Qatar. The median age at diagnosis being 49 years (interquartile range IQR 36-95 years; $p<0.001$)) for all lymphoma patients combined. Males were more likely to develop both lymphoma types; HL and NHL than females; accounting for 2/3 of cases in each, yet statistically insignificant (74% and 70%, $p=0.45$). Based on subtypes, mature B-cell neoplasms (61 cases, 60%) were the most common among 13 identifiable NHL-B subtypes. Majority of HL cases belonged to Lymphocyte rich subtype (54 cases, 49%). With a median follow up of 17.3 months, the 1-year, 3-year and

5-year OS for the entire population of lymphoma patients were 99%, 82% and 64% (Figure 12). When stratified by major subtypes; HL and NHL, some trends became evident at 3-years follow-up (94% versus 82%). The 5-year OS were 67% and 60%, respectively. Throughout the study period, the OS in HL group were higher than NHL ($p<0.001$), yet median OS was not reached.

Conclusions: Diffuse large B-cell lymphoma constitutes the most frequent subtype for all lymphomas in Qatar. Overall, the survival was generally better for HL than NHL 67% and 60% respectively. Survival can be slightly deflated than other countries or regions especially HL, this is in part due to higher immigration rate in the country, so changes in survival over time (especially for longer periods) need to be examined alongside trends in incidence rates to interpret improvement in cancer control policies implemented.

Citation: Adel A, Exarchakou A, Hamad A, Yasin R, Ghazouani H, Yassin M.Epidemiologic and Clinical Patterns of Lymphoma in Qatar 2013-2017: A Population-Based Cohort Study, *Blood,* V 138, Supplement 1,2021,ISSN 0006-4971,https://doi.org/10.1182/blood-2021-144637.

Characteristics and Outcomes of Adolescent and Young Adult (AYA) Patients with Myelodysplastic Syndrome (MDS) and Chronic Myelomonocytic Leukemia (CMML): A Single-Center Retrospective Analysis

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Abstract

Introduction: Myelodysplastic syndrome (MDS) is mainly a disease of the elderly, with a median age of 72 years. There is little information regarding Adolescent and Young Adult (AYA) Patients with Myelodysplastic syndrome (MDS). AYA cancer patients are defined as those patients ages between 15-39 years according to NCCN guidelines. This retrospective study describes the general characteristics, cytogenetics, mutational profiles, treatments, and outcomes of AYA with MDS Diagnosis.

Methodology: We analyzed the clinical database of a single tertiary care center for patients with MDS ages between 18- 39 years from January 2012 through December 2020. We used 18 years as age cut-off, and not 15, due to the structure of our cancer center.

Results: In this retrospective study, 65 patients were identified. The median age was 30 (18-39) years, with female sex predominance (n=37) (57%). Baseline laboratory findings: median hemoglobin (HgB) was 9.45gm/dL (6.2-14.8), white blood cells (WBC) (3.4x10e9/L [0.3-136.9], platelets 63,000 (5,000-479,000), bone marrow blast 4% [0-17], IPSS was low in 11 patients (17%), intermediate- 1 in 23 (35%), intermediate- 2 16(25%) and high 8 (12%). 58 patients (89%) had MDS and seven (11%) had CMML. Twenty patients (30.7%) had a previous history of other cancers, with sarcomas being the most frequent with 6 cases (9.2%). Therapy-related MDS (t-MDS) was observed in 18 patients (27.6%). Ten patients (15.3%) had bone marrow failure syndrome, with *GATA2* syndrome being the most frequent. Fanconi anemia and Schwachman-Diamond Syndrome was documented in two patients respectively. The most recurrent cytogenetics alterations were diploid in 20 patients (30.7%), followed by complex in 11 (16.9%). The most frequent mutations were *RUNX1* (somatic)15%, followed by *DNMT3A*, *TP53, NRAS, GATA2* and *TET2*, as shown in the Figure 1.

Hypomethylating agents (HMAs) were the most frequent first line treatment used in 16 patients (24.6%). Forty-three patients (66%) underwent an allogeneic bone marrow transplant with a median OS (95% CI) of 27 months (9-45). While for the group of patients who didn't receive transplant, it was 21 months (7-69) (p=0.19) vs patients who didn't receive transplant. Allogeneic transplantation in TP53-mutated patients resulted in a Median OS (95% CI) of 21 months (12-65). Patients who progressed into AML had an inferior median OS (95% CI) of 21 months (12-65) for vs 28 months (11-47) for those who did not progressed to AML(p=0.025). In multivariate analysis expression of *RUNX1* and *NOTCH1*, was associated with inferior outcomes (p-value=0.035, 0.004 respectively) (Figure 2,3 and 4)

Conclusion: In our cohort, MDS occurred as part of marrow failure syndrome or consequence of therapy t-MDS. Somatic *RUNX1* was the most frequent mutation in AYA group with MDS. *RUNX1*, *NOTCH1* and *Tp53* mutated patients had worse outcome. Most patients underwent bone marrow transplant

Citation: Mohamed, S. F., Abuasba, T., Chien, K. S., Montalban-Bravo, G., Darbaniyan, F., Pierce, S. A., Soltysiak, K. A., Haddad, F., McCall, D., Cuglievan, B., Jabbour, E. J., Daver, N., Kadia, T. M., Pemmaraju, N., Kantarjian, H., & Garcia-Manero, G. (2021). Characteristics and Outcomes of Adolescent and Young Adult (AYA) Patients with Myelodysplastic Syndrome (MDS) and Chronic Myelomonocytic Leukemia (CMML): A Single-Center Retrospective Analysis. *Blood, 138*, 3687.

Initial Results of Phase I/II Study of Azacitidine in Combination with Quizartinib for Patients with Myelodysplastic Syndrome and Myelodysplastic/ Myeloproliferative Neoplasm with *FLT3* or *CBL* Mutations

Tareq Abuasab, Elias J. Jabbour, Nicholas J. Short, Marina Konopleva, Kelly S. Chien, Shehab Fareed Mohamed, Naval Daver, Rashmi Kanagal-Shamanna, Hagop Kantarjian, Guillermo Garcia-Manero, Guillermo Montalban-Bravo

Abstract

Introduction: FMS-like tyrosine kinase 3 (*FLT3*) mutations occur in about 1% of patients with newly diagnosed myelodysplastic syndrome (MDS) and up to 19% at time of failure of hypomethylating agent (HMA). In addition, Casitas B-lineage Lymphoma mutations (*CBL*) are observed in 10% of patients with MDS/MPN and up to 13-15% of patients with CMML (mainly proliferative type). Preclinical studies suggest that *CBL*-mutant cells are dependent on FLT3 signaling. Specific targeting of *FLT3* and *CBL* mutations in MDS and MDS/MPN has not been thoroughly evaluated. Methods: We designed a phase I/II clinical trial of Azacitidine in Combination with quizartinib for newly diagnosed patients with MDS and MDS/MPN with detectable *FLT3* mutation and/or CBL exon 8 or 9 deletions or point mutations Mutation on patients that are HMA naïve or had prior treatment with HMA. The study included phase I dose escalation portion, following 3+3 design, followed by phase II dose expansion portion. Dose escalation included 3 dose levels of quizartinib on days 1-28 of every cycle: 30, 40 and 60 mg in the addition to azacitidine (75 mg/m ^{2}/day) on days 1-5 each 28-day cycle. The phase II/expansion phase will include two cohorts, Cohort A hypomethylating agent naïve patients and cohort B patients with prior hypomethylating agent. The primary objective of this study is to determine the safety, tolerability and maximum tolerable dose (MTD) of quizartinib. Secondary objectives include evaluation of overall response per IWG 2006 criteria, in addition to overall survival (OS), duration of response, leukemia-free survival (LFS), relapse-free survival (RFS). Results**:** At the end date of July 30 th 2021, a total of 6 patients have been enrolled: 4 patients with CMML, one with MDS excess blast and one with atypical Chronic myeloid leukemia (aCML). A total of 5 patients (83%) had normal karyotype and one patient (17%) had complex karyotype. Four patients were enrolled due to *FLT3* mutations and 2 due to *CBL* mutations. Patients characteristics are summarized in Figure 1a. Median number of cycles administered was 3.5 (range 1-6). All patients have achieved response so far with a total of 5 patients (67%) having achieved marrow CR (mCR) including HI in 1 patient, 1 patient had hematologic improvement-erythropoietic (HI-E) with control of leukocytosis and thrombocytosis to normal levels. Response dynamics and clonal changes through the course of therapy are shown in Figure 1b. Reduction of clearance of *FLT3-ITD* or other *FLT3* mutations was observed in all evaluable *FLT3*-mutant patients with no significant changes in *CBL* mutant

variant allele frequencies observed thus far. With a median follow up of 3.1 months (range 1-12 months), the median response duration is 2.1 months (range 0.5-6.3 months) and the median OS has not been reached with all patients alive at the time of evaluation. A total of 3 patients (50%) have stopped the treatment: 1 patient due to disease relapse, 1 due to progression and the other to proceed to allogenic stem cell transplantation after achieving response to therapy. No dose limiting toxicities (DLT) have been observed to date up to the maximum dose of 40 mg of quizartinib. One patient required dose reductions due to cytopenias with the rest of the patients having recovery of counts to pre-treatment levels. Regarding the grade 3 or more adverse events (AEs): Two patients (33%) had skin infection, one patient (17%) had cardiac arrythmia with Mobitz II AV block and one patient (17%) had lumbar epidural lesion most likely of infectious origin. Conclusion: Preliminary data suggest azacitidine in combination with quizartinib for patients with MDS and MDS/MPN with *FLT3* or *CBL* mutations have acceptable toxicity profile and associated with promising responses. Further follow up with a larger patient cohort are required to emphasize the safety and efficacy of this combination and evaluate depth and duration of response.

Citation: Abuasab, T., Jabbour, E. J., Short, N. J., Konopleva, M., Chien, K. S., Mohamed, S. F., Daver, N., Kanagal-Shamanna, R., Kantarjian, H., Garcia-Manero, G., & Montalban-Bravo, G. (2021). Initial Results of Phase I/II Study of Azacitidine in Combination with Quizartinib for Patients with Myelodysplastic Syndrome and Myelodysplastic/Myeloproliferative Neoplasm with FLT3 or CBL Mutations. *Blood, 138*, 1536.

Phase II Study of Cladribine, Idarubicin, Cytarabine (CLIA) Plus Gilteritinib in Patients with FLT3 Mutated Acute Myeloid Leukemia (AML)

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Abstract

Background: Addition of the FLT3 inhibitor midostaurin to intensive chemotherapy is the standard of care for newly diagnosed *FLT3*-mutated AML. Gilteritinib is a 2nd generation FLT-3 inhibitor approved for patients with relapsed/refractory (R/R) *FLT3*-mutated AML. We studied the combination of gilteritinib with a higher-dose araC-based regimen of Cladribine, Idarubicin, Cytarabine (CLIA) in patients with *FLT3*-mutated AML.

Methods: Patients aged 18-65 years, fit for intensive chemotherapy, with newly diagnosed *FLT3*-mutated AML were enrolled. Induction was: Cladribine 5 mg/m ^{2} IV on days 1-5, Cytarabine 1.5-2.0 g/m ^{2} IV on days 1-5, Idarubicin 10 mg/m ^{2} IV on days 1-3 and gilteritinib on days 1-14. Consolidation consisted of up to 5 more cycles of CLIA: cladribine 5 mg/m ^{2} IV on days 1-3, Cytarabine 750 mg/m ^{2} IV on days 1-3, and idarubicin 8 mg/m ^{2} IV on days 1-2 with gilteritinib 120 mg continuously during cycle 2 onward. An additional cohort studied the addition of venetoclax CLIA + gilteritinib. In this cohort, venetoclax was added days 1-7 of each cycle at a target dose of 400mg daily, with dose adjustments for concomitant CYP3A inhibitors.

Results**:** Eighteen patients were enrolled, with a median age of 56 years (range, 39-63). 15 pts (83%) had *FLT3*-ITD, 5 pts (27%) had *FLT3* D835, and 2 pts (11%) had both. The median allelic ratio of *FLT3*-ITD was 0.36 (0.06-1.45) and of *FLT3* D835 was 0.15 (.05-.084 Patient characteristics and outcomes are outlined in TABLE 1. Fifteen patients (83%) had diploid cytogenetics, one patient with -5, one with trisomy 8, one with Inv (16) and one patient with complex karyotype. The most commonly co-occurring mutations were: *NPM1* (67%), *TET2* (33%), *ASXL1* (33%), and *DNMT3A* (33%), *KDM6A* (27%).

Ten patients (56%) received CLIA + gilteritinib and 8 patients (44%) received CLIA + gilteritinib + venetoclax. 13 out of 18 pts (72%) achieved complete remission (CR). The rate of CR / CRi was 83%, including 8/10 pts (80%) in the CLIA + gilteritinib cohort and 7/8 pts (88%) in the CLIA + gilteritnib + venetoclax cohort. The median number of cycles to response was one (x-y). Patients received a median of 2 cycles (1-3) of therapy on protocol.

The 4- and 8-week mortality rate was 6% (one patient in the venetoclax cohort, no early mortality with CLIA + gilteritinib). The most common adverse effects were: Neutropenic fever (12/18, 67%), Grade 2-3 ALT elevation in (3/18, 17%), grade 3 Headache (1/18, 6%) and grade 3 diarrhea (1/18, 6%).

The median time to neutrophil ≥ 0.5 K/uL was 33 days (26-40) and 38 days (30-40) for the CLIA-gilteritinib and CLIA-gilteritinib-venetoclax cohorts. The median time to neutrophil ≥ 1 K/uL was 36.5 days (26-48) and 40 days (31-45) for the CLIA-gilteritinib and CLIA-gilteritinib-venetoclax cohorts, respectively. The median time to platelet ≥ 100 K/uL was 34.5 days (24-48) and 40 days (34-45) for 2 cohorts, respectively.

Twelve of fifteen responding patients (80%) had undetectable minimal residual disease (MRD) tested by multiparameter flow cytometry by the time of response: 7/8 (88%) of the CLIA + Gilteritinib cohort and 5/7 patients (71%) of the CLIA + gilteritnib + venetoclax. Additionally, 13/15 patients (87%) had no detectable FLT3 mutation by PCR at time of response (7/8 patients (88%) of the CLIA + Gilteritinib cohort and 6/7 patients (86%) of the CLIA + gilteritnib + venetoclax cohort).

The median overall survival for the entire cohort was 21.95 months (not reached for the CLIA + gilteritnib cohort and 22.4 months for the CLIA + gilteritnib+ venetoclax cohort) (Figures 1 and 2). Eleven of the 15 responding patients (73%) underwent to allogenic stem cell transplantation in CR1 (7 and 4 patients in the CLIA + gilteritnib and the CLIA + Gilteritinib + venetoclax cohort respectively).

Conclusion: The combination of the FLT3 inhibitor gilteritinib to CLIA produced high rates of complete remission in patients with newly diagnosed FLT3-mutated AML. The addition of venetoclax to the backbone was associated with similar outcomes but prolonged count recovery. The combination resulted in high rates of MRD negativity by flow and molecular testing at the time of response. Further study of the combination of CLIA + gilteritinib in fit patients with newly diagnosed FLT3-mutated AML patients is planned.

Citation: Abuasab, T., Kantarjian, H., Garcia-Manero, G., Montalban-Bravo, G., Alvarado, Y., Yilmaz, M., Pemmaraju, N., Chien, K. S., Mohamed, S. F., Daver, N., Kornblau, S. M., Burger, J. A., Jain, N., Islam, R., DiNardo, C. D., Borthakur, G., Ravandi, F., & Kadia, T. M. (2021). Phase II Study of Cladribine, Idarubicin, Cytarabine (CLIA) Plus Gilteritinib in Patients with FLT3 Mutated Acute Myeloid Leukemia (AML). *Blood, 138*, 2330.

First Case of Association between Autoimmune Autonomic Ganglionopathy (AAG) and Myeloproliferative Neoplasms (MPNs)

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Abstract

Introduction: Autoimmune autonomic ganglionopathy (AAG) is a rare disease that presents with different autonomic symptoms and positive autoantibodies against the ganglionic acetylcholine receptor (gAChR) in 50 % of the cases. Eighty percent of seropositive patient has extra-autonomic manifestations. Extra-autonomic manifestations include sensory disturbance, central nervous system involvement, endocrine disorders autoimmune diseases, and cancers. It has been reported with various malignancies, such as small lung cancer, thymoma, ovarian tumors and others.

Method: We report a case from MD Anderson cancer center (MDACC) and to our knowledge it is first case in literature of a patient Autoimmune autonomic ganglionopathy associated with primary myelofibrosis

Result: A 55-year-old African American male diagnosed with JAK2 V617F positive primary myelofibrosis in 2005 and placed on observation until September 2012 when he was referred to MDACC for further management. He was started on protocol with Ruxolitinib + lenalidomide and did well initially, but during the course of treatment, he started to experience leg weakness. Initially in the left leg and then the right leg. lenalidomide was placed on hold and in April 2015, ruxolitinib was held as well. On examination he has left leg weakness in addition to weak hand grip on the same side.

On Further evaluation, he was diagnosed with inclusion body myositis after muscle biopsy He was then lost to follow up and followed with outside hematologist

In February 2020, he developed cytopenias and was referred back to MDACC for management. He was seen and we performed a bone marrow shortly thereafter. He continued to have PMF, molecular, cytogenetics could not be performed on bone marrow due to dry tap. Patient started on "investigational agent. In early 2021 patient started to have orthostatic hypotension and syncope. Serum paraneoplastic antibody panel revealed acetylcholine Receptor Gang Neuronal Ab.The above finding along with his automimic symptoms consists with diagnosis of autoimmune autonomic ganglionopathy.

Conclusion: Autoimmune autonomic ganglionopathy (AAG) with extra-autonomic manifestations is a very rare and not well known. It is reported before to be associated with solid malignancy, we describe here first association with hematological malignancy which is primary myelofibrosis. We aim

to add this to literature, and to increase the knowledge and awareness of both hematologists and neurologists about this association and possible other hematological malignancies may be reported in the future

Citation: Mohamed, S. F., Hadad, F., Abuasba, T., Verstovsek, S., & Harrison, R. (2021). First Case of Association between Autoimmune Autonomic Ganglionopathy (AAG) and Myeloproliferative Neoplasms (MPNs). *Blood, 138*, 4629.

Characteristics and Outcomes of Adult Patients with Malignancy-Associated Hemophagocytic Lymphohistiocytosis: A Single-Center, Prospective Analysis

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Abstract

Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome characterized by sustained immune overactivation and dysregulation. Malignancy-associated HLH (M-HLH) is associated with particularly dismal outcomes, likely perpetuated by inflammation from neoplastic cells, as well dysfunctional immune regulation secondary to the underlying malignancy and/or chemotherapy, infection, immunotherapies, or hematopoietic stem cell transplantation.

Methods: We retrospectively reviewed patients (pts) aged ≥ 18 years with an underlying hematological malignancy (HM) who fulfilled ≥5 HLH-2004 criteria at our institution between 2011 - 2020. High risk disease for the underlying HM was defined according to WHO Risk stratifications.

Results: Forty-seven pts were diagnosed with M-HLH with a median age of 61 years (range, 19-81), 32 (68.1 %) were male, and most were Caucasian (87.3%). The underlying malignancy was myeloid in 70% and lymphoid in the rest. HLH was diagnosed during active malignancy in 33 (70%), malignancy in remission in four (8%), and during or after relapse in 10 (21%) pts. Table 1

The median (med) time from diagnosis of HM to HLH manifestations was 7.5 months (m) (range, 0 - 177). HLH preceded an overt diagnosis of HM in 4 cases (all 4 eventually diagnosed with AML and MDS). Forty pts (85%) had received prior treatment for their HM. Three pts were diagnosed with HLH 2.0m, 4.0m, and 7.5m following ASCT, while their HM was in remission. The median number of fulfilled HLH criteria in these 47 pts was 6 (range, 5-8): 33 (71%) pts met 5-6 variables and 14 (29%) met 7-8 criteria. At the time of HLH diagnosis, high-grade fever and splenomegaly were present in 44 (93%) and 27 (57%) pts, respectively. All pts had serum ferritin >500 ng/mL at HLH diagnosis with a med of 56,707ng/mL (range, 3,059 - 47,1540); 30 (76.5%), 24 (51%), 14 (29%), and 9 (20%) patients had serum ferritin >10,000 ng/mL, >25,000 ng/mL, >50,000 ng/mL, and >100,000 ng/mL, respectively at diagnosis. Serum triglyceride (TG) level was 318 mg/dL (range, 8.6 - 971) and 64% of evaluable pts had elevated serum TG at diagnosis. Similarly, the plasma fibrinogen level at diagnosis was 241 mg/dL (range, 27 - 702). Of the 32-pts tested, the sIL2r level was 7010 U/mL (range, 749-

127,000) and 72% had elevated sIL2r levels at diagnosis. NK function was decreased in 12 (66.6%) of 18 evaluated pts. Based on bone marrow, spleen, and/or liver assessments, hemophagocytosis was seen in 18 (43%) of pts. Table 2Mutation panels and were negative in (15 patients, 31.9%). The most common mutation identified was TP53 (7, 14.9%) patients.

We compared outcomes of pts who received etoposide and dexamethasone (DE) with those who received etoposide, dexamethasone, and tocilizumab (DET.) High-risk HM was observed in 13 of 17 pts treated with (DE) and in all 19-pts treated with (DET) (P=0.02). Of the 47 treated pts, seven (14.9%) had complete response, nine (19%) had PR and 31 (66%) did not respond. Eight of the 18 pts who received DE had either CR or PR, compared with five of 19 treated with DET (P=0.3133).

Thirty-eight of the 47 pts have died. With a median follow-up of 8.8m (95% CI, 4.43 - NR), the estimated med OS was 0.95m (95% CI, 0.59-3.25) with a 1-year survival probability of 16.6% (95% CI, 7.91%-34.6%. Patients with lymphoid malignancies had improved OS (95%CI, 0.1865-0.9092, P=0.027,) Fig 1. Pts with CR/PR response had improved OS compared with non-responders (95% CI, 0.1377-0.6664) P=0.03). Pts with ferritin <50,000 had better OS than those with higher ferritin (95% 1.0245-4,004, P=_0.04_) and IL_10 was associated with a higher risk of death (HR=1.0008, p=0.0443).

The OS was higher in patients treated with DE compared with DET, (95%CI,1.1407-5.3375, P=0.02) Fig 2. DET group had higher proportion of high-risk disease, admitted more to the ICU, more use of pressor and increase in length of stay. Table 3

Conclusion: M-HLH remains a highly fatal disease with a 1-year survival <20% despite therapy. In our report, etoposide-based therapies with or without malignancy-directed therapy induced a response in only about 35% of pts and achieving a response improved survival. The OS was improved in patients treated with (DE), with lymphoid malignancies and those with ferritin level less than 50,000 (P=0.04). The implementation of adult specific HLH programs and multidisciplinary collaboration are required to foster directed clinical guidelines and improve outcomes.

Citation: Mohamed, S. F., Assi, R., Ning, J., Xiao, L., Jabbour, E. J., Pemmaraju, N., Kadia, T. M., Jain, N., DiNardo, C. D., Yilmaz, M., Maiti, A., Issa, G. C., Short, N. J., Bose, P., Masarova, L., Garcia-Manero, G., Ravandi, F., Konopleva, M., & Daver, N. (2021). Characteristics and Outcomes of Adult Patients with Malignancy-Associated Hemophagocytic Lymphohistiocytosis: A Single-Center, Prospective Analysis. *Blood,* 138, 1213.

General Characteristics and Association of Myeloid Neoplasm with Thyroid Cancer

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Abstract

Introduction: Differentiated thyroid cancer (DTC) is the most common endocrine malignancy. Treatment options include surgery, radioiodine & hormonal therapy. Radioiodine therapy (RAI) is often used after surgery with the purpose of ablation of residual thyroid tissue, adjuvant therapy or clinically evident metastatic disease. However, the use of RAI carries a risk of secondary malignancies, such as leukemias.

The 10-yr survival rate of patients with DTC > 90%. However, several studies showed those patients may be at risk for secondary cancers.

Therapy related myeloid neoplasm (tMN) can develop after RAI exposure.

The relationship between thyroid and myeloid neoplasm (MN) may not be fully explained by exposure to RAI.

In this retrospective study, we investigated the association between MN & DTC.

Methods: This study included patients >18years with DTC and either MN ((Acute Myeloid Leukemia (AML), Myelodysplastic syndrome (MDS), Chronic myelomonocytic leukemia (CMML), or Myeloproliferative Neoplasms (MPN) who had been diagnosed and/or treated at UTMD Anderson Cancer Center from 1/2012-12/2020

Descriptive statistics were performed to define the demographic, clinical and biological characteristics of the patients included in the study.

Results: Fifty-four pts had both DTC and MN. The median age was 52 yrs (18-77). Most of the patients were white 41/54 (75.9%) with equal sex distribution and of the papillary subtype of DTC 48 (88.8%). DTC stages were I (15(42.86%), II -15 (42.86%) III & IV- 5 cases (14.29%). Of the MN patients, AML/MDS cases were 30 (56.36%), while MPNs cases were 24(43.64%). Majority were CML 13/24 (54%) (p =0.01). The most common cytogenetics karyotypes detected were diploid in 17 (30.91%) followed by complex in 8 patients (14.55%). The most frequent positive mutation was FLT3 in 6 cases (10%) followed by TP53 and ASXL1 with 5 (9.26%) patients respectively. While the mutation panel were negative in 16 patients (29.63%).

RAI was used in 42(76.36%) patients, with a median dose 142 mCi (75-290). Thirty patients (70%) of those treated with RAI developed therapy related MN, while 12 patients had MN earlier occurred first in 34 patients (61.82%) (proceeded AML/MDS in 23 (74.19%) and 11(45.83%) (P= 0.005) in cases of MPNs. The median time lapse from developing thyroid to myeloid cancer was 4 years. Thyroid cancer proceeded AML or MDS by 2.5 years, while thyroid cancer happened around the same year (0.09) with MPNs (p= 0.04) Table 1

A hypomethylating agent (HMA) based therapy for myeloid neoplasm was the most commonly used in 15 (42.86%), other therapies included cytarabine (5), cladribine (4) & fludarabine (3) based .37 pts (67.27 %) achieved complete remission, while 18 (32.73%) underwent stem cell transplantation.

Overall survival showed that 40 (74%) were still alive. Therapy related AML/MDS Overall survival were inferior to non-therapy related patient (p= 0.29) figure 1. Patients who had 3 or 4 types of cancer to the group who had only thyroid and myeloid cancer showed increase risk of death with a hazard ratio of 1.72 (0.62-4.77 however this was not statistically significant also (p= 0.30).

Conclusion: In our cohort patients who were exposed to Radioiodine (RAI) had developed therapy related myeloid neoplasm (t-MN) AML/MDS even with doses < 100 mCi. Median to develop neoplasm (t-MN) were 4 years, complex cytogenetics is frequent. No statistically significant difference in survival between therapy related and none therapy related group. DTC did occur with MPNs as well with CML most frequent subtype. Prospective studies need to be done to further elucidate the relationship between DTC & MPN.

Citation: Mohamed, S. F., Pemmaraju, N., Sasaki, K., Borthakur, G., Abuasba, T., Khan, M., Hwang, H., Wang, X., Verstovsek, S., & Busaidy, N. (2021). General Characteristics and Association of Myeloid Neoplasm with Thyroid Cancer. *Blood, 138*, 4634.

Disease Characteristics of Multiple Myeloma Involving BRAF Mutations

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Abstract

Introduction: In multiple myeloma (MM), the RAS-RAF-MEK-ERK pathway plays a key role in regulation of cell growth, differentiation, proliferation, and cell death. The BRAF gene, located on chromosome 7, is the most potent component of the RAF group, and usually involves missense mutations clustered in exons 11 and 15.

In this retrospective study, we investigated the prevalence of BRAF mutations in MM, the clinical and pathological significance of these mutations, and whether these BRAF mutations occur as initial or acquired mutations.

Methods: Patient data was retrieved from the clinical database of patients with MM who had been diagnosed and/or treated at The University of Texas MD Anderson Cancer Center during January 2015 through December 2020. To be included, participants had to be aged >18 years, have been diagnosed with MM, and have a positive BRAF mutation, identified using an 81-gene panel that had been performed on their bone marrow samples.

The primary outcome variable was overall survival (OS) time. The secondary outcome variable was progression-free survival (PFS). Patients were classified as sustained when repeat bone marrow in relapse or refractory patient showed a persistent BRAF mutation, and as non-sustained when repeat bone marrow in relapse or refractory patient did not have a persistent BRAF mutation.

Results: Of the 22 patients in our study, most were men (73%), and the median age at diagnosis, for all patients, was 66 years (range, 28-79 years). Half of patients (50%) had a monoclonal immunoglobulin G as part of their MM, while 9 (40.9%) patients had monoclonal immunoglobulin A MM. Most patients (68.4%) had stage III disease.

For BRAF mutation, only 3 (13.6%) patients had the V600E variant, and 5 (22.7%) had the G469A variant which was the most common. Other prominent variants were D594N (13.6%), G466A (9.1%), and G466E (9.1%). Of the 11 patients who had a sustained BRAF mutation, 8 (72.7%) patients had remission after first-line therapy, and 9 underwent an autologous stem cell transplant.

Seven patients (31.8%) had only a BRAF mutation. Other commonly mutated genes were KRAS in

5 (22.7%), DNMT3A in 4 (18.2%), NRAS in 4 (18.2%), and TP53 in 3 (13.6%). We found that exon 11 (72.7%) was more frequently affected than exon 15 (27.3%). The most common chromosomal change was diploid (30.0%), and complex in 6 patients (30.0%).

Complete response was achieved in 7 (31.8%) patients, a partial response was seen in 8 (36.4%) patients, and 4 (18.2%) patients had stable disease. Overall, 14 (63.6%) patients underwent an autologous stem cell transplant.

The median follow-up time was 45.5 months (range, 12.0-280.9 months), and the median survival time was 72.7 months (95% CI, 29.7 months-not reached). The 5-year OS rate was 52.3% (95% CI, 0.337-0.811). For patients with sustained BRAF mutations and patients without a sustained BRAF mutations, the 5-year OS rates were 77.8% (95% CI, 54.9%-100.0%) and 27.8% (95% CI: 8.9%-86.9%), respectively. In univariable analysis, patients in whom BRAF was not sustained had marginally significantly poorer OS (HR, 4.20; 95% CI, 1.01-17.39; P=0.048).

The median PFS time was 16.6 months (95% CI, 11.2-44.5 months), and the 5-year PFS rate was 14.3% (95% CI, 5.0%-40.7%). On univariate analysis, we observed significantly worse PFS rates in patients who had initial disease (HR, 2.84; 95% CI, 1.05-7.68; P=0.049), did not have sustained BRAF mutations (HR, 2.74; 95% CI, 0.98-7.69; P=0.037), or achieved stable disease (HR, 6.82; 95% CI, 1.51-30.73; P=0.012). Patients who achieved remission after first-line therapy (HR, 0.14; 95% CI, 0.04-0.49; P=0.002) had significantly better PFS.

Conclusion: In our study, patients with sustained BRAF mutations versus those who did not have sustained BRAF mutations, had higher 5-year OS rates (77.8% vs. 27.8%); and had better 5-year PFS rates, 27.3% versus all patients showing progression within 3 years.

We have shown that the loss of BRAF mutations negatively affects patient outcomes and survival. However, the small size of our study limits the generalizability of our results to BRAF mutation-positive MM. We encourage other studies to assess the prognostic value of BRAF mutations in MM, and recommend the use of a routine panel to check for BRAF mutations in order to appropriately adjust therapy for such MM patients. Also, despite the low incidence of BRAF-mutated MM, more trials are needed to accurately evaluate the response to BRAF-targeting therapy.

Citation: Mohamed, S. F., Khan, M., Quesada, A., Ma, J., Lin, P., Yin, C. C., Sasaki, K., Borthakur, G., Pemmaraju, N., Bashir, Q., Qazilbash, M. H., Kaufman, G. P., & Becnel, M. R. (2021). Disease Characteristics of Multiple Myeloma Involving BRAF Mutations. *Blood, 138*, 4755.

TCL-309: Prognostic Role of CD30 From a Retrospective Review of 295 Patients with Angioimmunoblastic T-Cell Lymphoma

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Abstract

Objective:The main aim of this single-institution retrospective study was to elucidate the prognostic significance of CD30 expression in AITL.

Methods: We analyzed patients newly diagnosed with AITL at our institution between 2000 and 2020. Along with CD30 receptor testing, variables, including date of diagnosis, age, gender, stage, LDH level, platelets, hemoglobin, bone marrow involvement, and EBV receptor positivity, were collected. Treatment and progression data, including response to frontline therapy, presence of consolidation stem cell transplant (SCT), and usage of brentuximab-based treatment, were collected. Endpoints were progression-free survival (PFS) and OS. Univariate (UVA) and multivariate (MVA) Cox proportional hazard models were used to determine the significance of variables at diagnosis on PFS and OS.

Results: Out of the 295 individuals diagnosed with AITL, 129 patients with CD30 testing who had both response and survival data were included. This group had a median age of 65 (range 29–83) years and a male predominance (51%). Median follow-up time was 40 (range 2–137) months, with three-year PFS and OS of 48% and 23%, respectively. Sixty-seven individuals died within the first three years of the study. The 3-year OS is 46% in CD30+ individuals and 55% in those who are CD30– (p=0.578). PFS is 20% in CD30+ individuals and 29% in those who are CD30– (p=0.675). SCT (p=0.0003) was statistically associated with improved survival. For OS, age >65 (HR: 3.131, 95%CI: 1.545–6.344, p=0.0015), BM involvement (HR: 2.134, 95% CI: 1.151–3.956, p=0.0161), incomplete remission (HR: 2.208, 95% CI: 1–4.876, p=0.0499), male gender (HR: 0.367, 95% CI: 0.199–0.678, p=0.0014), no SCT (HR: 4.085, 95% CI: 2.119–7.872, p≤0.0001), and positive CD30 (HR: 0.322, 95% CI: 0.158–0.656, p=0.0018) were associated with inferior OS.

Conclusion: Age <65, achieving CR to induction treatment, and upfront SCT proved to be strong predictors of improved OS. In our cohort, only 20% of patients received BV; nevertheless, unlike previous studies, individuals with CD30 positivity did not trend towards better OS. Therefore, additional work on CD30 biology in AITL is warranted.

Citation: Mohamed, S., Parrish, J., Khan, M., Premji, S., Elias, A., Malpica, L., Nair, R., Chihara, D., Srour, S., Miranda, R., Xu, J., Vega, F., & Iyer, S. (2021). TCL-309: Prognostic Role of CD30 From a Retrospective Review of 295 Patients with Angioimmunoblastic T-Cell Lymphoma. *Clinical Lymphoma Myeloma and Leukemia, 21*, S414. https://doi.org/10.1016/S2152-2650(21)01930-3

ABCL-312: Survival Outcomes of Primary Intraocular Lymphoma

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Abstract

Objectives: To report the clinical presentation, treatment, and outcome of patients diagnosed with primary intraocular lymphoma (PIOL) at a single institution in the time period between July 1996 and December 2020.

Materials and Methods**:** We identified 38 patients who were consecutively diagnosed or seen between 1996 and the present and had pathology-confirmed PIOL. Data regarding initial presentation, staging, treatment, progression, and survival were collected and analyzed for trends related to survival.

Results: In our cohort of 38 patients, the mean age is 65 years, although it is not limited by age and can present in other age groups. Most patients (33 cases, 85%) were diagnosed with vitrectomy. At initial presentation, bilateral eye involvement was present in 11/38 cases (25%), progression to the CNS was present in 10 cases (23%), and 4 patients had CSF involvement (37 had CSF evaluation; therefore, 9% of those evaluated, 5 patients had atypical CSF results). Thirty-five (80%) patients had B-cell lymphomas and 20% T-cell lymphomas. Tumors commonly expressed B-cell markers (CD20, PAX5, CD19, or/and CD79). Twenty-nine patients were treated with ocular targeted external beam radiation or whole-brain radiation (66%). Methotrexate-based systemic plus intrathecal regimen with an average of 3.5 cycles was given to 33 patients (75%). Although 19 patients (47%) achieved complete remission after first-line therapy, 17 relapsed (39%) and received second-line treatment, and 3 received third-line therapy, which includes chemotherapy with or without radiation. Those who relapsed were less likely to have undergone radiation and methotrexate chemotherapy. Of the 38 patients, 30 (76%) underwent autologous stem cell transplant. The overall survival is 75% (29 patients), while progression-free survival is 41% (16 patients), with a median follow-up of 49.7 months.

Conclusion: PIOL remains a rare disease, which, in opposition to its scarcity, has a poor prognosis, being potentially fatal. The use of ocular radiotherapy, combined with HD MTX-based systemic chemotherapy, has become the mainstay of ocular lymphoma treatment, highlighting the highly therapeutic effects through significantly improved patient outcomes. Prospective studies are needed to improve outcomes in this rare disease.

Citation: Mohamed, S., Khan, M., Parrish, J., Barrios, P. C., Dabaja, B., Fowler, N., Gombos, D., Feng, L., & Iyer, S. (2021). ABCL-312: Survival Outcomes of Primary Intraocular Lymphoma. *Clinical Lymphoma Myeloma and Leukemia, 21*, S389-S390. https://doi.org/10.1016/S2152-2650(21)01886-3

NON-MALIGNANT HEMATOLOGY

Original Articles

The Prevalence of glucose dysregulations (GDs) in patients with β-thalassemias in different countries: A preliminary ICET-A survey

Vincenzo De Sanctis [1], Ashraf Soliman [2], Ploutarchos Tzoulis [3], Shahina Daar [4], Antonis Kattamis [5], Polyxeni Delaporta [5], Mohamed A Yassin [6], Mehran Karimi [7], Duran Canatan [8], Soad Al Jaouni [9], Maria Concetta Galati [10], Giuseppe Raiola [11], Giuseppe Messina [12], Saveria Campisi [13], Forough Saki [14], Dulani Kottahachchi [15], Valeria Kaleva [16], Kristina Petrova [16], Atanas Banchev [17], Christos Kattamis [18]

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Citation: De Sanctis V, Soliman A, Tzoulis P, Daar S, Kattamis A, Delaporta P, Yassin MA, Karimi M, Canatan D, Al Jaouni S, Galati MC, Raiola G, Messina G, Campisi S, Saki F, Kottahachchi D, Kaleva V, Petrova K, Banchev A, Kattamis C. The Prevalence of glucose dysregulations (GDs) in patients with β-thalassemias in different countries: A preliminary ICET-A survey. *Acta Biomed.* 2021 Jul 1;92(3):e2021240.

Impact Factor: 3.79

Efficacy and cost effectiveness of intravenous ferric carboxymaltose versus iron sucrose in adult patients with iron deficiency anaemia

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Abstract

Background: Iron deficiency anaemia (IDA) is a major health issues and common type of nutritional deficiency worldwide. For IDA treatment, intravenous (IV) iron is a useful therapy.

Objective: To determine the efficacy and cost-effectiveness (CE) of intravenous (IV) Ferric Carboxymaltose (FCM) versus IV Iron Sucrose (IS) in treating IDA.

Data sources: Electronic medical record i.e. Cerner® system.

Target population: Adults patients with iron deficiency anaemia.

Time horizon: A 12-month period (01/01/2018-31/12/2018).

Perspective: Hamad Medical Corporation (HMC, a public hospital).

Intervention: IV Ferric Carboxymaltose versus IV Iron Sucrose.

Outcome measures: With regard to responses to treatment i.e., efficacy of treatment with FCM & IS in IDA patients, hemoglobin (Hgb), ferritin, and transferrin saturation (TSAT) levels were the primary outcomes. Additionally, the researchers also collected levels of iron, platelet, white blood cell (WBC),

red blood cell (RBC), mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV). The costs i.e. resources consumed (obtained from NCCCR-HMC) and the CE of FCM versus IS were the secondary outcomes.

Results of base-case analysis: There was a significant improvement in Hgb, RBC and MCH levels in the IS group than the FCM group. The overall cost of IS therapy was significantly higher than FCM. The medication cost for FCM was approximately 6.5 times higher than IS, nonetheless, it is cheaper in terms of bed cost and nursing cost. The cost effectiveness (CE) ratio illustrated that FCM and IS were significantly different in terms of Hgb, ferritin and MCH levels. Further, Incremental Cost Effectiveness Ratio (ICER) indicated that further justifications and decisions need to be made for FCM when using Hgb, iron, TSAT, MCH and MCV levels as surrogate outcomes.

Results of sensitivity analysis: Not applicable.

Limitations: The study did not consider the clinical or humanistic outcome.

Conclusions: The higher cost of FCM versus IS can be offset by savings in healthcare personnel time and bed space. ICER indicated that further justifications and decisions need to be made for FCM when using Hgb, iron, TSAT, MCH and MCV levels as surrogate outcomes.

Citation: Basha A, Ibrahim MIM, Hamad A, Chandra P, Omar NE, Abdullah MAJ, Aldapt MB, Hussein RM, Mahfouz A, Adel AA, Shwaylia HM, Ekeibed Y, AbuMousa R, Yassin MA. Efficacy and cost effectiveness of intravenous ferric carboxymaltose versus iron sucrose in adult patients with iron deficiency anaemia. *PLoS One.* 2021 Aug 10;16(8):e0255104

Impact Factor: 3.752

Red blood cell derived extracellular vesicles during the process of autologous blood doping

S C Voss [1], M Yassin [2], J C Grivel [3], S Al Hmissi [2], N Allahverdi [2], A Nashwan [2], Z Merenkov [2], M Abdulla [2], A Al Malki [2], C Raynaud [3], W Elsaftawy [1], A Al Kaabi [1], F Donati [4], F Botre [4], V Mohamed Ali [1 5], C Georgakopoulos [1], M Al Maadheed [1 5]

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Abstract

The purpose of this pilot study was to investigate the effects of the transfusion of one erythrocyte concentrate on the number of circulating red blood cell extracellular vesicles (RBC-EVs) and their clearance time. Six, healthy volunteers donated their blood and were transfused with their RBC concentrate after 35-36 days of storage. One K_2 EDTA and one serum sample were collected before donation, at four timepoints after donation and at another six timepoints after transfusion. RBC-EVs were analyzed on a Cytek Aurora flow cytometer. A highly significant increase ($p < 0.001$) of RBC-EVs from an average of 60.1 ± 19.8 (10^3 /µL) at baseline to 179.3 ± 84.7 (10^3 /µL) in the first 1-3 h after transfusion could be observed. Individual differences in the response to transfusion became apparent with one volunteer showing no increase and another an increased concentration at one timepoint after donation due to an influenza infection. We concluded that in an individualized passport approach, increased RBC-EVs might be considered as additional evidence when interpreting suspicious Athletes Biological Passport (ABPs) but for this additional research related to sample collection and transport processes as well as method development and harmonization would be necessary.

Keywords: biomarker; blood doping; extracellular vesicles; flow cytometry; transfusion.

Citation: Voss SC, Yassin M, Grivel JC, Al Hmissi S, Allahverdi N, Nashwan A, Merenkov Z, Abdulla M, Al Malki A, Raynaud C, Elsaftawy W, Al Kaabi A, Donati F, Botre F, Mohamed Ali V, Georgakopoulos C, Al Maadheed M. Red blood cell derived extracellular vesicles during the process of autologous blood doping. *Drug Test Anal.* 2021 Aug 28.

Impact Factor: 3.234

NON-MALIGNANT HEMATOLOGY

Case Reports

Case report of active pulmonary TB in a sickle cell disease patient

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Abstract

Both Sickle cell disease (SCD) and Tuberculosis (TB) are prevalent, and mostly concentrated in similar geographic areas. Since there is an overlap of the possible presenting symptoms of SCD complications and TB, a low threshold for suspicion of TB in these patients is recommended. We present a case of an active TB infection in a SCD patient that presented mainly with chronic cough.

Keywords: Cavities; Pulmonary; SCD, Sickle cell disease; Sickle cell disease; TB, Tuberculosis; Tuberculosis.

Citation: Okar L, Rezek M, Abdelhamid MT, Yassin MA. Case report of active pulmonary TB in a sickle cell disease patient. *Ann Med Surg (Lond).* 2021 Nov 16;72:103073.

Impact Factor: 1.75

Use of rivaroxaban in sickle cell disease and venous thromboembolism: A case report

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Abstract

Introduction: Sickle cell disease (SCD) is a hematological disorder characterized by sickling of red blood cells. Patients are at increased risk of venous thromboembolism. There are no guidelines for the management of venous thromboembolism in sickle cell disease specifically in terms of the anticoagulant of choice.

Patient concerns: Here, we report a case of a 30-year-old lady with past medical history of sickle cell disease who came with chest pain and shortness of breath.

Diagnosis: We found that she has bilateral pulmonary embolism (PE).

Intervention: She was started on rivaroxaban.

Outcome: The patient was followed for 18 months, she did not suffer from recurrence of PE, and she did not develop any complications related to rivaroxaban.

Conclusion: We concluded that rivaroxaban is effective in treating PE in sicklers and also it is safe.

Citation: Rozi W, Ali EAH, Al-Mashdali AF, Abdelrazek M, Yassin MA. Use of rivaroxaban in sickle cell disease and venous thromboembolism: A case report. *Medicine (Baltimore).* 2021 Dec 23;100(51):e27988.

Impact Factor: 1.74

Eltrombopag Dose Adjustment During Infection-Induced Thrombocytosis in a Patient with Chronic Idiopathic Thrombocytopenic Purpura

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Abstract

Idiopathic thrombocytopenic purpura (ITP) is an immune disorder in which antibodies attack platelets, leading to platelet destruction and increased bleeding risk. Standard treatment is to maintain a platelet count sufficient to mitigate the bleeding risk. First-line therapies include steroids and IV immunoglobulins, and second-line therapy includes thrombopoietin receptor agonists like eltrombopag in combination with other medications (e.g., rituximab) to reduce immune attack. Eltrombopag is a nonpeptide oral thrombopoietin (TPO)-receptor agonist that increases platelet counts by binding to and activating the human TPO receptor. While using eltrombopag, the target platelet count range is usually between 50,000/mm³ and 200,000/mm³, so the dose should be adjusted accordingly. However, this dose adjustment is based on platelet count increments in response to eltrombopag administration. Adjusting the dose when the platelet count is elevated due to a different factor can be challenging. Data are not yet available on whether stopping the treatment or reducing the dose will harm the patient or result in an acute drop in platelet count and increased bleeding. We present the case of a 60-year-old woman with ITP on a stable eltrombopag regimen who completed an eltrombopag-free period after developing infection-induced thrombocytosis.

Keywords: eltrombopag; infection induced thrombocytosis; itp.

Citation: Ahmed M, Abdelmahmuod E, Ali EA, Yassin MA. Eltrombopag Dose Adjustment During Infection-Induced Thrombocytosis in a Patient With Chronic Idiopathic Thrombocytopenic Purpura. Cureus. 2021 Mar 29;13(3):e14166.

Impact Factor: 1.15

Rebound of platelet count in a patient with type 2 calreticulin-mutant essential thrombocythemia in the postpartum period: A case report

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Abstract

Introduction: Essential thrombocythemia (ET) is an uncommon myeloproliferative neoplasm. It is more common in females; 20% of them are below 40 years old. The optimal management of ET during pregnancy and postpartum periods is still not well established.

Patient concern: We report a case of a young lady with type 2 calreticulin-mutant ET who developed a marked rebound in her platelet count (reaching 2030 × 103/μL) 2 weeks after premature delivery of her baby (24th week of gestation). She was on Pegylated Interferon alfa 2-a during pregnancy (her platelet was around 500 × 103/μL during the second trimester), but she had stopped it on her own from the 20th week of gestation.

Diagnosis: Postpartum rebound of platelet count due to medication non-compliance.

Intervention and outcome: We resumed her regular Pegylated Interferon, and subsequently, her platelet count reduced dramatically within 4 weeks to an acceptable level (684 × 103 /μL).

Conclusion: The guideline is still not well-established regarding the optimal approach for postpartum rebound of platelet count in patients with ET. It is still unclear if the platelet count will fall spontaneously without intervention after the rebound phase. Further research is required to establish the optimal management of ET during the postpartum phase. This case emphasizes the importance of platelet count follow-up during the postpartum period and outlines our management approach in such cases.

Citation: Al-Mashdali AF, Yassin MA. Rebound of platelet count in a patient with type 2 calreticulin-mutant essential thrombocythemia in the postpartum period: A case report. *Medicine (Baltimore).* 2021 Nov 5;100(44):e27725.

Impact Factor: 1.15

Immune thrombocytopenia relapse post covid-19 vaccine in young male patient

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Abstract

Immune thrombocytopenic purpura (ITP) is a blood disorder in which antibodies coating platelets cause platelets destruction in the spleen with resultant low platelets count and an increased tendency for bleeding. Coronavirus disease 2019 (COVID-19) is an illness caused by SARS-COV2; it was first identified in December/2019; though it mainly affects the respiratory system, multisystemic complications are identified. Several ITP cases post mRNA SARS-CoV-2 vaccines were reported, and different pathophysiology theories about the underlying pathophysiology were discussed, but only a few ITP relapse cases have been reported so far. We present a 28-year-old Asian male, a known patient of ITP and in partial remission for eighteen months, who presented to the emergency department with ITP relapse (platelets count of 1 × 10^3 /μL), four days after receiving the second dose of Pfizer SARS-CoV-2 vaccine, which required treatment with intravenous immunoglobulins and dexamethasone. We further discuss the preferred approach in ITP patients who are willing to receive the COVID-19 vaccine.

Keywords: ITP; Pfizer vaccine; Relapse; SARS-CoV-2.

Citation: Qasim H, Ali E, Yassin MA. Immune thrombocytopenia relapse post covid-19 vaccine in young male patient. *IDCases.* 2021;26:e01344.

Impact Factor: 0.9

Concomitant autoimmune hemolytic anemia and pulmonary embolism associated with mild COVID-19: A case report

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Abstract

Despite its rarity, AIHA can be associated with COVID-19. It should be suspected in a patient with recent COVID-19 presenting with unexplained anemia.

Keywords: COVID-19; anemia; autoimmune hemolytic anemia; case report; pulmonary embolism.

Citation: Al-Mashdali AF, Ata YM, Yassin MA. Concomitant autoimmune hemolytic anemia and pulmonary embolism associated with mild COVID-19: A case report. *Clin Case Rep.* 2021 Oct 18;9(10):e04952.

Impact Factor: 0.532

Favism-induced methemoglobinemia in a G6PD deficient male with a subsequent hemolytic cascade, a therapeutic challenge: Case report and review of literature

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Abstract

The co- occurrence of acute hemolysis and methemoglobinemia secondary to favism in G6PD deficient individuals is rare. Identifying it promptly is of high clinical significance as treating methemoglobinemia (with methylene blue) can worsen hemolysis.

Keywords: fava beans, Favism, G6PD, glucose- 6-phosphate dehydrogenase, Hemolysis, methemoglobinemia

Citation: Ata F, Javed S, Muthanna B, Dakhlia I, Bint I Bilal A, Musa M, Uddin M, Yassin MA. Favism-induced methemoglobinemia in a G6PD deficient male with a subsequent hemolytic cascade, a therapeutic challenge: Case report and review of literature. *Clin Case Rep*. 2021 Feb 20;9(4):2048-2052.

Impact Factor: 0.532

Acute chest syndrome in sickle cell disease/HBE patient, A case report

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Abstract

The presented case will shed some light on one of the rarest complications of HBSE disease, which is acute chest syndrome, and will highlight the management of that complication.

Keywords: HBSE; acute chest syndrome; hemoglobin E; hemoglobin S; sickle cell disease.

Citation: Khamees I, Rozi W, Yassin MA. Acute chest syndrome in sickle cell disease/HBE patient, A case report. *Clin Case Rep.* 2021 Aug 21;9(8):e04575.

Impact Factor: 0.532

Low back pain in beta thalassemia major revealing sacral extramedullay hematopoeisis: A case report

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Abstract

Extramedullary hematopoiesis (EMH) is a well-known complication of beta thalassemia major and frequently occurs in typical sites such as liver or spleen. However, when presenting in unusual sites as sacrum, other diagnosis should be excluded by histopathology prior to deciding on treatment plan.

Keywords: beta thalassemia; extramedullary hematopoiesis; low back pain; thalassemia.

Citation: Ahmad RW, Okar LA, Elhiday A, Almasri H, Ata F, Ahmed Mounir E, Barah A, Abdelrazek M, Gamil A, Sharaf Eldean MZ, Yassin MA. Low back pain in beta thalassemia major revealing sacral extramedullay hematopoeisis: A case report. *Clin Case Rep.* 2021 May 24;9(5):e04258.

Impact Factor: 0.532

Severe hemolysis and vaso-occlusive crisis due to COVID-19 infection in a sickle cell disease patient improved after red blood cell exchange

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Abstract

Even though most data suggest favorable outcome in patients with SCD and COVID-19 infection, close monitoring remains essential as acute complication may develop unexpectedly. Offering RBC exchange early in the course of infection might improve prognosis.

Keywords: COVID-19; Sickle cell disease; acute chest syndrome; hemoglobinopathies; hemolysis; red blood cell exchange.

Citation: Okar L, Rezek M, Gameil A, Mulikandayhil Y, Yassin MA. Severe hemolysis and vaso-occlusive crisis due to COVID-19 infection in a sickle cell disease patient improved after red blood cell exchange. *Clin Case Rep.* 2021 Feb 22;9(4):2117-2121.

Impact Factor: 0.532

First report of COVID-19 reinfection in a patient with beta thalassemia major

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Abstract

To optimize care for patients with hemoglobinopathies, frequent screening for COVID-19 is prudent as viral kinetics in asplenic patients are unknown and differentiating prolonged viral shedding versus reinfection remains a challenge.

Keywords: COVID-19 Reinfection; corona virus; hemoglobinopathies; thalassemia beta major.

Citation: Okar L, Ahmad R, Yassin MA. First report of COVID-19 reinfection in a patient with beta thalassemia major. *Clin Case Rep.* 2020 Dec 19;9(2):861-865.

Impact Factor: 0.532

Leukocyte chemotactic factor 2–related Amyloidosis presenting with severe jaundice and hepatic encephalopathy

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Abstract

Amyloidosis is a well-known disease with various types and subtypes. One of the most recently identified types is leukocyte chemotactic factor 2 amyloidosis (LECT 2), which was found to be common in certain ethnic backgrounds. It is suggested that the diagnosis of this type is vital to prevent any therapy-related complications when it is erroneously diagnosed as AL amyloidosis. The clinical presentation is usually slowly progressive kidney disease and mild hepatic impairment.

We report a case of LECT2 amyloidosis, which presented with severe painless cholestasis and hepatic encephalopathy alongside progressive kidney disease.

Keywords: cholestasis, end-stage renal disease, Leukocyte chemotactic factor 2 amyloidosis

Citation: Almasri H, Razok A,Badi A, et al. Leukocyte chemotactic factor2–related amyloidosis presenting with severe jaundice and hepatic encephalopathy. *Clin Case Rep.* 2021;9:e05185.

Impact Factor: 0.532

Thrombocytopenia secondary to iron deficiency anemia responding to iron therapy

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Abstract

A broad spectrum of diseases can cause anemia and thrombocytopenia. Some of these diseases are a hematological emergency; others are benign diseases, so early and accurate diagnosis is crucial in managing such patients. Usually, IDA is associated with thrombocytosis or normal platelets; however, in rare cases, IDA can be associated with thrombocytopenia; even though, thrombocytopenia that occurs with IDA responds to iron therapy. Iron therapy rarely causes transient thrombocytopenia per se. We are reporting an African female patient who is found to have thrombocytopenia secondary to iron deficiency anemia (IDA), and she responded to iron replacement therapy initially with a transient drop in platelets, followed by a rapid rise in platelets till platelets reached the normal level.

Keywords: anemia; iron; iron deficiency anemia; thrombocytopenia.

Citation: Eisa MS, Al-Tikrity MA, Babikikir MM, Yassin MA. Thrombocytopenia secondary to iron deficiency anemia responding to iron therapy. *Clin Case Rep*. 2021 Jun 18;9(7):10.1002/ccr3.3983.

Impact Factor: 0.532

COVID-19 in a pregnant patient with beta-thalassemia major: A case report

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Abstract

Further studies are needed on this unique population to better manage them and increase their chances of normal pregnancy and fewer complications and more favorable outcomes.

Keywords: COVID-19; beta-thalassemia major; pregnancy; stillbirth; thalassemia; transfusion-dependent.

Citation: Hailan YMA, Sayed G, Yassin MA. CO VID-19 in a pregnant patient with beta-thalassemia major: A case report. *Clin Case Rep.* 2021 Jul 11;9(7):e04331.

Impact Factor: 0.532

Immune thrombocytopenia purpura flare post COVID-19 vaccine

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Abstract

Introduction and importance: Coronavirus disease 2019 (COVID-19) is a recently discovered disease that has yet to be thoroughly described. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel virus that can be transmitted easily from human to human, mainly by the respiratory route. The disease often presents with non-specific symptoms such as fever, headache, and fatigue, accompanied by respiratory symptoms (e.g., cough and dyspnea) and other systemic involvement. Currently, vaccination is the primary strategy to prevent transmission and reduce disease severity. However, vaccines have side effects, and the consequences of vaccination in different diseases are not well established. Moreover, the impact of SARS-CoV-2 vaccination during pregnancy is another not well-known area.

Case presentation: We present a young lady known to have ITP, which was controlled for years, presented with relapse after taking the SARS-CoV-2 vaccine during pregnancy.

Clinical discussion: The patient had a relapse of ITP after the introduction of the first dose of the COVID-19 vaccine, which worsened further after the second dose. This suggests that patients with ITP who develop flare post-SARS-CoV-2 vaccine should have their second dose delayed, particularly if pregnant.

Conclusion: To avoid further deterioration in platelet count, and avoid confusion due to the presence of different causes of thrombocytopenia and avoid complications related to thrombocytopenia during pregnancy which can affect the mode of delivery.

The case is reported in line with the scare 2020 criteria: Agha RA, Franchi T, Sohrabi C, Mathew G, for the SCARE Group. The SCARE 2020 Guideline: Updating Consensus Surgical CAse REport (SCARE) Guidelines, International Journal of Surgery 2020; 84:226-230.

Keywords: COVID-19; Immune thrombocytopenic purpura; SARS-CoV-2; Vaccine.

Citation: A Ali E, Al-Maharmeh Q, Rozi WM, Habib MB, Yassin M. Immune thrombocytopenia purpura flare post COVID-19 vaccine. *Ann Med Surg (Lond).* 2022 Mar;75:103164.

Impact Factor: 0.373

Sickle Cell Anemia Presenting with Vaso-Occlusive Pain: Should We Screen for COVID-19?

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Abstract

Despite the widespread of coronavirus disease-19 (COVID-19) infection around the world, there are very scarce reported literature about the care of patients with a known diagnosis of hemoglobin disorders such as sickle cell disease (SCD) or thalassemia and confirmed COVID-19 infection. Thalassemia International Federation issued a position statement to include patients with thalassemia and SCD among the high-risk groups of patients. Here, we present an interesting case of a 42-year-old patient know to have SCD presenting with Vaso-occlusive (VOC) pain episode in the absence of COVID-19 signs and symptoms, who tested positive for COVID-19 infection and had a smooth recovery. This case highlights the importance of screening SCD patients presenting with VOC-related events even in the absence of COVID-19 signs and symptoms.

Keywords: Sickle cell disease, Vaso-occlusive, Coronavirus disease 19, Acute chest syndrome

Citation: Ali M, Okar L, Omar NE, Parengal J, Soliman A, Yassin MA. Sickle Cell Anemia Presenting with Vaso-Occlusive Pain: Should We Screen for COVID-19?. *Dubai Medical Journal.* 2021;4(1):36-9.

Impact factor: -

Tuberculosis with immune thrombocytopenia Case reports and review of the literature

Alkhatib, Mohammed[1], Elfert, Khaled A.[2], Saleh, Ahmed O. [3], Elkourashy, Sarah A. [4], Fadul, Afraa M.[5], Taha, Ruba Y. [4,] Imam, Yahia Z. [5,6], Fareed, Shehab [4,7]

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Abstract

Rationale: Immune thrombocytopenia (ITP) is a platelet disorder that is caused by antibodies against platelet cells. ITP can be either primary or secondary. One of the secondary causes of ITP is infectious diseases. Tuberculosis (TB) has been reported as a rare cause of secondary ITP.

We report 3 cases of TB that were associated with ITP with favorable response to therapy. We also compared these cases with similar published cases in the literature.

Patient concerns: The first case was an Ethiopian female who presented with cough, fever, night sweats, and weight loss and was found to have isolated thrombocytopenia without manifestations. The second case was a Nepalese man who presented with mucocutaneous bleeding and respiratory symptoms. The third case was for a Nepalese male who presented with mucocutaneous bleeding without pulmonary symptoms but with lymphadenopathy on chest imaging.

Diagnoses: The first and second cases were diagnosed as pulmonary TB based on positive acid-fast Bacillus smear and PCR from the sputum. In the third case, mediastinal lymph node biopsy

came positive for TB PCR and culture was consistent with extrapulmonary TB. ITP diagnosis was established in the 3 cases after ruling out other causes of thrombocytopenia.

Interventions: The first case received intravenous immunoglobulin and anti-tubercular treatment (ATT). The second case received ATT followed by prednisolone. The third case was started on intravenous Immunoglobulin and prednisolone; ATT was added after the diagnosis of TB was established later.

Outcomes: All the cases achieved a good response to the treatment with normalization of platelets count.

Lessons: It is important to consider TB as 1 of the causes of secondary ITP, especially in countries with a high TB burden. In our literature review, we found that ITP-specific therapy alone was not effective in treating ITP associated with TB; almost all the cases required ATT for achieving good platelet response.

Citation: Alkhatib M, Elfert KA, Saleh AO, Elkourashy SA, Fadul AM, Taha RY, Imam YZ, Fareed S. Tuberculosis with immune thrombocytopenia: case reports and review of the literature. *Med Case Rep Study Protoc.* 2021;2:3(e0062).

Impact Factor: -

NON-MALIGNANT HEMATOLOGY

Review Articles

Manifestations of HbSE sickle cell disease: a systematic review

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Abstract

Background: Sickle cell disease (SCD) is commonly encountered in Africa and Middle Eastern countries. The causative mutation in the gene encoding the hemoglobin subunit β (HBB) leads to various genotypic variants of the disease. This results in varied phenotypes, with a spectrum of complications, from benign to fatal. Hemoglobin SS (HBSS) genotype is associated with most of these complications; hence, it is a severe form of SCD. On the other hand, rare genotypes such as hemoglobin SE (HBSE) are considered benign. There is limited literature about the clinical manifestations and characteristics of patients with HBSE. We pooled all available data describing the phenotypic manifestations of HBSE heterozygote worldwide to perform a systematic review.

Methods: We performed a systematic review according to PRISMA guidelines using PubMed, SCOPUS, and Google Scholar databases. Two independent reviewers (FA and IK) evaluated studies for eligibility and extracted data. We synthesized data on demographics, manifestations, and management of HBSE disease. PROSPERO Registration Number: CRD42021229877.

Results: We found 68 HBSE patients reported in the literature. 24 cases were extracted from case reports whereas 44 cases from case series and retrospective studies. Turkey reported the highest number of patients (n = 22). 32 (47%) of the patients were males. The mean age was 20.9 ± 18.26 years. The mean HBS and HBE percentages were 61.1% ± 7.25% and 32.3% ± 5.06%, respectively, whereas the mean hemoglobin was 11.64 ± 1.73 g/dl. Reported manifestations of HBSE disease

included acute vaso-occlusive pain crisis (n = 22, 32.3%), splenomegaly (n = 11, 16.1%), hemolytic anemia (n = 10, 14.7%), infections (n = 8. 11.7%), bone infarction (n = 4, 5.8%), gallstones (n = 3, 4.4%), venous thromboembolism (VTE) (n = 2, 2.9%) and stroke (n = 2, 2.9%), and hematuria (n = 2, 2.9%). Death due to HBSE complications was reported in three patients.

Conclusion: HBSE is a rare genotypic variant of SCD. It has been considered a benign form; however, there are multiple reports of severe complications. Severe complications observed in HBSE disease include vaso-occlusive crisis, acute chest syndrome, stroke, bone marrow embolism, and death.

Keywords: HBSE; Hemoglobin SE; SCD; Sickle cell disease; Sickle genotype.

Citation: Khamees I, Ata F, Choudry H, Soliman AT, De Sanctis V, Yassin MA. Manifestations of HbSE sickle cell disease: a systematic review. *J Transl Med.* 2021 Jun 16;19(1):262.

Impact Factor: 8.440

Prevalence of Venous Thromboembolism in Critically Ill COVID-19 Patients: Systematic Review and Meta-Analysis

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Abstract

Background: Recent studies revealed a high prevalence of venous thromboembolism (VTE) events in coronavirus disease 2019 (COVID-19) patients, especially in those who are critically ill. Available studies report varying prevalence rates. Hence, the exact prevalence remains uncertain. Moreover, there is an ongoing debate regarding the appropriate dosage of thromboprophylaxis. Methods: We performed a systematic review and proportion meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched PubMed and EMBASE for studies exploring the prevalence of VTE in critically ill COVID-19 patients till 25/07/2020. We pooled the proportion of VTE. Additionally, in a subgroup analysis, we pooled VTE events detected by systematic screening. Finally, in an exploratory analysis, we compared the odds of VTE in patients on prophylactic compared with therapeutic anticoagulation. Results: The review comprised 24 studies and over 2,500 patients. The pooled proportion of VTE prevalence was 0.31 [95% confidence interval (CI) 0.24, 0.39; I^2 94%], of VTE utilizing systematic screening was 0.48 (95% CI 0.33, 0.63; I^2 91%), of deep venous thrombosis was 0.23 (95% CI 0.14, 0.32; I^2 96%), and of pulmonary embolism was 0.14 (95% CI 0.09, 0.20; I^2 90%). Exploratory analysis of few studies, utilizing systematic screening, VTE risk increased significantly with prophylactic, compared with therapeutic anticoagulation [odds ratio (OR) 5.45; 95% CI 1.90, 15.57; I^2 0%]. Discussion: Our review revealed a high prevalence of VTE in critically ill COVID-19 patients. Almost 50% of patients had VTE detected by systematic screening. Higher thromboprophylaxis dosages may reduce VTE burden in this patient's

cohort compared with standard prophylactic anticoagulation; however, this is to be ascertained by ongoing randomized controlled trials.

Keywords: COVID-19; DVT—deep vein thrombosis; ICU; SARS-CoV-2; VTE; thrombosis; venous.

Citation: Mohamed MFH, Al-Shokri SD, Shunnar KM, Mohamed SF, Najim MS, Ibrahim SI, Elewa H, Abdalla LO, El-Bardissy A, Elshafei MN, Abubeker IY, Danjuma M, Dousa KM, Yassin MA. Prevalence of Venous Thromboembolism in Critically Ill COVID-19 Patients: Systematic Review and Meta-Analysis. *Front Cardiovasc Med.* 2021 Jan 8;7:598846.

Impact Factor: 6.050

On Iron Metabolism and Its Regulation

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Abstract

Iron is a critical metal for several vital biological processes. Most of the body's iron is bound to hemoglobin in erythrocytes. Iron from senescent red blood cells is recycled by macrophages in the spleen, liver and bone marrow. Dietary iron is taken up by the divalent metal transporter 1 (DMT1) in enterocytes and transported to portal blood via ferroportin (FPN), where it is bound to transferrin and taken up by hepatocytes, macrophages and bone marrow cells via transferrin receptor 1 (TfR1). While most of the physiologically active iron is bound hemoglobin, the major storage of most iron occurs in the liver in a ferritin-bound fashion. In response to an increased iron load, hepatocytes secrete the peptide hormone hepcidin, which binds to and induces internalization and degradation of the iron transporter FPN, thus controlling the amount of iron released from the cells into the blood. This review summarizes the key mechanisms and players involved in cellular and systemic iron regulation.

Keywords: hepcidin; iron; macrophages.

Citation: Vogt AS, Arsiwala T, Mohsen M, Vogel M, Manolova V, Bachmann MF. On Iron Metabolism and Its Regulation. *Int J Mol Sci.* 2021 Apr 27;22(9):4591.

Impact Factor: 6.208

The Effects of Treatment with Blood Transfusion, Iron Chelation and Hydroxyurea on Puberty, Growth and Spermatogenesis in Sickle Cell Disease (SCD): A short update

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Abstract

Sickle cell disease (SCD) is traditionally associated with growth failure and delayed puberty. Wasting and stunting are still prevalent in children and adolescents with SCD, especially in developing countries. In addition, sperm abnormalities are frequent in males with SCD, with high rates of low sperm density, low sperm counts, poor motility, and increased abnormal morphology. Severe anemia, vaso-occlusive attacks with ischemic injury to different organs including the pituitary gland and testis, and nutritional factors are incriminated in the pathogenesis of defective growth, puberty, and spermatogenesis. There is great phenotypic variability among patients with SCD. The variability in the clinical severity of SCA can partly be explained by genetic modifiers, including HbF level and co-inheritance of α-thalassemia. In the past, severe disease led to early mortality. Advancements in treatment have allowed patients with SCD to have a longer and better quality of life. For most patients, the mainstays of treatment are preventive and supportive. For those with severe SCD, three major therapeutic options are currently available: erythrocyte transfusion or exchange, hydroxyurea, and hematopoietic stem cell transplantation. In this mini-review, the authors tried to recognize, delineate, and update knowledge on abnormalities due to SCD from those created by the use of different treatment modalities.

Citation: Soliman AT, Alaaraj N, Yassin M. The Effects of Treatment with Blood Transfusion, Iron Chelation and Hydroxyurea on Puberty, Growth and Spermatogenesis in Sickle Cell Disease (SCD): A short update. *Acta Biomed.* 2021 Sep 2;92(4):e2021386.

Impact Factor: 3.79

Protocol for extramedullary hematopoiesis in patients with transfusion-dependent β-thalassemia (TDT): A systematic review

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Abstract

Background and aims: Thalassemia is one of the most common hemoglobinopathies, with around 5% of the world's population expected to have some degree and type of thalassemia. Beta thalassemia (BT) occurs due to a deficient production of the beta-globin chain of hemoglobin. Extramedullary hematopoiesis (EMH) is one of the complications of BT, mainly observed in minor/intermedia subtypes. EMH is the production of blood cells outside the marrow as a compensatory response to longstanding hypoxia. Due to chronic transfusions, it is not expected in patients with beta-thalassemia major (BTM). However, there are increasingly reported cases of EMH in BTM. The incidence of EMH in BTM is thought to be <1%. However, it seems that the true incidence is much higher than expected. This review aims to pool the available data and provide cumulative evidence on the reports of EMH in BTM patients.

Methods: We aim to conduct a systematic review via searching multiple electronic databases (PubMed, Scopus, Google Scholar) to identify eligible articles from any date up to December 2020. Eligible studies should report extramedullary hematopoiesis in BTM. Case reports, case series, observational studies with cross-sectional or prospective research design, case-control studies, and experimental studies will be included if found relevant. Two reviewers (FA and ES) will individually analyze the study quality using the statistical methodology and categories guided by the Cochrane Collaboration Handbook, PRISMA guidelines, and Joanna Briggs Institute checklist for case reports and series.

Results: This study will analyze and incorporate the available evidence on EMH in BTM concerning patient demographics, sites of EMH, management, and clinical outcomes of EMH.

Conclusion: By summarizing and statistically analyzing the data about EMH in BTM, this study will generate extensive knowledge on the topic for a better understanding of atypical presentations in BTM, a common hemoglobinopathy.

Keywords: beta-thalassemia major; extramedullary hematopoiesis; non-medullary hematopoiesis; transfusion-dependent thalassemia.

Citation: Ata F, Subahi EA, Choudry H, Yassin MA. Protocol for extramedullary hematopoiesis in patients with transfusion-dependent β-thalassemia (TDT): A systematic review. *Health Sci Rep.* 2021 Nov 3;4(4):e429.

Impact Factor: 1.95

Thalassemia and Priapism: A Literature Review of a Rare Association

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Abstract

Thalassemia is a hematologic disorder caused by genetic mutation resulting in impaired hemoglobin chain production. Patients with thalassemia commonly experience complications such as anemia, blood transfusion-related issues, hepatic or cardiac involvement, and psychosocial impacts. Rarely, priapism has been associated with thalassemia as an initial presentation or subsequently occurring at any time in the disease course. Our literature review summarizes the reported cases of thalassemia-associated priapism and delves into underlying mechanisms of its pathophysiology and appropriate management.

Keywords: hematology; priapism; thalassemia.

Citation: Sardar S, Ali EA, Yassin MA. Thalassemia and Priapism: A Literature Review of a Rare Association. *Cureus*. 2021 Apr 7;13(4):e14335.

Impact Factor: 1.15

NON-MALIGNANT HEMATOLOGY

Abstracts

Glutamine and Crizanlizumab for Adults with Sickle Cell Disease (SCD) in Qatar: A Cost Effectiveness Analysis

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Abstract

Background: Sickle cell disease (SCD) is a hereditary disease that is caused by autosomal recessive gene fault in the beta (β) allele of the hemoglobin (Hb) gene. As a result, sickled cells are characterized by easy and abnormal hemolysis with resultant varying degrees of anemia. Globally, the incidence of SCD is estimated to reach 400,000 persons per year, and in the United States alone, for example, the prevalence estimation is approximately 100,000 patients. Possible clinical presentations of SCD may come from different pathophysiologic mechanisms: the disfiguration of the RBC with subsequent loss of function can lead to vascular occlusion and a short lifetime of these RBCs that leads to hemolysis. The most severe and serious manifestation of SCD is the recurrent acute pain, or better known as vaso-occlusive crisis (VOC). Additionally, other clinical manifestations that SCD patients may show are acute complications such as acute chest syndrome (ACS), recurrent infections, kidney necrosis, and stroke. Such complications may affect multiple organs and can result in early death. Acute pain crisis is another common complication of SCD and is usually managed with pain medications, especially opioids,

This is the first study to address two of novel therapies in patients with SCD in the Middle East. Our study was comprehensive in terms of outcome mostly encountered by SCD patients which is VOC and inclusivity of interventions mostly used for its management and was focused on the target population of in one of areas of high prevalence of SCD in the world. Our analysis tracked the CHEERS guidelines and checklist for reporting. To be also complete, we used only RCT evidence in our analysis. Additionally, in considering VOC, we ensured only studies with a definition compatible with that of the principal Crizanlizumab study were analyzed.

Objectives: Treatment options for preventing vaso-occlusive crises (VOC) among sickle cell disease (SCD) patients are on the rise, especially if hydroxyurea treatment has failed. This economic analysis is conducted to assess the comparative clinical effectiveness, safety and acquisition cost of L-glutamine and Crizanlizumab for older adolescent and adults (≥16 years old) SCD in Qatar, with an emphasis on treatment costs and acute pain crises.

Methods: We conduct a decision tree model, where we compare the clinical and economic outcomes of two novel FDA-approved medications which are available in Qatar; L-glutamine and Crizanlizumab

over a time horizon of one year in a hypothetical cohort of adult SCD patients from a Qatar healthcare perspective. The main outcome is incremental cost per SCD-related acute pain crises averted. Model clinical parameters were derived from individual drug randomized trials, published literature, whereas cost parameters from Qatar healthcare payer system. A sensitivity analysis was carried out, and the study results were robust around model inputs. Costs were converted to 2020 US dollars.

Results: Study results showed that both treatment modalities' costs were the main driver of this analysis, with average annual cost of the treatments per patient being $189,014 for Crizanlizumab (5mg/Kg), $143,798 Crizanlizumab (2.5mg/Kg) and $74,323 for L-glutamine. The probability of no first time SCD-related VOC averted were 0.001/year for Glutamine, 0.26/year for Crizanlizumab (5mg/Kg) and 0.34/year for Crizanlizumab (2.5mg/Kg). Lower dose Crizanlizumab (2.5mg/Kg) dominated the higher one (5mg/Kg). The ICER of Crizanlizumab (2.5mg/Kg), when compared to L-Glutamine was $81,265 per SCD-related VOC averted. When comparing Crizanlizumab (5mg/Kg) and L-Glutamine, Crizanlizumab (5mg/Kg) showed higher efficacy, yet the Crizanlizumab ICER was at $459,620 than L-glutamine.

Conclusions: Crizanlizumab (2.5mg/Kg) may be cost-effective interventions yet it is not the approved dose for preventing VOC in adolescents and adults with sickle cell disease. Crizanlizumab (5mg/Kg) was more cost effective than the approved L-glutamine per SCD vaso-occlusive crisis prevented.

Citation: Adel A, Abushanab D, Hamad A, Al-Badriyeh D, Yassin M. (2021) L-Glutamine and Crizanlizumab for Adults with Sickle Cell Disease (SCD) in Qatar: A Cost Effectiveness Analysis. *Blood,* 138(Supp.1):4945

Conference Abstracts and Poster Presentations

Title	Speakers
Multinational Association of Supportive Care in Cancer (MASCC) International Society of Oral Oncology (ISOO) 2021 Annual Meeting (Virtual) 24-26 June 2021	
Medication use evaluation of trabectedin safety and effectiveness at a tertiary cancer center in Qatar: a retrospective analysis.	Nabil E. Omar, F. Jibril, O. Abdallah, F. Saleh, A. Hamad.
European Society Radiation Oncology (ESTRO) Spain August 2021	
Non-invasive grading of cervix cancer using diffusion weighted imaging	Souha Aouadi
Generation of synthetic CT with 3D deep convolutional neural networks for brain MR-only radiotherapy	Souha Aouadi
Characterization of the geometric distortion and the quality of MR images used for spine SBRT	Tarraf Torfeh
33rd European Congress of Pathology (ECP 2021) 29th -31st August 2021	
Primary Leiomyosarcoma of Bone: A Rare Diagnostically Challenging Bone Tumor	Khaled Murshed
A rare case of paratesticular mesothelioma successfully treated by surgery and adjuvant chemotherapy	Khaled Murshed
Papillary Thyroid Carcinoma with Mucinous Features Harbouring *ETV6-NTRK3* Fusion: Expanding the Morphologic Spectrum of *NTRK*-Rearranged Thyroid Carcinomas	Khaled Murshed

ID week 2021(Virtual) September 29-October 2, 2021	
Early Predictors of Intensive Care Unit Admission among COVID-19 Patients in Qatar.	Abuyousef S, Alnaimi S, Omar N, Elajez R, Elmekaty E, Abdelfattah-Arafa E, Barazi R, Ghasoub R, Rahhal A, Hamou F, Al-Amri M.
American College of Clinical Pharmacy (ACCP) (Virtual) October 2021	
A Comparative Analysis of Efficacy and Safety of Enoxaparin and Direct Oral Anticoagulants (DOACs) amongst Cancer Patients in Qatar. A Retrospective Cohort Study.	Radoa Al-Ansari, Sahar Nasser, Kawthar Tawengi, Fatima Al-Maraghi, Lana Awad, Mariam Nashwan, Amir Nounou, Anas Hamad, Moza Al-Hail, Halima El-Omri, Salha Bujassoum, Shereen Elazzazy.
Society of Immunotherapy of Cancer (SITC) 36th Annual Meeting & Pre-Conference Programs 14th October 2021, Washington, DC	
Predictive soluble biomarkers of immune response to checkpoint blockade in NSCLC patients	Afsheen Raza
4th Best of ASCO Kurdistan Erbil 26-27 November 2021	
HCC and Esopgeogastric	Kakil Rasul
Precision Medicine and Functional Genomics 2021 **Virtual meeting at Sidra Medicine** 4-6 December 2021	
??	Kakil Rasul

San Antonio Breast Cancer Symposium (Virtual) Dec 7-10,2021	
Clinical and pharmacoeconomic analyses of CDK4/6 inhibitors use in stage IV breast cancer females in the state of Qatar: A comparative retrospective observational study with cost effectiveness and cost utility analyses.	Nour Hisham Al-Ziftawi, Shereen Elazzazy, Mohammed Fasihul Alam, Asrul Akmal Shafie, Anas Hamad, Salha Bujassoum, Mohamed Izham Ibrahim.
Annual Breast Cancer Conference 2021 Doha-Qatar 10 – 11 October 2021	
Clinical and Pharmacoeconomic Analyses of CDK4/6 Inhibitors Use in Stage IV Breast Cancer Females in the State of Qatar: A Comparative Retrospective Observational Study with Cost-Effectiveness and Cost-Utility Analyses.	Nour Hisham Al-Ziftawi, Shereen Elazzazy, Mohammed Fasihul Alam, Asrul Akmal Shafie, Anas Hamad, Salha Bujassoum and Mohamed Izham Ibrahim.

Awards and Prizes

First place in Qatar National Three-Minute Thesis Competition, October 2021, Qatar

Cost Effectiveness Analysis of the Use of Ribociclib Versus Palbociclib for Hormone-Receptor Positive and HER2 Negative Stage IV Breast Cancer in Qatar

Nour Hisham Al-Ziftawi, Shereen Elazzazy, Mohammed Fasihul Alam, Asrul Akmal Shafie, Anas Hamad, Salha Bujassoum, Mohamed Izham Ibrahim

Third-place research award in the Three-Minute Thesis Competition of Qatar University, November 2021, Qatar

Cost Effectiveness Analysis of the Use of Ribociclib Versus Palbociclib for Hormone-Receptor Positive and HER2 Negative Stage IV Breast Cancer in Qatar

Nour Hisham Al-Ziftawi, Shereen Elazzazy, Mohammed Fasihul Alam, Asrul Akmal Shafie, Anas Hamad, Salha Bujassoum, Mohamed Izham Ibrahim

Second place best research in the regional Third Youth Research Forum, May 2021, Qatar

Cost Effectiveness Analysis of the Use of Ribociclib Versus Palbociclib for Hormone-Receptor Positive and HER2 Negative Stage IV Breast Cancer in Qatar

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Educational meetings 2021

Date	Title	Organization Team
10 – 11 October 2021	Annual Breast Cancer Conference 2021 "Management of Breast Cancer in the era of Covid 19 Pandemic"	
26 - 27 November 2021	Best of ASCO 2021 in Qatar	Cancer services

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