ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2023 March 24; 14(3): 99-137

Published by Baishideng Publishing Group Inc

World Journal of Clinical Oncology

Contents

Monthly Volume 14 Number 3 March 24, 2023

REVIEW

MINIREVIEWS

CASE REPORT

World Journal of Clinical Oncology

Monthly Volume 14 Number 3 March 24, 2023

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Clinical Oncology*, Zheng Wang, MD, PhD, Attending Surgeon, Senior Researcher, Assistant Professor, Comprehensive Breast Health Center, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, No. 197 Ruijin Second Road, Shanghai 200025, China. zhengwang@shsmu.edu.cn

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Oncology* (*WJCO*, *World J Clin Oncol*) is to provide scholars and readers from various fields of oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCO mainly publishes articles reporting research results and findings obtained in the field of oncology and covering a wide range of topics including art of oncology, biology of neoplasia, breast cancer, cancer prevention and control, cancer-related complications, diagnosis in oncology, gastrointestinal cancer, genetic testing for cancer, gynecologic cancer, head and neck cancer, hematologic malignancy, lung cancer, melanoma, molecular oncology, neurooncology, palliative and supportive care, pediatric oncology, surgical oncology, translational oncology, and urologic oncology.

INDEXING/ABSTRACTING

The *WJCO* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 Journal Citation Indicator (JCI) for *WJCO* as 0.35.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Monthly

PUBLICATION DATE
March 24, 2023

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2023 March 24; 14(3): 99-116

DOI: 10.5306/wjco.v14.i3.99

ISSN 2218-4333 (online)

REVIEW

Budd-Chiari syndrome in myeloproliferative neoplasms: A review of literature

Mihnea-Alexandru Găman, Matei-Alexandru Cozma, Muhammad Romail Manan, Bahadar S Srichawla, Arkadeep Dhali, Sajjad Ali, Ahmed Nahian, Andrew C Elton, L V Simhachalam Kutikuppala, Richard Christian Suteja, Sebastian Diebel, Amelia Maria Găman, Camelia Cristina Diaconu

Specialty type: Hematology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Guo X, China; Manesis EK, Greece; Qi XS, China

Received: November 20, 2022
Peer-review started: November 20, 2022
First decision: January 3, 2023
Revised: February 10, 2023
Accepted: March 1, 2023
Article in press: March 1, 2023
Published online: March 24, 2023

Mihnea-Alexandru Găman, Matei-Alexandru Cozma, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest 050474, Romania

Mihnea-Alexandru Găman, Department of Hematology, Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest 022328, Romania

Muhammad Romail Manan, Services Institute of Medical Sciences, Lahore 54660, Pakistan

Bahadar S Srichawla, Department of Neurology, University of Massachusetts Chan Medical School, Worcester, Massachusetts 01655, United States

Arkadeep Dhali, Department of Internal Medicine, Nottingham University Hospitals NHS Trust, Nottingham NG7 2UH, United Kingdom

Sajjad Ali, Department of Medicine, Ziauddin University, Karachi 75600, Pakistan

Ahmed Nahian, California Baptist University-Lake Erie College of Osteopathic Medicine, Riverside, CA 92504, United States

Andrew C Elton, University of Minnesota Medical School, Minneapolis, MN 55455, United States

L V Simhachalam Kutikuppala, Department of General Surgery, Dr NTR University of Health Sciences, Andhra Pradesh, Vijayawada 520008, India

Richard Christian Suteja, Department of Undergraduate Medicine, Faculty of Medicine, Udayana University Denpasar, Bali 80232, Indonesia

Sebastian Diebel, Department of Family Medicine, Northern Ontario School of Medicine Timmins, Ontario 91762, Canada

Amelia Maria Găman, Department of Pathophysiology, University of Medicine and Pharmacy of Craiova, Romania & Clinic of Hematology, Filantropia City Hospital, Craiova 200143, Romania

Camelia Cristina Diaconu, Department of Internal Medicine, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Romania & Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest, Bucharest 105402, Romania

Corresponding author: Mihnea-Alexandru Găman, Doctor, MD, PhD, Research Fellow, Researcher, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, 8 Eroii Sanitari Blvd, Bucharest 050474, Romania. mihneagaman@yahoo.com

Abstract

Myeloproliferative neoplasms (MPNs) are defined as clonal disorders of the hematopoietic stem cell in which an exaggerated production of terminally differentiated myeloid cells occurs. Classical, Philadelphia-negative MPNs, *i.e.*, polycythemia vera, essential thrombocythemia and primary myelofibrosis, exhibit a propensity towards the development of thrombotic complications that can occur in unusual sites, *e.g.*, portal, splanchnic or hepatic veins, the placenta or cerebral sinuses. The pathogenesis of thrombotic events in MPNs is complex and requires an intricate mechanism involving endothelial injury, stasis, elevated leukocyte adhesion, integrins, neutrophil extracellular traps, somatic mutations (*e.g.*, the V617F point mutation in the *JAK2* gene), microparticles, circulating endothelial cells, and other factors, to name a few. Herein, we review the available data on Budd-Chiari syndrome in Philadelphia-negative MPNs, with a particular focus on its epidemiology, pathogenesis, histopathology, risk factors, classification, clinical presentation, diagnosis, and management.

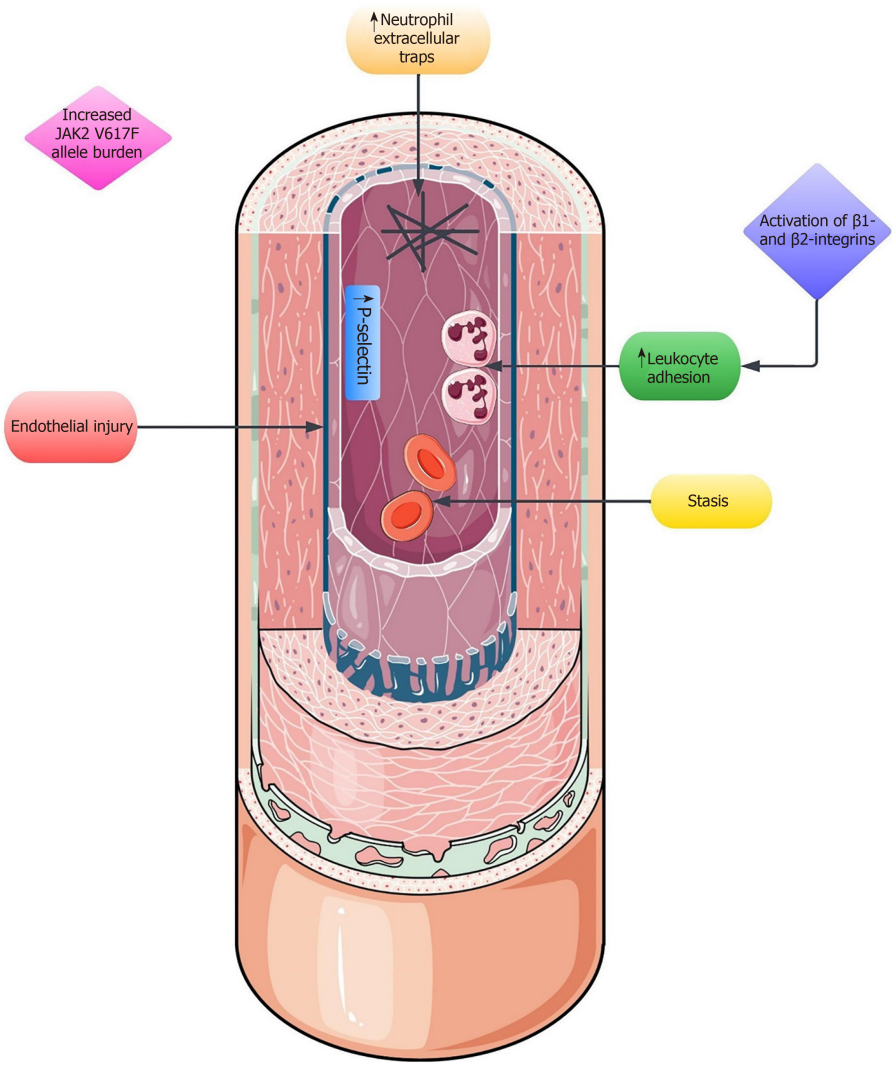
Key Words: Myeloproliferative neoplasms; Budd-Chiari syndrome; Thrombosis; Polycythemia vera; Essential thrombocythemia; Primary myelofibrosis

Core Tip: Myeloproliferative neoplasms (MPNs) are defined as clonal disorders of the hematopoietic stem cell in which an exaggerated production of terminally differentiated myeloid cells occurs. MPNs are characterized by a propensity towards the development of thrombotic complications, including Budd-Chiari syndrome (BCS). Herein, we review the available data on BCS in MPNs, with a particular focus on its epidemiology, pathogenesis, histopathology, risk factors, classification, clinical presentation, diagnosis, and management.

Citation: Găman MA, Cozma MA, Manan MR, Srichawla BS, Dhali A, Ali S, Nahian A, Elton AC, Simhachalam Kutikuppala LV, Suteja RC, Diebel S, Găman AM, Diaconu CC. Budd-Chiari syndrome in myeloproliferative neoplasms: A review of literature. *World J Clin Oncol* 2023; 14(3): 99-116
URL: https://www.wjgnet.com/2218-4333/full/v14/i3/99.htm
DOI: https://dx.doi.org/10.5306/wjco.v14.i3.99

INTRODUCTION

Myeloproliferative neoplasms (MPNs) are defined as clonal disorders of the hematopoietic stem cell in which an exaggerated production of terminally differentiated myeloid cells occurs[1]. Classical, Philadelphia-negative MPNs include polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis, whereas chronic myeloid leukemia (CML) is the hallmark Philadelphia-positive MPN[1,2]. Philadelphia-negative MPNs exhibit a propensity towards the development of thrombotic complications[2,3]. In MPNs, thrombosis can occur in unusual sites, *e.g.*, portal, splanchnic or hepatic veins, the placenta or cerebral sinuses[4]. The pathogenesis of thrombotic events in MPNs is complex and requires an intricate mechanism involving endothelial injury, stasis, elevated leukocyte adhesion, integrins, neutrophil extracellular traps (NETs), somatic mutations (*e.g.*, the V617F point mutation in the *JAK2* gene), microparticles, circulating endothelial cells, and other factors, to name a few (Figure 1)[4,5]. Herein, we review the available data on Budd-Chiari syndrome (BCS) in Philadelphia-negative MPNs, with a particular focus on its epidemiology, pathogenesis, histopathology, risk factors, classification, clinical presentation, diagnosis, and management. MPNs lead to an increased risk of thrombosis through various mechanisms. This includes increased P-selectin expression, activation of integrins causing leukocyte adhesion, and the novel mechanism of NETs formation.



DOI: 10.5306/wjco.v14.i3.99

Figure 1 Myeloproliferative neoplasms lead to an increased risk of thrombosis through various mechanisms. This includes increased *P*-selectin expression, activation of integrins causing leukocyte adhesion, and the novel mechanism of neutrophil extracellular traps formation.

BRIEF OVERVIEW OF BUDD-CHIARI SYNDROME

BCS is a heterogeneous group of disorders characterized by hepatic venous outflow tract obstruction, ranging from the small hepatic veins, the three suprahepatic veins and all the way to the junction of the inferior vena cava (IVC) and right atrium. This classification eliminates hepatic blood flow impairments caused by cardiac illness, pericardial disease, or sinusoidal obstruction syndrome (porto-sinusoidal vascular disorder)[6-9]. Primary BCS is the obstruction due to a predominantly venous process (thrombosis or phlebitis), whereas secondary BCS denominates the compression or invasion of the hepatic veins and/or IVC by a lesion that originates from outside of the vein (most commonly malignancy, abscess, or lymphadenopathy)[7,10,11]. It is a typical example of post-sinusoidal portal hypertension[6,8].

EPIDEMIOLOGY AND PATHOGENESIS OF BUDD-CHIARI SYNDROME IN MYELOPROLIFERATIVE NEOPLASMS

BCS is a rare condition across the globe. Expectedly, there is limited epidemiologic data on this entity. A recent meta-analysis involving data from Asian and European studies highlighted a pooled incidence of BCS at 1 case per million people and a prevalence of 11 cases per million people[12]. This report found significant heterogeneity among the analyzed assessments due to differences in study designs (diagnostic criteria, population characteristics, population sizes), as well as generally limited data on the topic from the Americas or Africa. The investigations were conducted on populations from Japan, South

Korea, Denmark, Sweden, Italy, and France. Earlier studies from China depicted the incidence of BCS at 0.88 per million and a prevalence ranging from 6.40 to 7.69 per million[13,14]. It is important to note, though, that most of these epidemiologic studies included both primary and secondary BCS. One study from France reported a median age of patients with primary BCS at 46.9 years. In their cohort, 30.6% were male and 69.4% female. Oral contraceptive use and pregnancy are gender-specific risk factors of BCS which may contribute to the female predominance[15]. In fact, hepatic vein thrombosis leading to BCS was more common in females, whereas obstruction of both the hepatic veins and IVC was more common in males[16]. There seems to be a geographic distribution of MPNs-related BCS cases. For example, Qi *et al*[17] reported that of their cohort of 246 cases of BCS diagnosed over nearly 12 years in China, only 5 cases were attributable to MPNs.

BCS, by definition, is the obstruction of the hepatic veins and/or outflow tract into the IVC. This entity is distinguished from portal vein thrombosis (PVT) and splanchnic vein thrombosis (SVT), which can coexist with BCS though are distinct pathologic processes[18]. Prior literature even reports presence of PVT in BCS at 10%-20%, which suggests a relatively poor prognosis[19]. Generally, the etiology of BCS is categorized as thrombotic or non-thrombotic. Thrombotic obstruction is the most common cause of BCS, and this is referred to as primary BCS. There are numerous conditions associated with primary BCS, including inherited thrombophilia, thalassemia, paroxysmal nocturnal hemoglobinuria, MPNs, pregnancy, oral contraceptive use, or even inflammatory conditions, *e.g.*, Behcet's disease, celiac disease, and ulcerative colitis[20-22]. Non-thrombotic causes of BCS, referred to as secondary BCS, typically involve a mass lesion involving the hepatic veins or compression by adjacent structures. There are many case reports describing unique causes of secondary BCS, *e.g.*, polycystic kidney disease, liver abscess, hydatid cysts, and cardiac myxoma; however, this etiology is uncommon[23-26]. MPNs are the most common cause of BCS, and the prevalence of BCS in the setting of MPN ranges from 32.9% up to 49.5% [27,28]. MPNs represent a malignant proliferation of myeloid cell lines, with the most common blood cancers classified in this category being CML, PV, ET and PMF. Thrombotic complications, such as BCS, are of particular concern in the setting of PV and ET, as these conditions carry significantly greater risk of such thrombotic processes[28]. A meta-analysis found that PV was the most common of MPNs to be diagnosed in the setting of BCS, even more than in subjects with PVT[28]. There is also evidence pointing towards increased thrombotic risk in MPNs carrying *JAK2* gene mutations[29] and about 41% of individuals with BCS exhibit genetic changes in the aforementioned gene[30,31].

HISTOPATHOLOGY OF BUDD-CHIARI SYNDROME

Histopathological features of BCS are studied in great detail and the histopathology of BCS is well established in the existing body of evidence[32-35]. Sinusoidal dilatation and congestion, centrilobular inflammation and necrosis, regenerative hyperplasia, macrovesicular steatosis, cholestasis, glycogenated nuclei, and perivenular fibrosis are the common histological features seen in this condition. Regenerative nodules, even though seen in both BCS and cardiac cirrhosis, is more common in BCS. Sinusoidal dilatation is the hallmark microscopic finding which can be appreciated in the initial stages of the disease[36]. However, this finding is not unique to BCS and can be seen in other conditions[37]. Having said that, in the presence of prominent sinusoidal dilatation, hepatic outflow obstruction should be ruled out as an important differential. Centrilobular necrosis is another important pathological feature that is more commonly seen in BCS compared to cardiac cirrhosis. This is attributed to the fact that hepatic hypoxia preferentially affects the centrilobular hepatocytes[38,39]. To the best of our knowledge, there is no literature on variation of the histopathological patterns in BCS secondary to MPNs. Moreover, a prognostic grading system for the same also does not exist and is a potential area for further studies.

RISK FACTORS OF BUDD-CHIARI SYNDROME IN MYELOPROLIFERATIVE NEOPLASMS

Smalberg *et al*[28] have depicted in their meta-analysis a strong relation between MPNs and SVT. This was confirmed by the high prevalence of *JAK2V617F* in BCS. MPNs and *JAK2V617F* are more commonly associated with BCS compared to PVT. This may be due to focal inflammatory insult to the portal venous system which is required for PVT[40]. There is a considerable difference between PVT and BCS with regard to the subtypes of MPNs. PV is more commonly associated with BCS than with PVT. There is a high pro-thrombotic effect as the hematocrit increases. In these situations, low-shear venous circulation is impacted more by the increased blood viscosity[41-43]. The interaction between adhesion molecules and red cells may be responsible for this mechanism. However, it was observed that PVT is more common in PMF compared to BCS[28]. This may be due to the fact that splenomegaly in PMF causes compression of the portal system leading to stasis of blood. In the same study, *JAK2V617F*-positive MPNs were found to be associated with PVT more frequently than BCS[28]. However, the exact reason is not known. In terms of *CALR* gene mutations, Li *et al*[45] highlighted that 1.41% of BCS cases exhibit genetic alterations in the *CALR* gene. In *JAK2V617F*-negative MPNs-related BCS cases, *CALR*

gene mutations were detected in 17.22% of the examined individuals [44].Mutations in other genes, *i.e.*, *MPL* or *TET2*, have rarely been depicted in BCS. However, the detection of a somatic gene mutation and especially of *JAK2V617F* in BCS should alert the clinician to screen for MPNs, including at follow-up if the diagnosis of overt MPNs is not established. In addition, work-up for hereditary thrombophilia should be performed as part of the molecular-driven diagnosis of BCS.

CLASSIFICATION OF BUDD-CHIARI SYNDROME

BCS can be classified based on three factors: (1) Origin of obstructive lesion (endoluminal/primary and extraluminal/secondary); (2) Site of obstruction; (3) Onset of disease pathology (fulminant, subacute, acute, and chronic) (Table 1). Primary BCS refers to occlusion resulting from endoluminal venous pathologies such as thrombosis, stenosis, endophlebitis, and webs, while secondary BCS is extraluminal in origin with compression being caused extrinsically by neighboring structures, *i.e.*, cysts, abscess, hyperplastic nodules, or invasive tumors[18]. Three classifications can be presented based on the site of the obstructive lesion (Table 2). As highlighted by Patil *et al* veno-occlusive disease (type III presented by Chaubal *et al*[46]) results when sinusoidal endothelial cells are primarily injured, and so it may be regarded as a separate entity known as the sinusoidal obstruction syndrome[46-48].

CLINICAL PRESENTATION OF BUDD-CHIARI SYNDROME

The clinical presentation of BCS varies widely depending upon the extent as well as the site and rapidity of hepatic venous outflow obstruction. This causes varied degrees of liver involvement, resulting in about 20% of the patients having little to no symptoms at all[49,50]. Owing to the development of intrahepatic, extrahepatic, or portosystemic collaterals, these patients do not show any discernible signs of venous obstruction. In contrast, patients with symptomatic hepatic vein obstruction present with symptoms of portal hypertension such as ascites, upper gastrointestinal bleeding, and hepatic encephalopathy with right upper quadrant abdominal pain. Abdominal examination may further reveal a tender hepatomegaly with splenomegaly. Therefore, a classical triad of abdominal pain, ascites, and hepatomegaly should raise a clinical suspicion of BCS. In patients with obstruction of the IVC, the signs and symptoms greatly vary. As a result, some authors refer to the hepatic complications of IVC obstruction as "obliterative hepatocavopathy"[51]. These patients may have signs of caval obstruction such as pedal edema, varicocele, lower limb ulcers, and/or dilated subcutaneous veins in the abdomen, chest, and back[52]. The rapidity of venous obstruction may give rise to varied degrees and forms of presentation, *i.e.*, fulminant, acute, subacute, and chronic. Patients with fulminant disease have a hyperacute onset of disease pathology (≤ 2 month), which is manifested as acute hepatic failure with ascites, hyperbilirubinemia, tender hepatomegaly, and renal failure secondary to renal outflow compromise resulting from hepatic vein obstruction[8,53]. Particularly, the development of hepatic encephalopathy within 2 months of onset of jaundice is regarded as fulminant disease[54]. Fulminant disease requires acute obstruction of all three hepatic veins and so its recorded incidence is quite low [55]. Acute BCS has a short duration of onset which is usually within a month while the onset of subacute ranges from one to six months[54]. Interestingly, there is data to suggest geographical variation in the incidence of various types of BCS based on onset of pathology. In the eastern geographic regions, chronic presentations are more prevalent with onset ranging from 6 months to 30 years[54,56]. In the western geographic region, acute presentation is encountered relatively more frequently[56]. Esophageal bleeding, ascites, and hepatic necrosis may be absent in patients of subacute BCS[8]. Finally, the chronic form may take more than 6 months to develop and is characterized by progressive abdominal distention without jaundice. These patients may have signs of portal hypertension including variceal bleeding as well as splenomegaly. Renal impairment may not be seen in 50% of these patients with chronic BCS[57]. These symptoms may or may not be accompanied by a wide range of nonspecific symptoms. Though a plethora of differential diagnosis may be present at this point-and though it is true that BCS is generally a rare disease-clinicians must not exclude the possibility of BCS and as discussed by Aydinli and Bayraktar, clinical suspicion of BCS should escalate in the following scenarios: Acute onset ascites with tender hepatomegaly, massive ascites with relatively preserved liver functions, fulminant hepatic failure associated with hepatomegaly and ascites, unexplained chronic liver disease, liver disease with thrombogenic disorder, and sinusoidal dilation on liver biopsy without heart disease [18].

Acute liver failure is a sequelae of BCS that is infrequent in its occurrence. According to two case series, BCS accounts for 0.9% to 15% of the cases of acute liver failure. Majority of the patients, in the larger case series reporting 20 cases of BCS in 2344 patients of acute liver failure, were middle aged Caucasian women with PV. Acute-on-chronic manifestation, however, is relatively more frequent as compared to acute liver failure. To direct appropriate management, the Asian Pacific Association for the Study of the Liver has further classified the acute-on-chronic manifestation of BCS into three types based on underlying liver disease and acute insult (Table 2)[56]. Table 3 depicts the clinical character-

Table 1 Classification of Budd-Chiari syndrome

Ref.	Type	Site of obstruction
Chaubal *et al*[46]	I	Obstruction of IVC with or without secondary hepatic vein occlusion
	II	Obstruction of major hepatic veins
	III	Obstruction of small centrilobular veins (considered by some as veno-occlusive disease)
Patil *et al*[48]	I	Lesions of the IVC
	IIa	Short segment (< 4 cm) lesion of the hepatic vein
	IIb	Diffuse lesion of the hepatic vein
	III	Mixed type with lesions of IVC and the hepatic vein
Bansal *et al*[47]	I	Hepatic vein obstruction or thrombosis without IVC obstruction or compression
	II	Hepatic vein obstruction or thrombosis with IVC obstruction or thrombosis
	III	Isolated hepatic venous webs
	IV	Isolated IVC webs

IVC: Inferior vena cava.

Table 2 Acute-on-chronic manifestation of Budd-Chiari syndrome classification

Type	Description of pathology
A	Acute hepatic vein thrombosis or stent block precipitates ACLF in a BCS
B	Non-thrombotic acute insult precipitates ACLF in a chronic BCS
C	Acute hepatic vein thrombosis precipitates ACLF in a non-vascular chronic
	Liver disease

ACLF: Acute-on-chronic liver failure; BCS: Budd-Chiari syndrome.

istics of BCS based on geographic region of the studies population.

DIAGNOSIS OF BUDD-CHIARI SYNDROME

Although BCS is considered a rare disease, it has the potential to rapidly deteriorate a patient's health. Therefore, the need to obtain a correct diagnosis, followed by rapid specific treatment is urgent and extremely important.

Medical history

As BCS may be classified as primary (endoluminal lesion-like thrombosis) or secondary (extra-venous system causes), assessment of medical history plays a key role in identifying predisposing factors towards BCS[95]. Knowledge about these key points might be suggestive, not sufficient, of BCS diagnosis. Treatments administered by clinicians must put into account not only the obstruction by itself, but also its possible underlying causes: MPNs, *e.g.*, PV, ET, PMF[63]; History of hereditary or acquired thrombogenic disorders[64]; Use of oral contraceptives[65,66]; Paroxysmal nocturnal hemoglobinuria[67]; Status and history of recent pregnancy[68,69]; History of hepatocellular carcinoma [70]; Chronic liver disease, remained unexplained after exclusion of alcoholism, chronic viral hepatitis B or C, autoimmunity, iron overload, Wilson's disease and alpha-1 antitrypsin deficiency[71]; and other possible risk factors towards thrombosis or obstruction.

Physical examination

Majority of BCS patients present with the classic triad of abdominal pain especially in the upper right quadrant presenting in 61% of cases, ascites presenting in 83% of cases, and hepatomegaly presenting in 67% of cases[6,72]. The classic triad may form suddenly in acute cases (< 6 months), or progressively in chronic cases (> 6 months)[73]. These symptoms may or may not be accompanied by a wide range of nonspecific symptoms. Though a plethora of differential diagnosis may be present at this point-and

Table 3 Clinical characteristics of Budd-Chiari syndrome based on geographic region of the studied population[15,58-62]

Clinical characteristics	Percentage in various geographic regions						
	Egypt	France	Sweden	China	Japan	United States	Algeria
Ascites/Abdominal distension	82	74.4	88	51.9	31.2	29.9	74.8
Abdominal fullness	-	-	-	-	26.1	-	-
Abdominal discomfort	-	-	-	-	17.8	-	-
Abdominal pain	96	72.4	81	-	2.5	-	42.6
Cirrhosis	-	-	-	-	-	18.6	-
Hepatomegaly	50	70.1	72	-	54.7	-	-
Splenomegaly	42	49.1	66	-	-	-	-
Esophageal varices	-	54.8	67	-	-	7.4	-
Hematemesis/Variceal bleed	36	-	9	16	8.3	3.2	-
Melena	-	-	-	-	2.5	-	-
Jaundice	16	20.3	29	-	5.7	-	13.9
Fever	-	20.1	27	-	-	-	15.7
Hydrothorax	-	13.0	-	-	-	-	-
Acute kidney injury	-	-	-	-	-	18.8	-
History of recurrent abortions	6	-	-	-	-	-	-
History of previous thrombosis	10	-	-	-	-	7	-
Recurrent orogenital ulcers	4	-	-	-	-	-	-
Leg ulcers	2	-	-	-	3.8	-	-
Lower limb edema	68	-	-	58.9	31.8	-	13
Dilated abdominal veins	40	-	-	57	27.3	-	-
Hepatic encephalopathy	36	-	12	0.7	-	9.5	5.2
Ileus	-	-	21	-	-	-	-
General malaise	-	-	-	-	12.1	-	-
Acute respiratory failure	-	-	-	-	-	7	-

though it is true that BCS is generally a rare disease – clinicians must not exclude the possibility of BCS.

General supporting examination

Routine laboratory examinations might help aid clinicians to further pursue the presumptive diagnosis of BCS. Results that suggest the possibility of BCS include[6,73]: Diagnosis of PV, ET or PMF; normal or increase in liver function tests (alanine aminotransferase; aspartate aminotransferase); or findings which indicate thrombosis.

Specific supporting examination: imaging modalities

If a patient presents with the suspected risk factors, clinical presentation, and general supporting examination, clinicians must continue the diagnostic work-up with a high index of suspicion towards BCS. Specific supporting examination lies all around imaging modalities. These are the investigation methods useful towards diagnosing BCS, in an arranged order from the first line to the last[71]: Doppler ultrasonography; Magnetic resonance imaging (MRI) or computed tomography (CT) scan; Venography; Liver biopsy. Doppler ultrasonography is regarded as the initial technique of choice, offering a pooled sensitivity of 89% and specificity of 68% across multiple studies[74]. Doppler ultrasonography will show findings of no venous flow, retrograde venous flow, no visualization of the vein (possibly due to venous collapse) in the affected areas[75]. These findings might indicate BCS, though still overlapped by advanced cirrhosis[71]. However, in conditions where sonographic examination is inadequate to evaluate BCS, or in conditions where the distinct characteristics of BCS were not found, imaging through MRI or CT scan may be used in place to evaluate the presumptive diagnosis of BCS. MRI scan offers a pooled sensitivity of 93% and specificity of 55%, while CT scan offers a pooled sensitivity of 89% and specificity of 72%[74]. These modalities usually offer a clear diagnosis, though there might be

uncertainty in patients with advanced cirrhosis[71]. Venography, and especially liver biopsy might be the last, most invasive, yet the gold standard of diagnosis. However, biopsy provides the best explanation towards the damage and specific etiologies contributing to the disease.

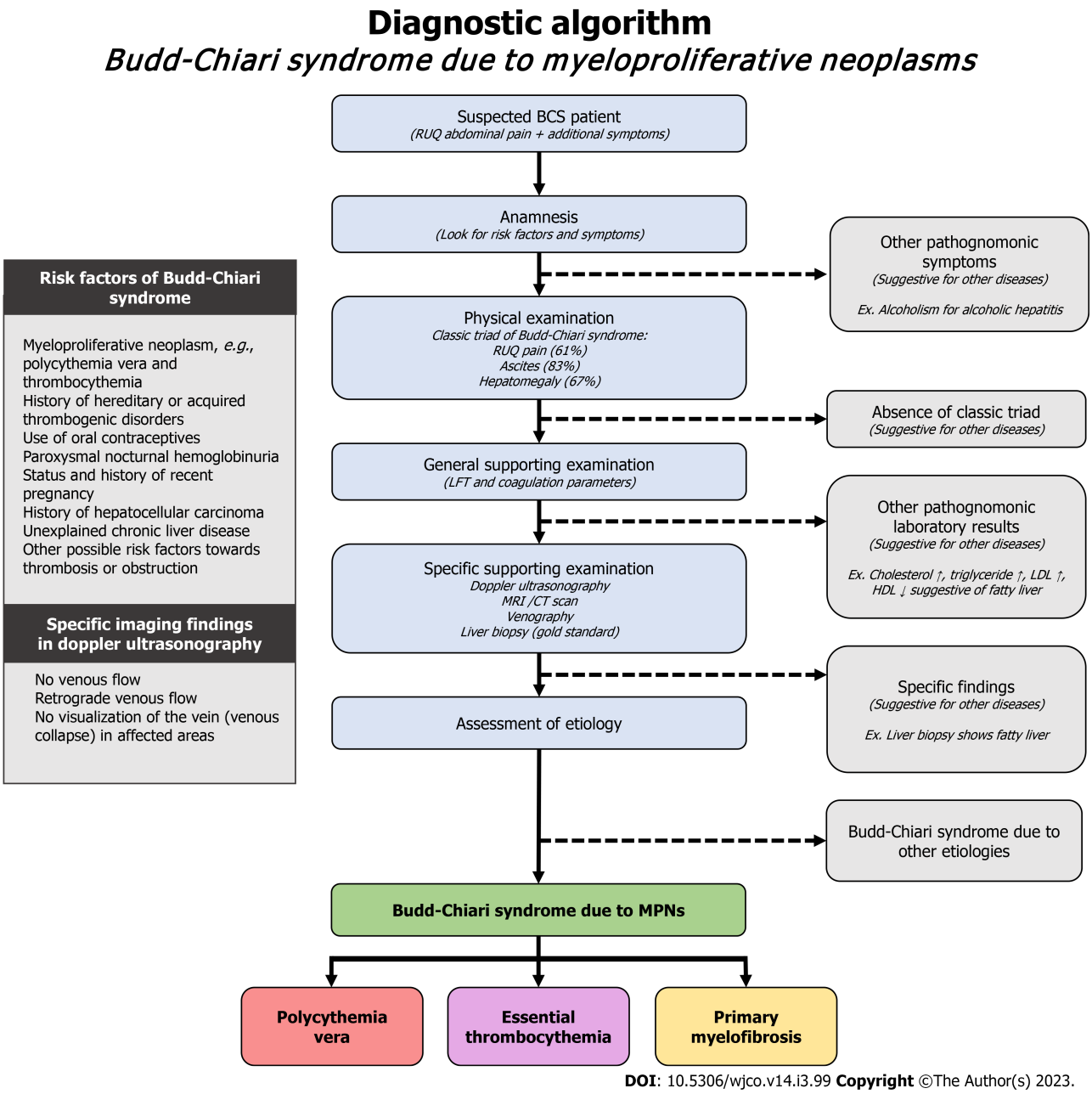
Assessment of etiology

The assessment of BCS etiology should definitely actively search for potential MPNs. A meta-analysis found that distribution of MPN subtypes in BCS were as follows: PV (52.9%), ET (24.6%), PMF (6.7%), and unclassifiable MPNs (17.0%)[28]. A presumption about the etiology of BCS might be estimated from the results of general supporting examination. We propose a diagnostic algorithm for this instance as reported in Figure 2.

MANAGEMENT OF BUDD-CHIARI SYNDROME IN MYELOPROLIFERATIVE NEOPLASMS

The treatment of BCS in MPNs requires a stepwise approach that may require a complete interdisciplinary team to adequately manage[54]. The goals of treatment aim at relieving obstruction, correcting the underlying conditions, and lastly to monitor for any liver deterioration[72]. The level of liver dysfunction can affect the coagulopathy of the patient and make anticoagulation difficult to predict in patients with BCS[54]. Despite this, the first line treatment for BCS due to MPNs still consists of anticoagulation therapy in order to relieve any obstruction. Furthermore, it is important to note that antiplatelet therapy should be initiated in patients as soon as possible once a diagnosis is established. Currently, the consensus when it comes to anticoagulation therapy is to treat with low molecular weight heparin (LMWH) and target an international normalized ratio (INR). In addition to the LMWH, patients should be started on an oral vitamin K antagonists (VKAs) (*i.e.*, warfarin). Once the INR is between 2 and 3, the LMWH can be discontinued, however, the oral vitamin K antagonist should be continued lifelong[6]. Although anticoagulation is the first line therapy for patients with BCS in MPNs, unfortunately, only 15%-20% of patients will respond to anticoagulation, as a result, other interventions may also need to be implemented in 80-85% of cases[54]. When looking at acute BCS it is important to consider methods that will restore patency of the thrombosed veins[76]. Treatment may start with thrombolytic therapy in select patients who have had symptoms for a few weeks and who have a well-established clot[54]. However, it is important to note that pharmacological thrombolysis has only been demonstrated to be effective in patients presenting with acute (less than a few weeks) BCS, therefore, at times other management options must also be considered. In addition, publications on thrombolytic agents in this particular setting have been limited to case reports and small case series[77,78]. It is also important to note that thrombolytic agents should not be considered when managing chronic BCS due to the fact that these clots have been demonstrated to be resistant to thrombolytic agents and may increase the bleeding risk for the patient far beyond the potential therapeutic benefit[78]. Another management option that is worth considering in acute or subacute BCS in MPNs include angioplasty and stenting [13]. Both angioplasty and stenting can be considered in patients that have a demonstrated obstruction that is appreciated on radiological findings[13]. In addition, this intervention is typically reserved for patients who are symptomatic[71,79]. It is also important to note that performing angioplasty can be done in combination with thrombolytic therapy for patients who have an acute obstruction and may benefit from both interventions[79].

Although angioplasty and stenting has started to play a major role and is a staple in the treatment of BCS it is not without risks. The primary risk associated with stenting is the risk of reocclusion. One intervention that has shown some promise in preventing reocclusion is the placement of a metal stent following angioplasty. However, it is important to also note that increased outcomes for this particular method is limited to some small case studies[40]. For BCS patients, inclusive of the individuals waiting for orthotopic liver transplantation, transjugular intrahepatic portosystemic shunt (TIPS) is suggested as a safer and very successful treatment strategy. TIPS is one of the major treatment options available for the treatment of BCS[81]. The Baveno IV consensus has resulted in a fairly uniform course of care for the patients of BCS, with prior consideration for the medical therapy alongside anticoagulation among all patients with no contraindications. This has been the case for more than 20 years of TIPS usage in BCS [82]. Because of the technical difficulty in sustaining venous patency for a longer period of time, TIPS should be specifically considered for the patients with Rotterdam class III, acute liver failure, or in those individuals who have failed medical therapy, diffuse hepatic vein thrombosis or prior hepatic venous stenting. Ascites is typically the most prevalent symptom, followed by variceal or gastrointestinal hemorrhage, with ascites rates in the trials under review reaching 100% and variceal bleeding rates reaching up to 30.9%. Since it has not been found as a potential risk factor in the occurrence of post-TIPS hepatic encephalopathy, prior hepatic encephalopathy need not be regarded as a contraindication to TIPS in BCS[81]. Additionally, pre-procedure jaundice is not regarded as a contraindication for TIPS in BCS patients, despite the fact that this is the case in patients with end-stage liver disease due to the higher mortality in that cohort, with the reason for the difference being hypothesized to be related to the absence of hepatocyte necrosis in the BCS patients[83]. Although there is no universal agreement across the studies regarding the ideal timing to perform TIPS, patients presenting with refractory ascites,



DOI: 10.5306/wjco.v14.i3.99

Figure 2 Diagnostic algorithm of Budd-Chiari syndrome due to myeloproliferative neoplasms.

hepatic failure, or the gastrointestinal hemorrhage should have access to this right away[84]. BCS patients have a greater rate of shunt dysfunction than other cirrhotic patients receiving TIPS (about 50% *vs* 80% within 1 year), which is likely related to the higher incidence of underlying thrombophilia[85]. Development of stents coated with polytetrafluoroethylene to be used during TIPS in the management of BCS has improved patients' prognosis, mainly due to the decrease in the need for re-interventions and due to the tripling of the shunt patency[86]. Hence, TIPS could be a safer and effective treatment option for managing BCS in MPNs.

Over time, transplantation results have significantly improved and liver transplant outcomes are not harmed by prior TIPS. For patients with BCS, establishing venous outflow after liver transplantation is very essential and necessitates a variety of surgical procedures. These patients' outcomes exhibit various issues, such as vascular thrombosis and biliary difficulties[87]. Anticoagulation therapy, angioplasty, and TIPS fail in the 10% to 20% of BCS patients treated with a step-by-step management method, either due to technical failure or due to subpar clinical outcomes of a technically successful procedure necessitating rescue transplantation. Additionally, patients with fulminant liver failure and those with extremely advanced liver cirrhosis may benefit most from liver transplantation as treatment[88]. In the case that a medical therapy does not succeed, interventional revascularization and TIPS are recommended. The only guaranteed alternative for treating BCS is liver transplantation, if the presumptive medications and procedures are ineffective. Liver transplantation may be recommended as

a last resort or in fulminant situations, with promising and favorable outcomes. Ibach *et al*[89] analyzed 46 cases of BCS of whom 22 suffered from MPNs and reported that individuals with BCS who were subjected to liver transplantation experienced a median survival of approximately 24 years. Mortality rates were higher in patients with BCS and MPNs (RR=3.44, P = 0.05), however, two patients diagnosed with these blood cancers died due to secondary acute myeloid leukemia and extramedullary hematopoiesis in the spleen with consequent organ rupture, events which can occur during disease evolution irrespective of the use of liver transplantation in these cases. Considering 5-year survival rates for PV and ET are of about 80% and of about 50% for PMF, the use of liver transplantation for MPNs-linked BCS is satisfactory in terms of survival prolongation[90]. Patients with BCS and Philadelphia-negative MPNs receive the same care as those without MPNs during the acute phase. LMWH or unfractionated heparin should be administered as soon as possible, followed by VKAs. It is advised to proceed gradually. A second-line approach based on invasive treatments, such as angioplasty with or without stenting, TIPS, or surgical portosystemic shunt, should be taken into consideration in the event that clinical deterioration persists despite anticoagulation [14,40,59]. While catheter-directed thrombolysis may be helpful for the treatment of acute and partially occlusive thrombosis, systemic thrombolytic therapy with tissue plasminogen activator is not very successful[78,91,92]. TIPS has recently been suggested as the preferred course of care for individuals with BCS who exhibit symptoms of portal hypertension. If TIPS is ineffective or inappropriate, angioplasty/stenting should be the second line of treatment for the subset of individuals. When TIPS and angioplasty/stenting are ineffective or inappropriate, surgical shunts ought to be the first line of treatment[93]. Consider liver transplantation as a curative measure[3,40,93,94].

Long-term antithrombotic treatment

An improved prognosis was introduced in the 1980s with the systematic use of VKAs in BCS patients [71,95], while the impact of oral anticoagulation on the survival of the most severe patients is debatable [6]. Although the ideal time frame for VKA is uncertain, lifelong medication is generally advised for BCS[40,94,96]. Only 5 (8%) of the 163 patients in the comprehensive survey-of whom the majority (86%) were getting VKA-experienced non-fatal variceal hemorrhage[97]. The rate of both recurrent thrombosis and bleeding complications was 11% in a different study on patients with BCS who underwent liver transplantation and received VKAs afterwards, but the mortality rate related to recurrence is higher than that related to bleeding (4.4% and 0.8% of patients, respectively)[98]. There are few specific studies on the effectiveness and safety of VKAs treatment in individuals with MPN-related BCS, and the majority of the studies refer to SVT as a whole. In total, 49 of the 604 patients with SVT in the aforementioned multicenter prospective cohort (55 had BCS) had MPNs and had a 9-fold increased risk of recurrent thrombosis during follow-up[99]. The presence of *JAK2* gene mutations was substantially correlated with liver-related thrombotic problems in a series of 36 BCS patients with recurrent thrombosis following liver transplantation in 42% of instances (15/36). Moreover, 11 of the 12 patients who experienced post-transplant thrombotic events and 10 of the 24 patients who did not (P = 0.005) both exhibited *JAK2V617F*. Additionally, an increased incidence of thrombosis at any site was linked to a *JAK2* gene mutation (14/15 *vs* 7/21, P = 0.005). Liver-related thrombotic problems were more common in people with overt MPNs (9/12 *vs* 8/24, P = 0.03)[100]. An investigation of 181 patients suffering from MPNs who had their first episode of SVT was conducted retrospectively. In total, 31 (17.1%) and 109 (60.3%) patients, respectively, had BCS and extra-hepatic portal vein obstruction diagnosis; isolated thrombosis of the mesenteric or splenic veins was found in 18 and 23 cases, respectively. Following this index occurrence, the subjects were observed for 735 patient-years, and during that time, 31 recurrences occurred, representing an incidence rate of 4.2 per 100 patient-years. The recurrence rate was 3.9 per 100 patient-years in the 85% of patients who received VKAs, compared to 7.2 per 100 patient-years in the small portion (15%) of patients who did not. Compared to those who had thrombosis at the portal or other abdominal sites, patients with BCS had an incidence rate of new events that was significantly higher at 8.0 per 100 patient-years. In contrast, there was no difference in the rate of new arterial thrombosis between the two groups. Of note, patients with BCS had a 3-fold higher risk of recurrent SVT than those with other index SVT[101]. This difference was caused by an increased rate of venous events in BCS patients. Nine individuals with BCS (4 without and 5 with liver cirrhosis) were included in a survey on the use of direct oral anticoagulants (DOACs) in 94 patients with SVT, but no information was provided regarding the presence of MPNs as the underlying cause of SVT[102]. Anecdotally, it has been mentioned that a patient with PV and BCS used the direct factor Xa oral inhibitor rivaroxaban [103]. Semmler *et al*[104] analyzed the potential efficacy of DOACs, specifically edoxaban, apixaban, rivaroxaban and dabigatran, in the management of BCS. Their sample size consisted of 47 BCS subjects: 22 (of whom 10 had MPNs) were put on DOACs, whereas 21 (of whom 9 had MPNs) received LMWHs or VKAs. Complete response was noted in >60% of the BCS subjects who were prescribed DOACs. Complications during DOAC use included major spontaneous or surgery-related hemorrhage (n = 4 and n = 1, respectively) and minor hemorrhages (n = 7), whereas transplant-free survival at 5 years exceeded 90% and at 10 years exceeded 80%. *JAK2V617F*-negative MPNs experienced better treatment responses to DOACs as compared to *JAK2V617F*-positive individuals. Nevertheless, further research needs to assess the benefits of DOAC use in MPN-related BCS as the sample of the aforementioned investigation was too small to draw pertinent conclusions.

Cytoreductive therapy

Cytoreduction is necessary in MPN patients who have experienced thrombosis in the past[105]. It is unknown whether it is appropriate to administer cytoreduction to SVT patients with *JAK2V617F* but without an explicit MPN diagnosis in accordance with the WHO criteria. Given the lack of evidence, care must be taken when prescribing cytoreductive regimens to *JAK2V617F*-positive SVT patients because approximately half of them will not develop MPN during the follow-up[106]. On the other hand, the *JAK2V617F* mutation increases the incidence of recurrent thrombosis in both BCS patients who have undergone liver transplantation[100] and SVT patients generally[107,108]. Therefore, it seems sensible to utilize medications to slow the growth of the mutant clone. Only one of the 17 MPN patients with BCS in a small retrospective cohort who received hydroxyurea and aspirin after liver donation developed recurrent extrahepatic portal vein obstruction (EHPVO)[109]. The rate of recurrence was 22% (4/18) in another small series of 18 MPN individuals with BCS; all new thrombotic events occurred in patients who were not receiving cytoreductive therapy[110]. In a pooled cohort of 1500 patients with MPNs and thrombosis, the multivariable analysis limited to the patients with first arterial thrombosis showed that recurrent arterial thrombosis was prevented by antiplatelet agents and by hydroxyurea and only partially by VKAs; on the contrary, in patients with the first venous thrombosis, venous recurrences were more prevented by VKAs than by antiplatelet agents or hydroxyurea. Notably, after adjusting for age, sex, antiplatelet treatment, VKA treatment, and cytoreductive drugs other than hydroxyurea in 218 patients with SVT (38 with BCS), it was verified that hydroxyurea had no significant impact on the rate of either recurrent thrombosis or recurrent VTE[111]. The cause of this finding is unclear; however, it may be hypothesized that since hypercytemia is less common in SVT patients[112], cytoreduction may not be as important as it might be in other circumstances.

Orthotopic liver transplantation

Patients with BCS who experience failure of the aforementioned therapies are candidates for orthotopic liver transplantation in the range of 10 to 20 percent of cases[6]. Following liver transplantation, the 1-year and 5-year survival rates in a group of 36 BCS patients were 84% and 69%, respectively; the presence of a molecular characteristic for MPNs had no bearing on these survival rates[100]. The mortality rate following liver transplantation in a different series of 25 BCS patients was comparable in MPN (3/18, 16.7%) and non-MPN patients (1/7, 14.3%)[110]. In a retrospective cohort of 78 BCS patients, the 5-year survival was 78% *vs* 76%, and the 10-year survival was 68% *vs* 73%, respectively. Long-term survival following liver transplantation was similar in MPN (n = 41) and non-MPN patients (n = 37), with P values of 0.81 and 0.66, respectively. Twelve of the 41 MPN patients (or 29%) passed away within the first three years following liver transplantation, but only one death with recurrent BCS was attributable to the hematologic condition[146]. Following liver transplantation, progression to myelofibrosis or acute leukemia was not noted in 17 cases with a follow-up period of up to 20 years [109], nor in 78 cases in a mean follow-up period of 12.4 years (range 3-28.4 years)[113] in two series of BCS patients. While there are many treatment options available for BCS, the availability of many creates obstacles in maintaining a standard treatment plan. It is usual for clinicians to use anticoagulation as the first line of treatment for tackling BCS[114]; however, in cases when the condition cannot be controlled by medical treatment alone, several trials have shown encouraging outcomes with the use of TIPS in BCS patients as an alternative to shunt surgery or liver transplantation[115,116].

Anticoagulant therapy has been an accepted standard of treatment in BCS[117]; however, this standard remains controversial amidst clinicians. Emergent anticoagulation may not significantly improve clinical outcomes for individuals with acute ischemic stroke, according to several clinical investigations[118-120]. The current mode of treatment also selects LT as a de-facto last resort when it requires for a complex venous outflow reconstruction that would be difficult to acquire in medically underserved areas[6,121]. We have previously established that TIPS is the equivocally accepted and proven form of treatment for most BCS patients; in fact, the 10-year survival of the procedure is 69% [122]. It naturally becomes a concern if the current chronology requires a deeper revision. For instance, if anticoagulants truly seem to have no significant impact on the pathophysiology of the condition, could we derive a better medicinal first line of treatment for the condition? Could TIPS become the first mode of treatment if more non-invasive mechanisms are innovated to perform it? BCS is a rare disease, and it is important to remember that time is an invaluable resource in situations as such. Resorting to ineffective treatment not only delays medical management, but it deters the patient's condition. If the first line of treatment leads a patient to the second line in the longer run, maybe it is a scope for physicians to rethink the chronology of treatment. Constant revisions of guidelines will allow us to not only discard what is counterintuitive, but it will promote clinicians to adapt to newer and more effective modes of treatment.

DIFFERENTIAL DIAGNOSIS, PROGNOSIS AND COMPLICATIONS OF BUDD-CHIARI SYNDROME IN MYELOPROLIFERATIVE NEOPLASMS

Hepatic vein obstruction in BCS may lead to abdominal pain, ascites, jaundice, and hepatomegaly. Given the significant overlap of these symptoms with other hepatic pathologies the differential diagnosis remains broad. PVT is distinct from BCS and directly involves the liver vasculature. MPNs are the most common cause of noncirrhotic, nonmalignant PVT[28]. Given the similar presentation of both PVT and BCS and its high prevalence in MPNs, diagnostic tests and imaging modalities should be utilized in differentiating both conditions. In BCS, Doppler ultrasound is effective in visualizing occlusion of the hepatic vein[123]. The absence of hepatic vein thrombosis and presence of reduced or absent flow in the portal veins with duplex ultrasound points towards PVT as the primary differential diagnosis[10]. Other differential diagnoses that should be given consideration include granulomatous liver disease, hemochromatosis, and alcoholic liver disease. A retrospective study across three centers in Europe studied the prognostic factors associated with BCS in MPNs. Their results indicated poorer baseline prognostic features, earlier hepatic decompression procedures, but no effect on 5-year survival. However, the presence of MPNs was associated with event free survival in BCS[124]. Generally, the determinants of prognosis in BCS are age, serum creatinine, Child-Pugh score, and ascites. A higher Child-Pugh score, older age, refractory ascites to diuretics, and higher serum creatinine are all factors pointing towards a poor prognosis[125]. In recent years 5-year survival rates have improved in BCS. Improved survival is largely attributed to the improved management of hypercoagulable states, and endovascular intervention[95]. Although rarely performed now, surgical portosystemic shunting improved survival in BCS patients who were determined to have a poor prognosis[126]. In a retrospective analysis of 78 BCS patients both with and without MPNs similar outcomes were measured after liver transplantation[113]. Janssen *et al* studied 172 patients with EHPVO, 24 of which carried a diagnosis of MPN. The five-year survival rates were similar between both groups (92% *vs* 53%, $P = 0.18$) [127]. Significant consideration must also be given to the role of VKAs in the prognosis of BCS. De Stefano *et al*[128] performed a retrospective analysis of 94 patients with MPNs (PV or ET), significant reduction of re-thrombosis was independently achieved with VKAs (HR 0.32; 95%CI: 0.15–0.64) and antiplatelet agents (HR 0.42; 95%CI: 0.22–0.77). DOACs may improve outcomes in patients with BCS. Semmler *et al*[104] in 2022 performed a retrospective analysis of 46 patients across three Australian centers with BCS. Six patients were managed with DOACs and 16 were switched to DOACs from LMWHs ($n = 12$) or VKAs ($n = 4$). In total, 4 major and 7 minor bleeding events were reported. Larger prospective studies need to be conducted assessing the safety and prognosis of VKAs *vs* DOACs in patients with BCS. Based on these previous studies it is determined that identification of BCS in patients with MPNs should be promptly treated, thereby improving prognosis. Complications secondary to BCS can be determined based on the varying degree of ensuing hepatic injury and dysfunction. When untreated BCS can progress to fulminant liver failure, hepatorenal syndrome, hepatocellular carcinoma, and hepatic encephalopathy amongst other complications. In 2021, Asl *et al*[129] retrospectively reported on complications associated with liver transplantation (LT) in 4225 patients. 108 patients had BCS and were matched with a non-BCS group of 108 patients. One-, 3-, 5-, and 10- year survival rates were the same in both groups (82%, 78%, 76%, and 76% *vs* 83%, 83%, 83%, and 76%, $P = 0.556$). No differences were noted in the 6-month follow-up after LT. However, at a later period vascular thrombosis was more prevalent in the BCS group. In 2016, Ki *et al*[130] conducted a population-based study in South Korea identifying a total of 423 BCS patients from 2009-2013. Among them, 10.3% developed hepatic malignancy, and 3.3% underwent LT. The annual-case fatality rate was 2.8%. Hayek *et al*[131] performed a retrospective analysis on the long-term safety of patients with BCS who underwent TIPS. In total, 54 patients were identified, 34 (52%) of which suffered from MPNs. TIPS dysfunction was associated with MPNs (HR, 8.18; 95%CI: 1.45-46.18; $P = 0.017$).

CONCLUSION

Although BCS and MPNs are rare disorders, BCS can develop in the setting of MPNs. In this patient population, individualized, distinctive counseling and multidisciplinary surveillance and treatment strategies are crucial in achieving better possible outcomes. Individuals with MPNs should be managed in accordance with the most recent guidelines to avoid the occurrence of BCS, whereas a diagnosis of BCS should warrant an active search for the potential diagnosis of MPNs.

FOOTNOTES

Author contributions: All authors contributed to writing the original draft; Găman MA, Găman AM and Diaconu CC contributed to writing, review and editing, and methodology; Găman AM and Diaconu CC contributed equally as senior/last authors; all authors read and approved the final version of this paper.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Country/Territory of origin: Romania

ORCID number: Mihnea-Alexandru Găman 0000-0001-7133-8875; Matei-Alexandru Cozma 0000-0002-4998-0105; Arkadeep Dhali 0000-0002-1794-2569; L V Simhachalam Kutikuppala 0000-0002-5685-6049; Amelia Maria Găman 0000-0001-6974-2772; Camelia Cristina Diaconu 0000-0001-6837-260X.

S-Editor: Xing YX
L-Editor: A
P-Editor: Xing YX

REFERENCES

1 **Nangalia J**, Green AR. Myeloproliferative neoplasms: from origins to outcomes. *Blood* 2017; **130**: 2475-2483 [PMID: 29212804 DOI: 10.1182/blood-2017-06-782037]
2 **Barbui T**, Thiele J, Gisslinger H, Kvasnicka HM, Vannucchi AM, Guglielmelli P, Orazi A, Tefferi A. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. *Blood Cancer J* 2018; **8**: 15 [PMID: 29426921 DOI: 10.1038/s41408-018-0054-y]
3 **Greenfield G**, McMullin MF, Mills K. Molecular pathogenesis of the myeloproliferative neoplasms. *J Hematol Oncol* 2021; **14**: 103 [PMID: 34193229 DOI: 10.1186/s13045-021-01116-z]
4 **Moliterno AR**, Ginzburg YZ, Hoffman R. Clinical insights into the origins of thrombosis in myeloproliferative neoplasms. *Blood* 2021; **137**: 1145-1153 [PMID: 33237986 DOI: 10.1182/blood.2020008043]
5 **Găman MA**, Cozma MA, Dobrică EC, Crețoiu SM, Găman AM, Diaconu CC. Liquid biopsy and potential liquid biopsy-based biomarkers in philadelphia-negative classical myeloproliferative neoplasms: A systematic review. *Life* 2021; 11 [PMID: 34357048 DOI: 10.3390/Life11070677]
6 **Darwish Murad S**, Plessier A, Hernandez-Guerra M, Fabris F, Eapen CE, Bahr MJ, Trebicka J, Morard I, Lasser L, Heller J, Hadengue A, Langlet P, Miranda H, Primignani M, Elias E, Leebeek FW, Rosendaal FR, Garcia-Pagan JC, Valla DC, Janssen HL; EN-Vie (European Network for Vascular Disorders of the Liver). Etiology, management, and outcome of the Budd-Chiari syndrome. *Ann Intern Med* 2009; **151**: 167-175 [PMID: 19652186 DOI: 10.7326/0003-4819-151-3-200908040-00004]
7 **Faraoun SA**, Boudjella Mel A, Debzi N, Afredj N, Guerrache Y, Benidir N, Bouzid C, Bentabak K, Soyer P, Bendib SE. Budd-Chiari syndrome: a prospective analysis of hepatic vein obstruction on ultrasonography, multidetector-row computed tomography and MR imaging. *Abdom Imaging* 2015; **40**: 1500-1509 [PMID: 25687630 DOI: 10.1007/s00261-015-0380-5]
8 **Ferral H**, Behrens G, Lopera J. Budd-Chiari syndrome. *AJR Am J Roentgenol* 2012; **199**: 737-745 [PMID: 22997363 DOI: 10.2214/AJR.12.9098]
9 **Menon KVN**, Shah V, Kamath PS. The Budd–Chiari Syndrome. *N Engl J Med* 2004; **350**: 578-585 [PMID: 14762185 DOI: 10.1056/NEJMra020282]
10 **Ponziani FR**, Zocco MA, Campanale C, Rinninella E, Tortora A, Di Maurizio L, Bombardieri G, De Cristofaro R, De Gaetano AM, Landolfi R, Gasbarrini A. Portal vein thrombosis: insight into physiopathology, diagnosis, and treatment. *World J Gastroenterol* 2010; **16**: 143-155 [PMID: 20066733 DOI: 10.3748/wjg.v16.i2.143]
11 **Plessier A**, Valla DC. Budd-Chiari syndrome. *Semin Liver Dis* 2008; **28**: 259-269 [PMID: 18814079 DOI: 10.1055/s-0028-1085094]
12 **Li Y**, De Stefano V, Li H, Zheng K, Bai Z, Guo X, Qi X. Epidemiology of Budd-Chiari syndrome: A systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 2019; **43**: 468-474 [PMID: 30528513 DOI: 10.1016/j.clinre.2018.10.014]
13 **Wang ZG**, Zhang FJ, Yi MQ, Qiang LX. Evolution of management for Budd-Chiari syndrome: a team's view from 2564 patients. *ANZ J Surg* 2005; **75**: 55-63 [PMID: 15740519 DOI: 10.1111/j.1445-2197.2005.03135.x]
14 **Zhang W**, Qi X, Zhang X, Su H, Zhong H, Shi J, Xu K. Budd-Chiari Syndrome in China: A Systematic Analysis of Epidemiological Features Based on the Chinese Literature Survey. *Gastroenterol Res Pract* 2015; **2015**: 738548 [PMID: 26504461 DOI: 10.1155/2015/738548]
15 **Ollivier-Hourmand I**, Allaire M, Goutte N, Morello R, Chagneau-Derrode C, Goria O, Dumortier J, Cervoni JP, Dharancy S, Ganne-Carrié N, Bureau C, Carbonell N, Abergel A, Nousbaum JB, Anty R, Barraud H, Ripault MP, De Ledinghen V, Minello A, Oberti F, Radenne S, Bendersky N, Farges O, Archambeaud I, Guillygomarc'h A, Ecochard M, Ozenne V, Hilleret MN, Nguyen-Khac E, Dauvois B, Perarnau JM, Lefilliatre P, Raabe JJ, Doffoel M, Becquart JP, Saillard E, Valla D, Dao T, Plessier A; French Network for Vascular Disorders of the Liver. The epidemiology of Budd-Chiari syndrome in France. *Dig Liver Dis* 2018; **50**: 931-937 [PMID: 29803757 DOI: 10.1016/j.dld.2018.04.004]
16 **Shin N**, Kim YH, Xu H, Shi HB, Zhang QQ, Colon Pons JP, Kim D, Xu Y, Wu FY, Han S, Lee BB, Li LS. Redefining Budd-Chiari syndrome: A systematic review. *World J Hepatol* 2016; **8**: 691-702 [PMID: 27326316 DOI:

10.4254/wjh.v8.i16.691]
17 **Qi X**, Wu F, Ren W, He C, Yin Z, Niu J, Bai M, Yang Z, Wu K, Fan D, Han G. Thrombotic risk factors in Chinese Budd-Chiari syndrome patients. An observational study with a systematic review of the literature. *Thromb Haemost* 2013; **109**: 878-884 [PMID: 23447059 DOI: 10.1160/TH12-10-0784]
18 **Aydinli M**, Bayraktar Y. Budd-Chiari syndrome: etiology, pathogenesis and diagnosis. *World J Gastroenterol* 2007; **13**: 2693-2696 [PMID: 17569137 DOI: 10.3748/wjg.v13.i19.2693]
19 **Mahmoud AE**, Helmy AS, Billingham L, Elias E. Poor prognosis and limited therapeutic options in patients with Budd-Chiari syndrome and portal venous system thrombosis. *Eur J Gastroenterol Hepatol* 1997; **9**: 485-489 [PMID: 9187882 DOI: 10.1097/00042737-199705000-00014]
20 **Dacha S**, Devidi M, Osmundson E. Budd-Chiari syndrome in a patient with ulcerative colitis and no inherited coagulopathy. *World J Hepatol* 2011; **3**: 164-169 [PMID: 21860676 DOI: 10.4254/wjh.v3.i6.164]
21 **Meena DS**, Sonwal VS, Bohra GK, Balesa J, Rohila AK. Celiac disease with Budd-Chiari syndrome: A rare association. *SAGE Open Med Case Rep* 2019; **7**: 2050313X19842697 [PMID: 31001425 DOI: 10.1177/2050313X19842697]
22 **Bayraktar Y**, Balkanci F, Bayraktar M, Calguneri M. Budd-Chiari syndrome: A common complication of Behçet's disease. *Am J Gastroenterol* 1997; **92**: 858-862 [PMID: 9149201]
23 **Anagnostopoulos GK**, Margantinis G, Kostopoulos P, Papadopoulou G, Roulias A, Sakorafas G, Liassis N. Budd-Chiari syndrome and portal vein thrombosis due to right atrial myxoma. *Ann Thorac Surg* 2004; **78**: 333-334 [PMID: 15223461 DOI: 10.1016/S0003-4975(03)01265-7]
24 **Neelakantan S**, Babu AA, Anandarajan R, Philip B. Hepatic hydatid disease presenting as secondary Budd-Chiari syndrome. *BMJ Case Rep* 2016; **2016** [PMID: 27681355 DOI: 10.1136/bcr-2016-217118]
25 **de Menezes Neves PDM**, Balbo BEP, Watanabe EH, Rocha-Santos V, Andraus W, D'Albuquerque LAC, Onuchic LF. Functional Budd-Chiari Syndrome Associated With Severe Polycystic Liver Disease. *Clin Med Insights Gastroenterol* 2017; **10**: 1179552217713003 [PMID: 28611533 DOI: 10.1177/1179552217713003]
26 **Karadag O**, Akinci D, Aksoy DY, Bayraktar Y. Acute Budd-Chiari syndrome resulting from a pyogenic liver abscess. *Hepatogastroenterology* 2005; **52**: 1554-1556 [PMID: 16201117]
27 **Mahmoud AE**, Mendoza A, Meshikhes AN, Olliff S, West R, Neuberger J, Buckels J, Wilde J, Elias E. Clinical spectrum, investigations and treatment of Budd-Chiari syndrome. *QJM* 1996; **89**: 37-43 [PMID: 8730341 DOI: 10.1093/oxfordjournals.qjmed.a030135]
28 **Smalberg JH**, Arends LR, Valla DC, Kiladjian JJ, Janssen HL, Leebeek FW. Myeloproliferative neoplasms in Budd-Chiari syndrome and portal vein thrombosis: a meta-analysis. *Blood* 2012; **120**: 4921-4928 [PMID: 23043069 DOI: 10.1182/blood-2011-09-376517]
29 **Palandri F**, Latagliata R, Polverelli N, Tieghi A, Crugnola M, Martino B, Perricone M, Breccia M, Ottaviani E, Testoni N, Merli F, Aversa F, Alimena G, Cavo M, Martinelli G, Catani L, Baccarani M, Vianelli N. Mutations and long-term outcome of 217 young patients with essential thrombocythemia or early primary myelofibrosis. *Leukemia* 2015; **29**: 1344-1349 [PMID: 25801912 DOI: 10.1038/LEU.2015.87]
30 **Kralovics R**, Passamonti F, Buser AS, Teo SS, Tiedt R, Passweg JR, Tichelli A, Cazzola M, Skoda RC. A gain-of-function mutation of JAK2 in myeloproliferative disorders. *N Engl J Med* 2005; **352**: 1779-1790 [PMID: 15858187 DOI: 10.1056/nejmoa051113]
31 **Smalberg JH**, Darwish Murad S, Braakman E, Valk PJ, Janssen HL, Leebeek FW. Myeloproliferative disease in the pathogenesis and survival of Budd-Chiari syndrome. *Haematologica* 2006; **91**: 1712-1713 [PMID: 17145613 DOI: 10.1182/blood.v108.11.1480.1480]
32 **Ibarrola C**, Castellano VM, Colina F. Focal hyperplastic hepatocellular nodules in hepatic venous outflow obstruction: a clinicopathological study of four patients and 24 nodules. *Histopathology* 2004; **44**: 172-179 [PMID: 14764061 DOI: 10.1111/j.1365-2559.2004.01795.x]
33 **Tanaka M**, Wanless IR. Pathology of the liver in Budd-Chiari syndrome: portal vein thrombosis and the histogenesis of veno-centric cirrhosis, veno-portal cirrhosis, and large regenerative nodules. *Hepatology* 1998; **27**: 488-496 [PMID: 9462648 DOI: 10.1002/hep.510270224]
34 **Lefkowitch JH**, Mendez L. Morphologic features of hepatic injury in cardiac disease and shock. *J Hepatol* 1986; **2**: 313-327 [PMID: 3722787 DOI: 10.1016/S0168-8278(86)80043-5]
35 **Cazals-Hatem D**, Vilgrain V, Genin P, Denninger MH, Durand F, Belghiti J, Valla D, Degott C. Arterial and portal circulation and parenchymal changes in Budd-Chiari syndrome: a study in 17 explanted livers. *Hepatology* 2003; **37**: 510-519 [PMID: 12601347 DOI: 10.1053/jhep.2003.50076]
36 **Gonzalez RS**, Gilger MA, Huh WJ, Washington MK. The Spectrum of Histologic Findings in Hepatic Outflow Obstruction. *Arch Pathol Lab Med* 2017; **141**: 98-103 [PMID: 27681331 DOI: 10.5858/arpa.2015-0388-OA]
37 **Brunt EM**, Gouw AS, Hubscher SG, Tiniakos DG, Bedossa P, Burt AD, Callea F, Clouston AD, Dienes HP, Goodman ZD, Roberts EA, Roskams T, Terracciano L, Torbenson MS, Wanless IR. Pathology of the liver sinusoids. *Histopathology* 2014; **64**: 907-920 [PMID: 24393125 DOI: 10.1111/his.12364]
38 **Arcidi JM**, Moore GW, Hutchins GM. Hepatic morphology in cardiac dysfunction. A clinicopathologic study of 1000 subjects at autopsy. *Am J Pathol* 1981; **104**: 159-166 [PMID: 6455066]
39 **Ghaferi AA**, Hutchins GM. Progression of liver pathology in patients undergoing the Fontan procedure: Chronic passive congestion, cardiac cirrhosis, hepatic adenoma, and hepatocellular carcinoma. *J Thorac Cardiovasc Surg* 2005; **129**: 1348-1352 [PMID: 15942576 DOI: 10.1016/j.jtcvs.2004.10.005]
40 **DeLeve LD**, Valla DC, Garcia-Tsao G; American Association for the Study Liver Diseases. Vascular disorders of the liver. *Hepatology* 2009; **49**: 1729-1764 [PMID: 19399912 DOI: 10.1002/hep.22772]
41 **Landolfi R**, Rocca B, Patrono C. Bleeding and thrombosis in myeloproliferative disorders: mechanisms and treatment. *Crit Rev Oncol Hematol* 1995; **20**: 203-222 [PMID: 8748010 DOI: 10.1016/1040-8428(94)00164-O]
42 **Landolfi R**, Di Gennaro L, Falanga A. Thrombosis in myeloproliferative disorders: pathogenetic facts and speculation. *Leukemia* 2008; **22**: 2020-2028 [PMID: 18800144 DOI: 10.1038/leu.2008.253]
43 **Pearson TC**, Wetherley-Mein G. Vascular occlusive episodes and venous haematocrit in primary proliferative

polycythaemia. *Lancet* 1978; **2**: 1219-1222 [PMID: 82733 DOI: 10.1016/S0140-6736(78)92098-6]
44 **Li M**, De Stefano V, Song T, Zhou X, Guo Z, Zhu J, Qi X. Prevalence of CALR mutations in splanchnic vein thrombosis: A systematic review and meta-analysis. *Thromb Res* 2018; **167**: 96-103 [PMID: 29803161 DOI: 10.1016/j.thromres.2018.05.007]
45 **De Stefano V**, Qi X, Betti S, Rossi E. Splanchnic vein thrombosis and myeloproliferative neoplasms: molecular-driven diagnosis and long-term treatment. *Thromb Haemost* 2016; **115**: 240-249 [PMID: 26333846 DOI: 10.1160/TH15-04-0326]
46 **Chaubal N**, Dighe M, Hanchate V, Thakkar H, Deshmukh H, Rathod K. Sonography in Budd-Chiari syndrome. *J Ultrasound Med* 2006; **25**: 373-379 [PMID: 16495498 DOI: 10.7863/jum.2006.25.3.373]
47 **Bansal V**, Gupta P, Sinha S, Dhaka N, Kalra N, Vijayvergiya R, Dutta U, Kochhar R. Budd-Chiari syndrome: imaging review. *Br J Radiol* 2018; **91**: 20180441 [PMID: 30004805 DOI: 10.1259/bjr.20180441]
48 **Patil P**, Deshmukh H, Popat B, Rathod K. Spectrum of imaging in Budd Chiari syndrome. *J Med Imaging Radiat Oncol* 2012; **56**: 75-83 [PMID: 22339749 DOI: 10.1111/j.1754-9485.2012.02341.x]
49 **Liu L**, Qi XS, Zhao Y, Chen H, Meng XC, Han GH. Budd-Chiari syndrome: Current perspectives and controversies. *Eur Rev Med Pharmacol Sci* 2016; **20**: 3273-3281 [PMID: 27467004]
50 **Falcão CK**, Fagundes GC, Lamos GC, Felipe-Silva A, Lovisolo SM, Martines JA, de Campos FP. Budd-Chiari Syndrome: an unnoticed diagnosis. *Autops Case Rep* 2015; **5**: 17-25 [PMID: 26484330 DOI: 10.4322/acr.2015.009]
51 **Okuda K**. Obliterative hepatocavopathy-inferior vena cava thrombosis at its hepatic portion. *Hepatobiliary Pancreat Dis Int* 2002; **1**: 499-509 [PMID: 14607675]
52 **Sharma A**, Keshava SN, Eapen A, Elias E, Eapen CE. An Update on the Management of Budd-Chiari Syndrome. *Dig Dis Sci* 2021; **66**: 1780-1790 [PMID: 32691382 DOI: 10.1007/s10620-020-06485-y]
53 **Lupasco I**, Dumbrava VT. Diagnosis and therapy of Budd Chiari syndrome. *Med Pharm Rep* 2021; **94**: S68-S71 [PMID: 34527916 DOI: 10.15386/mpr-2235]
54 **Gavriilidis P**, Marangoni G, Ahmad J, Azoulay D. State of the Art, Current Perspectives, and Controversies of Budd-Chiari Syndrome: A Review. *J Clin Med Res* 2022; **14**: 147-157 [PMID: 35573933 DOI: 10.14740/jocmr4724]
55 **Parekh J**, Matei VM, Canas-Coto A, Friedman D, Lee WM; Acute Liver Failure Study Group. Budd-chiari syndrome causing acute liver failure: A multicenter case series. *Liver Transpl* 2017; **23**: 135-142 [PMID: 27656864 DOI: 10.1002/lt.24643]
56 **Shukla A**, Shreshtha A, Mukund A, Bihari C, Eapen CE, Han G, Deshmukh H, Cua IHY, Lesmana CRA, Al Meshtab M, Kage M, Chaiteeraki R, Treeprasertsuk S, Giri S, Punamiya S, Paradis V, Qi X, Sugawara Y, Abbas Z, Sarin SK. Budd-Chiari syndrome: consensus guidance of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int* 2021; **15**: 531-567 [PMID: 34240318 DOI: 10.1007/s12072-021-10189-4]
57 **Valla DC**. Hepatic vein thrombosis (Budd-Chiari syndrome). *Semin Liver Dis* 2002; **22**: 5-14 [PMID: 11928075 DOI: 10.1055/s-2002-23202]
58 **Abdel Hameed MR**, Elbeih EAS, Abd El-Aziz HM, Afifi OA, Khalaf LMR, Ali Abu Rahma MZ, Sabry A. Epidemiological Characteristics and Etiology of Budd-Chiari Syndrome in Upper Egypt. *J Blood Med* 2020; **11**: 515-524 [PMID: 33408545 DOI: 10.2147/JBM.S278678]
59 **Zhang W**, Wang QZ, Chen XW, Zhong HS, Zhang XT, Chen XD, Xu K. Budd-Chiari syndrome in China: A 30-year retrospective study on survival from a single center. *World J Gastroenterol* 2018; **24**: 1134-1143 [PMID: 29563757 DOI: 10.3748/wjg.v24.i10.1134]
60 **Okuda H**, Yamagata H, Obata H, Iwata H, Sasaki R, Imai F, Okudaira M, Ohbu M, Okuda K. Epidemiological and clinical features of Budd-Chiari syndrome in Japan. *J Hepatol* 1995; **22**: 1-9 [PMID: 7751574 DOI: 10.1016/0168-8278(95)80252-5]
61 **Alukal JJ**, Zhang T, Thuluvath PJ. A Nationwide Analysis of Budd-Chiari Syndrome in the United States. *J Clin Exp Hepatol* 2021; **11**: 181-187 [PMID: 33746442 DOI: 10.1016/j.jceh.2020.08.005]
62 **Afredj N**, Guessab N, Nani A, Faraoun SA, Ouled Cheikh I, Kerbouche R, Hannoun D, Amir ZC, Ait Kaci H, Bentabak K, Plessier A, Valla DC, Cazals-Hatem V, Denninger MH, Boucekkine T, Debzi N. Aetiological factors of Budd-Chiari syndrome in Algeria. *World J Hepatol* 2015; **7**: 903-909 [PMID: 25937867 DOI: 10.4254/wjh.v7.i6.903]
63 **Vannucchi AM**. Insights into the pathogenesis and management of thrombosis in polycythemia vera and essential thrombocythemia. *Intern Emerg Med* 2010; **5**: 177-184 [PMID: 19789961 DOI: 10.1007/s11739-009-0319-3]
64 **Denninger MH**, Chaït Y, Casadevall N, Hillaire S, Guillin MC, Bezeaud A, Erlinger S, Briere J, Valla D. Cause of portal or hepatic venous thrombosis in adults: the role of multiple concurrent factors. *Hepatology* 2000; **31**: 587-591 [PMID: 10706547 DOI: 10.1002/hep.510310307]
65 **Ponnatapura J**, Kielar A, Burke LMB, Lockhart ME, Abualruz AR, Tappouni R, Lalwani N. Hepatic complications of oral contraceptive pills and estrogen on MRI: Controversies and update - Adenoma and beyond. *Magn Reson Imaging* 2019; **60**: 110-121 [PMID: 31009688 DOI: 10.1016/j.mri.2019.04.010]
66 **Valla D**, Le MG, Poynard T, Zucman N, Rueff B, Benhamou JP. Risk of hepatic vein thrombosis in relation to recent use of oral contraceptives. A case-control study. *Gastroenterology* 1986; **90**: 807-811 [PMID: 3949113 DOI: 10.1016/0016-5085(86)90855-3]
67 **Valla D**, Dhumeaux D, Babany G, Hillon P, Rueff B, Rochant H, Benhamou JP. Hepatic vein thrombosis in paroxysmal nocturnal hemoglobinuria. A spectrum from asymptomatic occlusion of hepatic venules to fatal Budd-Chiari syndrome. *Gastroenterology* 1987; **93**: 569-575 [PMID: 3609666 DOI: 10.1016/0016-5085(87)90920-6]
68 **Altunayoglu V**, Turedi S, Gunduz A, Karaca Y, Akdogan RA. Cerebral venous thrombosis and hepatic venous thrombosis during pregnancy. *J Obstet Gynaecol Res* 2007; **33**: 78-82 [PMID: 17212671 DOI: 10.1111/j.1447-0756.2007.00479.x]
69 **Khuroo MS**, Datta DV. Budd-Chiari syndrome following pregnancy. Report of 16 cases, with roentgenologic, hemodynamic and histologic studies of the hepatic outflow tract. *Am J Med* 1980; **68**: 113-121 [PMID: 7350798 DOI: 10.1016/0002-9343(80)90180-1]
70 **Ren W**, Qi X, Yang Z, Han G, Fan D. Prevalence and risk factors of hepatocellular carcinoma in Budd-Chiari syndrome:

a systematic review. *Eur J Gastroenterol Hepatol* 2013; **25**: 830-841 [PMID: 23411869 DOI: 10.1097/MEG.0b013e32835eb8d4]

71 **Janssen HL**, Garcia-Pagan JC, Elias E, Mentha G, Hadengue A, Valla DC; European Group for the Study of Vascular Disorders of the Liver. Budd-Chiari syndrome: a review by an expert panel. *J Hepatol* 2003; **38**: 364-371 [PMID: 12586305 DOI: 10.1016/S0168-8278(02)00434-8]

72 **Hitawala AA**, Gupta V. Budd Chiari Syndrome. 2022 Feb 9. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan- [PMID: 32644367]

73 **Niknam R**, Hajizadegan N, Mohammadkarimi V, Mahmoudi L. A study of the different parameters in acute and chronic Budd–Chiari syndrome. *Egypt Liver J* 2020; 10: 1-8 [DOI: 10.1186/s43066-020-00058-4]

74 **Gupta P**, Bansal V, Kumar-M P, Sinha SK, Samanta J, Mandavdhare H, Sharma V, Dutta U, Kochhar R. Diagnostic accuracy of Doppler ultrasound, CT and MRI in Budd Chiari syndrome: systematic review and meta-analysis. *Br J Radiol* 2020; **93**: 20190847 [PMID: 32150462 DOI: 10.1259/bjr.20190847]

75 **Millener P**, Grant EG, Rose S, Duerinckx A, Schiller VL, Tessler FN, Perrella RR, Ragavendra N. Color Doppler imaging findings in patients with Budd-Chiari syndrome: correlation with venographic findings. *AJR Am J Roentgenol* 1993; **161**: 307-312 [PMID: 8333368 DOI: 10.2214/ajr.161.2.8333368]

76 **Mukund A**, Gamanagatti S. Imaging and interventions in Budd-Chiari syndrome. *World J Radiol* 2011; **3**: 169-177 [PMID: 21860712 DOI: 10.4329/wjr.v3.i7.169]

77 **Raju GS**, Felver M, Olin JW, Satti SD. Thrombolysis for acute Budd-Chiari syndrome: Case report and literature review. *Am J Gastroenterol* 1996; **91**: 1262-1263 [PMID: 8651186]

78 **Sharma S**, Texeira A, Texeira P, Elias E, Wilde J, Olliff SP. Pharmacological thrombolysis in Budd Chiari syndrome: a single centre experience and review of the literature. *J Hepatol* 2004; **40**: 172-180 [PMID: 14672630 DOI: 10.1016/j.jhep.2003.09.028]

79 **Fisher NC**, McCafferty I, Dolapci M, Wali M, Buckels JA, Olliff SP, Elias E. Managing Budd-Chiari syndrome: a retrospective review of percutaneous hepatic vein angioplasty and surgical shunting. *Gut* 1999; **44**: 568-574 [PMID: 10075967 DOI: 10.1136/gut.44.4.568]

80 **Eapen CE**, Velissaris D, Heydtmann M, Gunson B, Olliff S, Elias E. Favourable medium term outcome following hepatic vein recanalisation and/or transjugular intrahepatic portosystemic shunt for Budd Chiari syndrome. *Gut* 2006; **55**: 878-884 [PMID: 16174658 DOI: 10.1136/gut.2005.071423]

81 **Khan F**, Mehrzad H, Tripathi D. Timing of Transjugular Intrahepatic Portosystemic Stent-shunt in Budd-Chiari Syndrome: A UK Hepatologist's Perspective. *J Transl Int Med* 2018; **6**: 97-104 [PMID: 30425945 DOI: 10.2478/jtim-2018-0022]

82 **Seijo S**, Plessier A, Hoekstra J, Dell'era A, Mandair D, Rifai K, Trebicka J, Morard I, Lasser L, Abraldes JG, Darwish Murad S, Heller J, Hadengue A, Primignani M, Elias E, Janssen HL, Valla DC, Garcia-Pagan JC; European Network for Vascular Disorders of the Liver. Good long-term outcome of Budd-Chiari syndrome with a step-wise management. *Hepatology* 2013; **57**: 1962-1968 [PMID: 23389867 DOI: 10.1002/hep.26306]

83 **Tripathi D**, Macnicholas R, Kothari C, Sunderraj L, Al-Hilou H, Rangarajan B, Chen F, Mangat K, Elias E, Olliff S. Good clinical outcomes following transjugular intrahepatic portosystemic stent-shunts in Budd-Chiari syndrome. *Aliment Pharmacol Ther* 2014; **39**: 864-872 [PMID: 24611957 DOI: 10.1111/apt.12668]

84 **Fitsiori K**, Tsitskari M, Kelekis A, Filippiadis D, Triantafyllou K, Brountzos E. Transjugular intrahepatic portosystemic shunt for the treatment of Budd-Chiari syndrome patients: results from a single center. *Cardiovasc Intervent Radiol* 2014; **37**: 691-697 [PMID: 23860938 DOI: 10.1007/s00270-013-0697-9]

85 **Qi X**, Yang M, Fan D, Han G. Transjugular intrahepatic portosystemic shunt in the treatment of Budd-Chiari syndrome: a critical review of literatures. *Scand J Gastroenterol* 2013; **48**: 771-784 [PMID: 23506234 DOI: 10.3109/00365521.2013.777775]

86 **Sonavane AD**, Amarapurkar DN, Rathod KR, Punamiya SJ. Long Term Survival of Patients Undergoing TIPS in Budd-Chiari Syndrome. *J Clin Exp Hepatol* 2019; **9**: 56-61 [PMID: 30765940 DOI: 10.1016/j.jceh.2018.02.008]

87 **Aktas H**, Ozer A, Yilmaz TU, Keceoglu S, Can MG, Emiroglu R. Liver transplantation for Budd-Chiari syndrome: A challenging but handable procedure. *Asian J Surg* 2022; **45**: 1396-1402 [PMID: 34688524 DOI: 10.1016/j.asjsur.2021.09.007]

88 **Akamatsu N**, Sugawara Y, Kokudo N. Budd-Chiari syndrome and liver transplantation. *Intractable Rare Dis Res* 2015; **4**: 24-32 [PMID: 25674385 DOI: 10.5582/irdr.2014.01031]

89 **Ibach M**, Eurich D, Dobrindt E, Lurje G, Schöning W, Öllinger R, Pratschke J, Globke B. Orthotopic Liver Transplantation for Budd-Chiari Syndrome: Observations from a 30-Year Liver Transplant Program. *Medicina (Kaunas)* 2021; **57** [PMID: 34441027 DOI: 10.3390/medicina57080821]

90 **Verstovsek S**, Yu J, Scherber RM, Verma S, Dieyi C, Chen CC, Parasuraman S. Changes in the incidence and overall survival of patients with myeloproliferative neoplasms between 2002 and 2016 in the United States. *Leuk Lymphoma* 2022; **63**: 694-702 [PMID: 34689695 DOI: 10.1080/10428194.2021.1992756]

91 **Smalberg JH**, Spaander MV, Jie KS, Pattynama PM, van Buuren HR, van den Berg B, Janssen HL, Leebeek FW. Risks and benefits of transcatheter thrombolytic therapy in patients with splanchnic venous thrombosis. *Thromb Haemost* 2008; **100**: 1084-1088 [PMID: 19132234]

92 **Zhang Q**, Xu H, Zu M, Gu Y, Wei N, Wang W, Gao Z, Shen B. Catheter-directed thrombolytic therapy combined with angioplasty for hepatic vein obstruction in Budd-Chiari syndrome complicated by thrombosis. *Exp Ther Med* 2013; **6**: 1015-1021 [PMID: 24137308 DOI: 10.3892/etm.2013.1239]

93 **Mancuso A**. An update on the management of Budd-Chiari syndrome: the issues of timing and choice of treatment. *Eur J Gastroenterol Hepatol* 2015; **27**: 200-203 [PMID: 25590783 DOI: 10.1097/MEG.0000000000000282]

94 **Senzolo M**, Riggio O, Primignani M; Italian Association for the Study of the Liver (AISF) ad hoc. Vascular disorders of the liver: recommendations from the Italian Association for the Study of the Liver (AISF) ad hoc committee. *Dig Liver Dis* 2011; **43**: 503-514 [PMID: 21185794 DOI: 10.1016/j.dld.2010.11.006]

95 **Zeitoun G**, Escolano S, Hadengue A, Azar N, El Younsi M, Mallet A, Boudet MJ, Hay JM, Erlinger S, Benhamou JP,

Belghiti J, Valla D. Outcome of Budd-Chiari syndrome: a multivariate analysis of factors related to survival including surgical portosystemic shunting. *Hepatology* 1999; **30**: 84-89 [PMID: 10385643 DOI: 10.1002/hep.510300125]

96 **de Franchis R**, Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; **63**: 743-752 [PMID: 26047908 DOI: 10.1016/j.jhep.2015.05.022]

97 **Hadengue A**, Poliquin M, Vilgrain V, Belghiti J, Degott C, Erlinger S, Benhamou JP. The changing scene of hepatic vein thrombosis: recognition of asymptomatic cases. *Gastroenterology* 1994; **106**: 1042-1047 [PMID: 8143970 DOI: 10.1016/0016-5085(94)90765-X]

98 **Mentha G**, Giostra E, Majno PE, Bechstein WO, Neuhaus P, O'Grady J, Praseedom RK, Burroughs AK, Le Treut YP, Kirkegaard P, Rogiers X, Ericzon BG, Hockerstedt K, Adam R, Klempnauer J. Liver transplantation for Budd-Chiari syndrome: A European study on 248 patients from 51 centres. *J Hepatol* 2006; **44**: 520-528 [PMID: 16427719 DOI: 10.1016/j.jhep.2005.12.002]

99 **Ageno W**, Riva N, Schulman S, Beyer-Westendorf J, Bang SM, Senzolo M, Grandone E, Pasca S, Di Minno MN, Duce R, Malato A, Santoro R, Poli D, Verhamme P, Martinelli I, Kamphuisen P, Oh D, D'Amico E, Becattini C, De Stefano V, Vidili G, Vaccarino A, Nardo B, Di Nisio M, Dentali F. Long-term Clinical Outcomes of Splanchnic Vein Thrombosis: Results of an International Registry. *JAMA Intern Med* 2015; **175**: 1474-1480 [PMID: 26168152 DOI: 10.1001/jamainternmed.2015.3184]

100 **Westbrook RH**, Lea NC, Mohamedali AM, Smith AE, Orr DW, Roberts LN, Heaton ND, Wendon JA, O'Grady JG, Heneghan MA, Mufti GJ. Prevalence and clinical outcomes of the 46/1 haplotype, Janus kinase 2 mutations, and ten-eleven translocation 2 mutations in Budd-Chiari syndrome and their impact on thrombotic complications post liver transplantation. *Liver Transpl* 2012; **18**: 819-827 [PMID: 22467227 DOI: 10.1002/lt.23443]

101 **De Stefano V**, Vannucchi AM, Ruggeri M, Cervantes F, Alvarez-Larrán A, Iurlo A, Randi ML, Pieri L, Rossi E, Guglielmelli P, Betti S, Elli E, Finazzi MC, Finazzi G, Zetterberg E, Vianelli N, Gaidano G, Nichele I, Cattaneo D, Palova M, Ellis MH, Cacciola E, Tieghi A, Hernandez-Boluda JC, Pungolino E, Specchia G, Rapezzi D, Forcina A, Musolino C, Carobbio A, Griesshammer M, Barbui T. Splanchnic vein thrombosis in myeloproliferative neoplasms: risk factors for recurrences in a cohort of 181 patients. *Blood Cancer J* 2016; **6**: e493 [PMID: 27813534 DOI: 10.1038/bcj.2016.103]

102 **De Gottardi A**, Trebicka J, Klinger C, Plessier A, Seijo S, Terziroli B, Magenta L, Semela D, Buscarini E, Langlet P, Görtzen J, Puente A, Müllhaupt B, Navascuès C, Nery F, Deltenre P, Turon F, Engelmann C, Arya R, Caca K, Peck-Radosavljevic M, Leebeek FWG, Valla D, Garcia-Pagan JC; VALDIG Investigators. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. *Liver Int* 2017; **37**: 694-699 [PMID: 27778440 DOI: 10.1111/liv.13285]

103 **Jones C**, Levy Y, Tong AW. Elevated serum erythropoietin in a patient with polycythaemia vera presenting with Budd-Chiari syndrome. *BMJ Case Rep* 2014; **2014** [PMID: 25452296 DOI: 10.1136/bcr-2014-205663]

104 **Semmler G**, Lindorfer A, Schäfer B, Bartl S, Hametner-Schreil S, Gensluckner S, Balcar L, Pomej K, Lampichler K, Trauner M, Aigner E, Datz C, Zoller H, Hofer H, Schöfl R, Mandorfer M, Reiberger T, Scheiner B. Outcome of Budd-Chiari Syndrome Patients Treated With Direct Oral Anticoagulants: An Austrian Multicenter Study. *Clin Gastroenterol Hepatol* 2022; S1542-3565(22)00449 [PMID: 35533994 DOI: 10.1016/j.cgh.2022.04.024]

105 **Barbui T**, Tefferi A, Vannucchi AM, Passamonti F, Silver RT, Hoffman R, Verstovsek S, Mesa R, Kiladjian JJ, Hehlmann R, Reiter A, Cervantes F, Harrison C, Mc Mullin MF, Hasselbalch HC, Koschmieder S, Marchetti M, Bacigalupo A, Finazzi G, Kroeger N, Griesshammer M, Birgegard G, Barosi G. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. *Leukemia* 2018; **32**: 1057-1069 [PMID: 29515238 DOI: 10.1038/s41375-018-0077-1]

106 **Dentali F**, Squizzato A, Brivio L, Appio L, Campiotti L, Crowther M, Grandi AM, Ageno W. JAK2V617F mutation for the early diagnosis of Ph- myeloproliferative neoplasms in patients with venous thromboembolism: a meta-analysis. *Blood* 2009; **113**: 5617-5623 [PMID: 19273837 DOI: 10.1182/blood-2008-12-196014]

107 **De Stefano V**, Ruggeri M, Cervantes F, Alvarez-Larrán A, Iurlo A, Randi ML, Elli E, Finazzi MC, Finazzi G, Zetterberg E, Vianelli N, Gaidano G, Rossi E, Betti S, Nichele I, Cattaneo D, Palova M, Ellis MH, Cacciola R, Tieghi A, Hernandez-Boluda JC, Pungolino E, Specchia G, Rapezzi D, Forcina A, Musolino C, Carobbio A, Griesshammer M, Sant'Antonio E, Vannucchi AM, Barbui T. High rate of recurrent venous thromboembolism in patients with myeloproliferative neoplasms and effect of prophylaxis with vitamin K antagonists. *Leukemia* 2016; **30**: 2032-2038 [PMID: 27113812 DOI: 10.1038/leu.2016.85]

108 **Colaizzo D**, Amitrano L, Guardascione MA, Tiscia GL, D'Andrea G, Longo VA, Grandone E, Margaglione M. Outcome of patients with splanchnic venous thrombosis presenting without overt MPN: a role for the JAK2 V617F mutation re-evaluation. *Thromb Res* 2013; **132**: e99-e104 [PMID: 23916380 DOI: 10.1016/j.thromres.2013.07.014]

109 **Chinnakotla S**, Klintmalm GB, Kim P, Tomiyama K, Klintmalm E, Davis GL, Trotter JF, Saad R, Landaverde C, Levy MF, Goldstein RM, Stone MJ. Long-term follow-up of liver transplantation for Budd-Chiari syndrome with antithrombotic therapy based on the etiology. *Transplantation* 2011; **92**: 341-345 [PMID: 21659946 DOI: 10.1097/TP.0b013e3182247b05]

110 **Oldakowska-Jedynak U**, Ziarkiewicz M, Ziarkiewicz-Wróblewska B, Dwilewicz-Trojaczek J, Górnicka B, Nyckowski P, Paluszkiewicz R, Wróblewski T, Zieniewicz K, Patkowski W, Pączek L, Jedrzejczak WW, Krawczyk M. Myeloproliferative neoplasms and recurrent thrombotic events in patients undergoing liver transplantation for Budd-Chiari syndrome: a single-center experience. *Ann Transplant* 2014; **19**: 591-597 [PMID: 25394736 DOI: 10.12659/AOT.890834]

111 **De Stefano V**, Rossi E, Carobbio A, Ghirardi A, Betti S, Finazzi G, Vannucchi AM, Barbui T. Hydroxyurea prevents arterial and late venous thrombotic recurrences in patients with myeloproliferative neoplasms but fails in the splanchnic venous district. Pooled analysis of 1500 cases. *Blood Cancer J* 2018; **8**: 112 [PMID: 30420642 DOI: 10.1038/s41408-018-0151-y]

112 **Chait Y**, Condat B, Cazals-Hatem D, Rufat P, Atmani S, Chaoui D, Guilmin F, Kiladjian JJ, Plessier A, Denninger MH, Casadevall N, Valla D, Brière JB. Relevance of the criteria commonly used to diagnose myeloproliferative disorder in patients with splanchnic vein thrombosis. *Br J Haematol* 2005; **129**: 553-560 [PMID: 15877740 DOI:

10.1111/j.1365-2141.2005.05490.x]
113 **Potthoff A**, Attia D, Pischke S, Mederacke I, Beutel G, Rifai K, Deterding K, Heiringhoff K, Klempnauer J, Strassburg CP, Manns MP, Bahr MJ. Long-term outcome of liver transplant patients with Budd-Chiari syndrome secondary to myeloproliferative neoplasms. *Liver Int* 2015; **35**: 2042-2049 [PMID: 25736096 DOI: 10.1111/liv.12816]
114 **Payancé A**, Plessier A. Anticoagulation for budd-chiari syndrome. *Budd-Chiari Syndr* 2019; 131-145 [DOI: 10.1007/978-981-32-9232-1_10/COVER]
115 **Mancuso A**, Fung K, Mela M, Tibballs J, Watkinson A, Burroughs AK, Patch D. TIPS for acute and chronic Budd-Chiari syndrome: a single-centre experience. *J Hepatol* 2003; **38**: 751-754 [PMID: 12763367 DOI: 10.1016/s0168-8278(03)00118-1]
116 **Tavill AS**, Wood EJ, Kreel L, Jones EA, Gregory M, Sherlock S. The Budd-Chiari syndrome: correlation between hepatic scintigraphy and the clinical, radiological, and pathological findings in nineteen cases of hepatic venous outflow obstruction. *Gastroenterology* 1975; **68**: 509-518 [PMID: 1112452 DOI: 10.1016/S0016-5085(75)80090-4]
117 **Adams HP Jr**. Emergent use of anticoagulation for treatment of patients with ischemic stroke. *Stroke* 2002; **33**: 856-861 [PMID: 11872915 DOI: 10.1161/hs0302.104628]
118 **Sandercock PAG**, Counsell C, Gubitz GJ, Tseng MC. Antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev* 2018; **16**: CD000029 [PMID: 18646056 DOI: 10.1002/14651858.CD000029.pub2]
119 **Pullicino P**, Thompson JL, Barton B, Levin B, Graham S, Freudenberger RS; WARCEF Investigators. Warfarin *vs* aspirin in patients with reduced cardiac ejection fraction (WARCEF): rationale, objectives, and design. *J Card Fail* 2006; **12**: 39-46 [PMID: 16500579 DOI: 10.1016/j.cardfail.2005.07.007]
120 **Adams HP Jr**, Bendixen BH, Leira E, Chang KC, Davis PH, Woolson RF, Clarke WR, Hansen MD. Antithrombotic treatment of ischemic stroke among patients with occlusion or severe stenosis of the internal carotid artery: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology* 1999; **53**: 122-125 [PMID: 10408547 DOI: 10.1212/wnl.53.1.122]
121 **Deltenre P**, Denninger MH, Hillaire S, Guillin MC, Casadevall N, Brière J, Erlinger S, Valla DC. Factor V Leiden related Budd-Chiari syndrome. *Gut* 2001; **48**: 264-268 [PMID: 11156651 DOI: 10.1136/gut.48.2.264]
122 **Hernández-Guerra M**, Turnes J, Rubinstein P, Olliff S, Elias E, Bosch J, García-Pagán JC. PTFE-covered stents improve TIPS patency in Budd-Chiari syndrome. *Hepatology* 2004; **40**: 1197-1202 [PMID: 15486923 DOI: 10.1002/hep.20436]
123 **Iliescu L**, Toma L, Mercan-Stanciu A, Grumeza M, Dodot M, Isac T, Ioanitescu S. Budd-Chiari syndrome - various etiologies and imagistic findings. A pictorial review. *Med Ultrason* 2019; **21**: 344-348 [PMID: 31476215 DOI: 10.11152/mu-1921]
124 **Kiladjian JJ**, Cervantes F, Leebeek FW, Marzac C, Cassinat B, Chevret S, Cazals-Hatem D, Plessier A, Garcia-Pagan JC, Darwish Murad S, Raffa S, Janssen HL, Gardin C, Cereja S, Tonetti C, Giraudier S, Condat B, Casadevall N, Fenaux P, Valla DC. The impact of JAK2 and MPL mutations on diagnosis and prognosis of splanchnic vein thrombosis: a report on 241 cases. *Blood* 2008; **111**: 4922-4929 [PMID: 18250227 DOI: 10.1182/blood-2007-11-125328]
125 **Langlet P**, Escolano S, Valla D, Coste-Zeitoun D, Denie C, Mallet A, Levy VG, Franco D, Vinel JP, Belghiti J, Lebrec D, Hay JM, Zeitoun G. Clinicopathological forms and prognostic index in Budd-Chiari syndrome. *J Hepatol* 2003; **39**: 496-501 [PMID: 12971957 DOI: 10.1016/S0168-8278(03)00323-4]
126 **Darwish Murad S**, Valla DC, de Groen PC, Zeitoun G, Hopmans JA, Haagsma EB, van Hoek B, Hansen BE, Rosendaal FR, Janssen HL. Determinants of survival and the effect of portosystemic shunting in patients with Budd-Chiari syndrome. *Hepatology* 2004; **39**: 500-508 [PMID: 14768004 DOI: 10.1002/hep.20064]
127 **Janssen HL**, Wijnhoud A, Haagsma EB, van Uum SH, van Nieuwkerk CM, Adang RP, Chamuleau RA, van Hattum J, Vleggaar FP, Hansen BE, Rosendaal FR, van Hoek B. Extrahepatic portal vein thrombosis: aetiology and determinants of survival. *Gut* 2001; **49**: 720-724 [PMID: 11600478 DOI: 10.1136/gut.49.5.720]
128 **De Stefano V**, Za T, Rossi E, Vannucchi AM, Ruggeri M, Elli E, Micò C, Tieghi A, Cacciola RR, Santoro C, Gerli G, Vianelli N, Guglielmelli P, Pieri L, Scognamiglio F, Rodeghiero F, Pogliani EM, Finazzi G, Gugliotta L, Marchioli R, Leone G, Barbui T; GIMEMA CMD-Working Party. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. *Haematologica* 2008; **93**: 372-380 [PMID: 18268279 DOI: 10.3324/haematol.12053]
129 **Asl AA**, Lankarani KB, Nikeghbalian S, Kazemi K, Shamsaieefar A, Alizade-Naini M, Fattahi MR, Taghavi SA, Niknam R, Ejtehadi F, Dehghan M, Sivandzadeh G, Ghahramani S, Malek-Hosseini SA. Post liver transplant complications of Budd-Chiari syndrome. *Indian J Gastroenterol* 2021; **40**: 281-286 [PMID: 33743161 DOI: 10.1007/s12664-020-01139-3]
130 **Ki M**, Choi HY, Kim KA, Kim BH, Jang ES, Jeong SH. Incidence, prevalence and complications of Budd-Chiari syndrome in South Korea: a nationwide, population-based study. *Liver Int* 2016; **36**: 1067-1073 [PMID: 26558363 DOI: 10.1111/liv.13008]
131 **Hayek G**, Ronot M, Plessier A, Sibert A, Abdel-Rehim M, Zappa M, Rautou PE, Valla D, Vilgrain V. Long-term Outcome and Analysis of Dysfunction of Transjugular Intrahepatic Portosystemic Shunt Placement in Chronic Primary Budd-Chiari Syndrome. *Radiology* 2017; **283**: 280-292 [PMID: 27797679 DOI: 10.1148/radiol.2016152641]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2023 March 24; 14(3): 117-130

DOI: 10.5306/wjco.v14.i3.117

ISSN 2218-4333 (online)

MINIREVIEWS

Immune microenvironment of medulloblastoma: The association between its molecular subgroups and potential targeted immunotherapeutic receptors

Maher Kurdi, Nasser Mulla, Husam Malibary, Ahmed K Bamaga, Motaz M Fadul, Eyad Faizo, Sahar Hakamy, Saleh Baeesa

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mduma E, Tanzania; Ogino S, United States

Received: December 14, 2022
Peer-review started: December 14, 2022
First decision: January 20, 2023
Revised: February 8, 2023
Accepted: February 22, 2023
Article in press: February 22, 2023
Published online: March 24, 2023

Maher Kurdi, Motaz M Fadul, Department of Pathology, Faculty of Medicine, King Abdulaziz University, Rabigh 213733, Saudi Arabia

Maher Kurdi, Neuromuscular Unit, King Fahad Medical Research Center, King Abdulaziz University, Jeddah 213733, Saudi Arabia

Nasser Mulla, Department of Internal Medicine, Faculty of Medicine, Taibah University, Medina 213733, Saudi Arabia

Husam Malibary, Department of Internal Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah 213733, Saudi Arabia

Ahmed K Bamaga, Department of Paediatrics, Faculty of Medicine, King Abdulaziz University, Jeddah 213733, Saudi Arabia

Eyad Faizo, Division of Neurosurgery, Department of Surgery, Faculty of Medicine, Tabuk University, Tabuk 213733, Saudi Arabia

Sahar Hakamy, Neurmuscular Unit, Center of Excellence of Genomic Medicine, Jeddah 21423, Saudi Arabia

Saleh Baeesa, Department of Neuroscience, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia

Corresponding author: Maher Kurdi, FRCPC, MD, Associate Professor, Department of Pathology, Faculty of Medicine in Rabigh, King Abdulaziz University, Rabigh 213733, Saudi Arabia. ahkurdi@kau.edu.sa

Abstract

Medulloblastoma (MB) is considered the commonest malignant brain tumor in children. Multimodal treatments consisting of surgery, radiation, and chemotherapy have improved patients' survival. Nevertheless, the recurrence occurs in 30% of cases. The persistent mortality rates, the failure of current therapies to extend life expectancy, and the serious complications of non-targeted cytotoxic treatment indicate the need for more refined therapeutic approaches. Most MBs originating from the neurons of external granular layer line the outer surface of

neocerebellum and responsible for the afferent and efferent connections. Recently, MBs have been segregated into four molecular subgroups: Wingless-activated (WNT-MB) (Group 1); Sonic-hedgehog-activated (SHH-MB) (Group 2); Group 3 and 4 MBs. These molecular alterations follow specific gene mutations and disease-risk stratifications. The current treatment protocols and ongoing clinical trials against these molecular subgroups are still using common chemotherapeutic agents by which their efficacy have improved the progression-free survival but did not change the overall survival. However, the need to explore new therapies targeting specific receptors in MB microenvironment became essential. The immune microenvironment of MBs consists of distinctive cellular heterogeneities including immune cells and none-immune cells. Tumour associate macrophage and tumour infiltrating lymphocyte are considered the main principal cells in tumour microenvironment, and their role are still under investigation. In this review, we discuss the mechanism of interaction between MB cells and immune cells in the microenvironment, with an overview of the recent investigations and clinical trials

Key Words: Medulloblastoma; Tumour microenvironment; Tumour associated macrophages; Tumour infiltrating lymphocyte; Immunotherapies

Core Tip: Medulloblastoma (MB) is the most common malignant childhood tumor of the brain. Multimodal treatments consisting of surgery, radiation, and chemotherapy have reduced the cumulative incidence of late mortality. Nevertheless, the recurrence rate remains high. In this review, we discuss the mechanism of interaction between tumour cells of MB and immune cells in the microenvironment, with an overview of the recent investigations and clinical trials.

Citation: Kurdi M, Mulla N, Malibary H, Bamaga AK, Fadul MM, Faizo E, Hakamy S, Baeesa S. Immune microenvironment of medulloblastoma: The association between its molecular subgroups and potential targeted immunotherapeutic receptors. *World J Clin Oncol* 2023; 14(3): 117-130
URL: https://www.wjgnet.com/2218-4333/full/v14/i3/117.htm
DOI: https://dx.doi.org/10.5306/wjco.v14.i3.117

INTRODUCTION

Brain tumors are the leading cause of oncological death during childhood, and medulloblastoma (MB) is the commonest malignant tumor of the brain, accounting for 20%-30% of all central nervous system (CNS) tumors[1]. Diverse treatment modalities consisting of surgery and chemoradiotherapy have improved the patient's survival. Nevertheless, more than 1/3 of children with MB die within 5-years after diagnosis[2]. Late mortality remains a significant problem in disease consequences, which is attributed to tumour recurrence[3]. The persistent mortality, the failure of current drug therapies to extend life expectancy, and the serious complications of cytotoxic therapies indicate the necessity to explore new targeted treatments. Over the past decades, several tumor-centric studies have identified mutant genes and signaling pathways dysfunction that encourage MB growth. Most of MBs originate from the granular layer of cerebellum, which reside in the external granular layer and line the neocerebellum of newborns[4]. The existence of irregular biological signaling pathways created signaling dysregulation and genetic mutations affecting cerebellar development. Hence, the anatomical and cellular complexity of developing human tissues within the rhombic lip germinal zone produces glutamatergic neuronal lineages before its centralization. Molecular signatures encoded within a human rhombic-lip-derived lineage trajectory aligned with photoreceptor and unipolar cell profiles that are maintained in some medulloblastomas, suggesting a convergent basis. The advanced genomic studies over decades led to the assemblage of large amount of genetic information which resulted in four distinguishing molecular subgroups of MB including (Group 1) Wingless-activated (WNT-MB); (Group 2) Sonic-hedgehog-activated (SHH-MB); and Group 3 and Group 4[5] (Figure 1). Each group is characterized by distinct genetic abnormalities, methylation profiles, and clinical outcome. WNT- and SHH-type MBs are clearly detached from the other groups with lack of signaling pathway dysregulation identified in Group 3 and 4[5].

Molecular subgroups of MB

WNT-MB is the least common type, accounting for about 10%-15% of all MB patients. They are classically absent in infants and are seen more among children above 10 years of age[6-8] (Figure 1). The

Molecular subtype	WNT	SHH	Group 3	Group 4
Prevalence	10- 15 %	25%	25%	35%
Age	10-12 years old	< 16 years old	< 3 years old	Children
Gender	1:1	1:1	2:1	3:1
Location	Midline 4th ventricle	Cerebellar vermis	Midline 4th ventricle	Midline 4th ventricle
Pathology	Classic, rare LCA	DN, classic, LCA	Classic, rarely LCA	Classic, rarely LCA
Metastasis	5 - 10%	15-20%	45%	30-40%
Recurrence	Rare	Local	Metastatic	Metastatic
Common driver genetic mutation	1.CTNNB1 (90%)-WNT 2.DDX3X (50 %) 3.SMARCA4 (25%) 4.TP53 (<20 %)	1.TERT (83%) 2.PTCH1 (45%) -SHH 3.TP53 (15%) 4.SUFU (10 %) 5.SMO (rare) 6.MYCN (rare) 7.GLI2 (very rare)	1.GFI1(30 %) 2.MYC (10-20 %) 3.PVT1 (10 %) 4.SMARCA4 (rare) 5.OTX2 (very rare)	1. KDM6A (15 %) 2.SNCAIP (10%) 3.MYCN (5%) 4.CDK6 (rare) 5.GFI1 (very rare)
Chromosome alteration	Monosomy 6	Loss of 9q (PTCH1)	Isochromosome 17q	Isochromosome 17q
MYC status	+	+	+++	-
5-year survival	>90%	70%	40%	70-80%

DOI: 10.5306/wjco.v14.i3.117

Figure 1 Molecular subgroups of medulloblastoma based on 2021 World Health Organization classification of central nervous system tumours. SHH: Sonic-hedgehog; MYC: Myelocytomatosis oncogene; LCA: Life cycle assessment; WNT: Wingless.

clinical outcome of the disease under 16-years of age is usually good, with 90% 5-year survival[8]. The genetic mutation of the Catenin Beta-1 (*CTNNB1*) gene is the most common genetic alteration accounting for 85% of all WNT-MBs[9,10]. A gene expression with methylation profiling performed on several MB cases in 2016 has divided WNT- MBs into two variants: WNT-α, which consists of patients with chromosome 6 monosomy and WNT-β, that occurs in adults with chromosomal diploidy[11,12]. *CTNNB1* mutation usually occurs with other chromatin remodeling mutations such as Cyclic Adenosine Monophosphate Response Element Binding Protein (*CREBBP*), Mediator Complex Subunit 13 (*MED13*) and subunits of the nucleosome-remodeling complex such as SWI Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily A, Member 4 (*SMARCA4*), At-rich interaction Domain 1A (*ARID1A*) [9,10,13]. Most of WNT-MBs carries DEAD-Box Helicase 3 X-Linked (*DDX3X*) mutations, which participates in mRNA translation[12,14]. The germline mutation of antigen presenting cells (APC) on chromosome 5 as inherited Turcot syndrome and Anaplastic Lymphoma Kinase (*ALK*) gene also contribute to the development of WNT-MBs[9,15].

SHH-MB accounts for about 25% of all MBs with a 70% 5-years overall survival (OS). It is frequently seen in infants and adult patients[16,17]. The majority shows histologically nodular or desmoplastic morphology, which predicts a favourable prognosis[18]. *TP53* mutation segregates SHH-MBs into tumors with *TP53*-wildtype, often seen in young children and associated with favorable prognosis, and *TP53* mutant SHH-MB classically seen among older children and associated with poorer prognosis. SHH-MB with Protein Patch Homolog-1 (*PTCH1*) and Suppressor of Fused Homolog (*SUFU*) mutation are associated with Gorlin syndrome[19,20]. In children, *TP53* mutations frequently occurs with *GLI2* and *MYCN*-amplifications[9] (Figure 1).

Group 3 MB, a classical histological variant, accounts for 25% of all MBs and considered the deadliest subtype[7,21]. Tumours in this group with *MYC*-amplification carries a 20% risk of 5-years survival[22]. However, the most common cytogenetic abnormalities seen in Group 3 is the 17 ploss followed 16q and 9q losses[19]. Rare genetic variants in Group 3 MBs include Orthodenticle Homebox-2 (*OTX2*) and Enhancer of Zeste 2 Polycomb Repressive Complex 2 Subunit (*EZH2*) amplifications and *SMARCA4* mutations[23] (Figure 1).

Group 4 MB is the most frequent type among all MBs and often occurs in male more than females[6]. Isochromosome 17q is the most common cytogenetic aberration seen in this group. Other genetic variants include the loss of chromosome 8p, 10q, and the aberrations of 11p and 18q[2,17]. The clinical outcome is better in patients with chromosome 11 loss with an OS above 90%[19]. Zhou *et al*[24] reported that around 40% of Group 4 patients showed metastasis and treated as a high-risk disease. As we mentioned before, Group 3 and Group 4 MBs are genetically heterogeneous and not associated with germline mutations[25].

Current treatment options in MB

The magnitude of surgical resection in MB may not be as significant as earlier. After surgery, patients are treated with radiotherapy of the whole spinal axis with an additional boost targeting the tumor margins[26]. Radiotherapy usually starts 20-30 d after surgery however, delay of radiation may increase

risk of recurrence and is therefore not recommended for patients older than 3 years[27,28]. Post-operative radiotherapy for children less than 3 years of old may increase risk of cognitive dysfunction [18]. Postoperative chemotherapy in MB patients is essential strategy to reduce the radiation effects and improve the survival, particularly in young children. The treatment varies based on the risk of drug toxicity and recurrence rate. Both risks are correlated with MB molecular alterations and considered as prognostic factors prior treatment. The risk of toxicity should be taken carefully in infants and children younger than three years of age while the recurrence is usually high in metastatic cases or cases undergoing subtotal resection. Anaplastic and large cell variants may have poor response and worsening outcome[29] (Figure 2). The high-risk group consists of SHH-MBs with *MYCN*-amplification; SHH-MB with metastatic dissemination and wildtype *TP53*, and metastatic Group 4 MBs[7]. High-risk population includes mutant *TP53* SHH-MB patients and metastatic Group 3 MBs with *MYCN*-amplifications[7] (Figure 2).

Multi-modality treatments have been used in multiple clinical trials for ten years. The standard protocols included different chemotherapeutic agents with long-term or maintenance dose-related regime including ifosfamide, etoposide, methotrexate, cisplatin, and cytarabine, lomustine, and vincristine[30]. The maintenance regimen has improved the overall survival compared to the sandwich approach among patients with M0 or M1 disease[30,31]. Nonetheless, the most frequent and current treatment strategy includes risk-adapted radiotherapy followed by 4 cycles of cyclophosphamide, and a high dose of chemotherapy such as cisplatin, vincristine, followed by autologous stem cell transplantation. This protocol has improved the 5-year OS into 95%[16]. Additional clinical trials are ongoing to explore the efficacy of different treatment regimes in newly diagnosed MBs (Clinicaltrials.gov). The current treatment protocols and ongoing clinical trials are still using the same circulating chemotherapeutic agents but with different regimes. Multiple clinical trials have tested new therapies. Those trials were completed with positive and negative results (Clinicaltrials.gov). For example, a combined everolimus and ribociclib (cyclin D and CDK6 inhibitors) has been tested as a phase I trial (NCT03387020) in children with recurrent MBs. Some novel therapeutic strategies are currently recruiting, and their target are to reduce recurrence and to avoid the cytotoxic effects of chemoradiation (Table 1). For example, the usage of Entrectinib, a *TRK* inhibitor, and *ALK* inhibitor has been studied in a phase I/II trial (NCT02650401). There is a high tendency to discover the efficacy of molecularly targeted agents for MBs with dominant genetic alterations, regardless of the tumor subgroup. Patients with *FGFR*-gene mutation can be treated with erdafitinib (NCT03210714); MBs with *TSC*-gene mutations can be treated with samotolisib (NCT03213678); *SMARCA4*-gene mutations can be treated with tazemetostat, an *EZH2* inhibitor.

Immune microenvironment of MB

All the previously mentioned clinical trials are stratified based on disease risk, molecular subgroups, patients age, and all are targeting tumour cells. The necessity to explore MB microenvironment is encouraged to help discovering new targeted receptors. The immune microenvironment of any cancer represents all types of cells surrounding the tumour cells including immune and none-immune cells. The relationship between these cells is mechanical and heterogeneous, by which they can facilitate in promoting or inhibiting tumor growth[32]. Because some studies have indicated that MBs have fewer immune cells than glioblastoma[33,34], the role of immune microenvironment in promoting or suppressing MB progression was found to be difficult to understand. Some cellular factors in tumour microenvironment may act against immune reaction and can promote tumour growth progression and angiogenesis. The infiltration of immune cells in MB might be limited due to the blood–brain barrier (BBB), which acts as physical barrier for immune cells infiltration[35]. Despite of some immune cells bypass across BBB, there may be an increase in trafficking toward the brain under certain conditions due to destruction of the BBB[36]. Some experimental models showed that the reactive astrocytes surrounding the tumour microenvironment form perivascular barriers to restrict the immune cells infiltration to the brain through BBB[37].

The presence of inflammatory cells in the tumor microenvironment has been scientifically accepted as an essential element in tumour progression. A study done by Gururangan *et al*[38] found that treated MB patients exhibited more CD4+T-cell lymphopenia. We can also presume that pre-operative and post-operative steroid treatment may induce systemic immunosuppression which prevents antitumor immunity in MB patients. Tumours with a low mutational burden respond less efficiently to immune checkpoint inhibitor compared to tumors with a high mutational burden[39]. Moreover, the acidification of the tumour microenvironment causing glycolytic activity can encourage macrophages infiltration through G protein coupled receptor, which in turn enhances vascular endothelial growth factor, thus promoting M2-like features of tumor-associated macrophage (TAM)[40].

APC, the immune cells in microenvironment, were proven to infiltrate malignant brain tumours in children. APCs is expressed by Major Histocompatibility Complex (MHC) class-I on tumor cells to allow them to be identified and killed by CD8 cytotoxic T- cells. MBs and atypical teratoid/rhabdoid tumors showed the lowermost cellular infiltration of this type among all malignant brain tumors[34]. Microglia, resident macrophages in the brain, are the most dominant APCs in brain tumors[35]. It is not clear if microglia promote anti-MB immune response. Mundt *et al*[41] showed that microglia are dispensable for T-cell entry into the brain and for local reactivation of T-cells. The loss of MHC class-I expression on

Table 1 The most recent active and recruiting clinical trials of medulloblastoma that are targeting immune receptors or using different chemotherapeutic agents

Clinical Trial	Trial objective	Samples	Targeted subgroup	Completion date
NCT01878617	Clinical and molecular risk directed therapy of newly diagnosed MB	660	WNT, non-WNT, SHH	2028
NCT00089245	Intrathecal radioimmunotherapy using I-8H9	120	8H9 reactive MB confirmed by IHC	2024
NCT02905110	Simultaneous methotrexate/etoposide infusion	10	All MB subtypes	2023
NCT02962167	Modified measles virus (MV-NIS)	46	All MB subtypes	2024
NCT02271711	Expanded NK cells infusion with recurrent medulloblastoma	12	All MB subtypes	2023
NCT02359565	Pembrolizumab in patient with recurrent medulloblastoma	45	All MB subtypes	2023
NCT03389802	APX005M, a humanized IgG1κ monoclonal Ab that binds to CD40	45	MB with CD40 activity	2023
NCT03299309	PEP (CMV)-specific peptide vaccine in medulloblastoma	30	All MB subtypes	2024
NCT03598244	Volitinib, a small molecule inhibitor of c-Met in recurrent MB	50	All MB subtypes	2023
NCT03173950	Nivolumab, Immune check point inhibitor, in refractory MB	180	All MB subtypes	2024
NCT03500991	HER2-Specific CAR T-cell locoregional immunotherapy	48	Her-2 expressed medulloblastoma	2039
NCT01356290	Antiangiogenic therapy for recurrent medulloblastoma	100	All MB subtypes	2026
NCT03911388	G207, an oncolytic herpes simplex virus-1 (HSV)	15	All MB subtypes	2025
NCT03638167	EGFR806-specific CAR T-cell locoregional immunotherapy	36	EGFR positive tumours	2040
NCT03893487	Fimepinostat, a small molecule inhibitor in young MB	30	All MB subtypes	2027
NCT03709680	Palbociclib in combination with temozolomide and irinotecan	184	All MB subtypes	2028
NCT03904862	CX-4945 inhibitor of casein kinase II (CK2) tolerability	60	SHH-medulloblastoma	2028
NCT03936465	BMS-986158, a bromodomain inhibitor	66	MYCN amplification or BRD3 translocation MB	2024
NCT02650401	Entrectinib (RXDX-101), a TRKA/B/C, ROS1, and ALK inhibitor	68	MB harboring- NTRK1/2/3, ROS1, ALK fusions	2027
NCT03210714	Erdafitinib, an oral pan-FGFR inhibitor	49	Mutations in the FGFR1/2/3/4 pathway	2024
NCT03213678	Samotolisib, a PI3K/mTOR inhibitor	24	PI3K/MTOR activating mutations	2024
NCT03213704	Larotrectinib, NTRK fusion inhibitor for medulloblastoma	49	MB with NTRK fusions	2024
NCT03213665	Tazemetostat, a small molecule EZH2 inhibitor	20	EZH2, SMARCB1, or SMARCA4 mutations	2023
NCT03233204	Olaparib for refractory or aggressive medulloblastoma	29	Defects in DNA damage repair genes	2024
NCT04023669	LY2606368, a molecularly targeted CHK1/2 inhibitor	21	Group3/Group4; SHH; indeterminate types	2026
NCT03526250	Palbociclib (Pediatric MATCH treating trials	49	Rb positive solid tumours	2025
NCT02444546	Wild-Type Reovirus in Combination with Sargramostim	06	All MB subtypes	2026
NCT04185038	B7-H3-Specific CAR-T Cell Locoregional Immunotherapy	90	All MB subtypes	2041

NCT01601184	Vismodegib combined with Temozolomide	24	SHH-MB group	2023
NCT03155620	Targeted therapy directed by genetic testing	2316	All MB subtypes	2027
NCT00089245	Iodine I 131 monoclonal antibody 8H9	120	All MB subtypes	2025
NCT02271711	Natural killer cell therapy	12	All MB subtypes	
NCT04315064	Infusion of Panobinostat (MTX110)	5	All MB subtypes	2024
NCT04743661	131I-Omburtamab in recurrent medullo-blastoma	62	All MB subtypes	2030
NCT03257631	Pomalidomide onotherapy for recurrent or progressive MB	53	All MB subtypes	2023
NCT04320888	Selpercatinib for treatment of advanced medulloblastoma	49	Tumour with activating RET alteration	2027

ALK: Anaplastic Lymphoma Kinase; CMV: Cytomegalovirus; EGFR: Epidermal Growth Factor Receptor; MB: Medulloblastoma; PEP: Post-exposure prophylaxis; SHH: Sonic-hedgehog; IHC: Immunohistochemistry; RET: Rearranged in transfection; NK: Natural killer; WNT: Wingless.

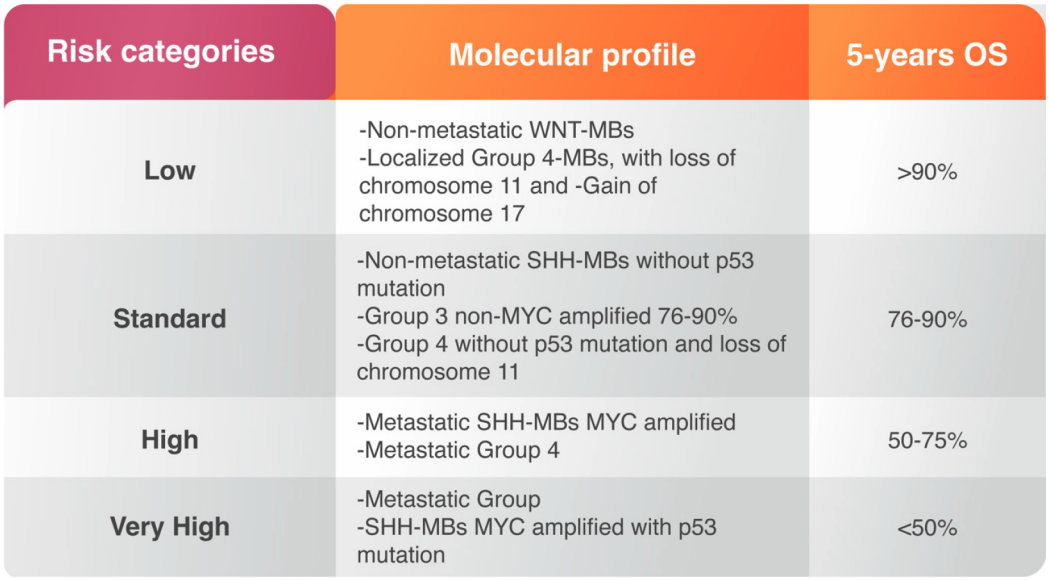
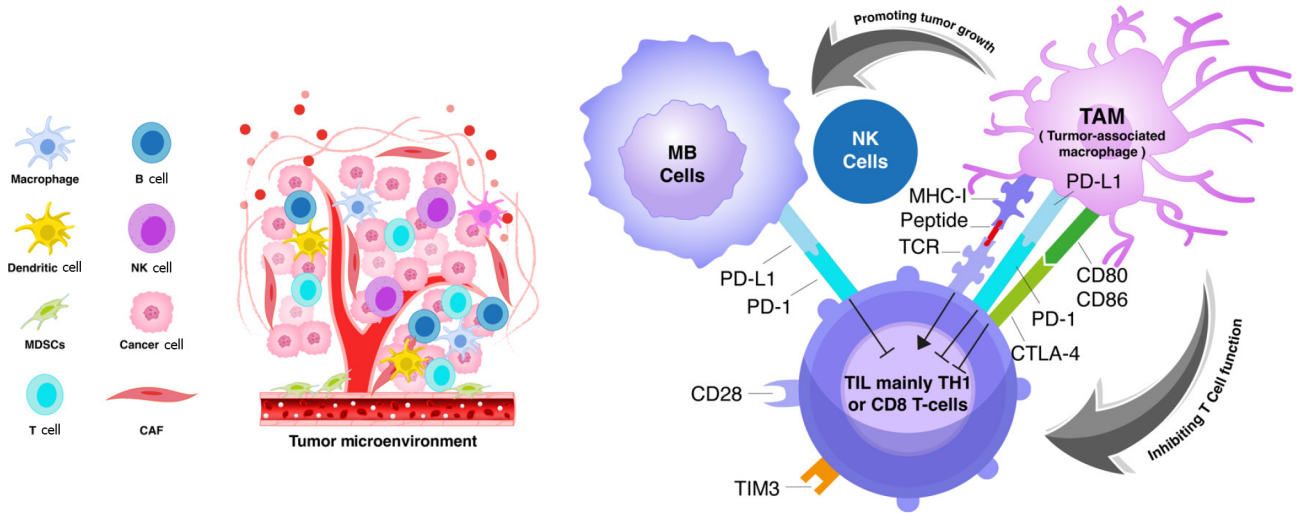


Figure 2 Risk groups and categories of medulloblastoma with their molecular profiles and the 5-years survival associated with each group. The information presented in this figure were taken with permission from the reference: Luzzi *et al*[91], 2020. SHH: Sonic-hedgehog; MB: Medulloblastoma; MYC: Myelocytomatosis oncogene; OS: Overall survival; WNT: Wingless.

tumor surface is also a common mechanism of immune escape in MB[42,43]. Because MHC class-I helps in the activation of CD8 cytotoxic T-cells, it acts as a passive regulator of natural killer (NK) cells. Thus, the loss of MHC-class I in tumor cells may increase tumour cell evasion[42,43].

Tumour associated macrophages in immune microenvironment

TAM is considered the major immune cell in the tumor microenvironment that can either support or inhibit tumor growth[44,45]. TAMs interact with tumour cells to promote tumour progression and invasion[46]. They are subclassified into two groups: (1) TAMs with M1 polarization, are induced by IFN-γ to release proinflammatory particles and are associated with some inflammatory response; and (2) TAMs with M2 polarization, are induced by interleukin-4 to release growth factors (*e.g.*, epidermal growth factor, fibroblast growth factor-1, vascular endothelial growth factor) and involved in tumour progression and immunosuppression[47-49]. Uncontrolled activation of M1-polarzed TAM can shift towards M2-polarization in long term. However, the M2-like macrophages, which mimic TAMs in the tumour microenvironment, can be stimulated by cytokines[50]. EGF released by TAMs stimulate carcinogenesis, while VEGF regulates angiogenesis. These processes emphasize the actual immune-suppressive function of TAMs[51]. TAMs infiltration in the tumour microenvironment was proven to be a poor prognostic factor[50]. Clinical data have indicated that a large number of M2-polarized TAMs expressing CD163 and CD204 were correlated with a poor outcome of several body cancers[47] (Figure 3). Moreover, the presence of TAMs, mainly M2- type, has been also noted in many adult malignancies including CNS tumors[52-54]. In response to hypoxia, TAMs overexpress the PD-1 ligands



DOI: 10.5306/wjco.v14.i3.117

Figure 3 The signaling interaction between tumour cells, tumor-associated macrophages, and tumour infiltrating lymphocytes in medulloblastoma microenvironment. Tumour microenvironment represents diverse cellular heterogeneities including immune and none-immune cells. The targeted receptors linked between immune cells represent a potential targeted therapy. CAF: Cancer-associated fibroblasts; MB: Medulloblastoma; NK: Natural killer; TAM: Tumor-associated macrophage; TIL: Tumour infiltrating lymphocytes.

[55]. PD-L1 overexpression in TAM has been reported in glioblastoma[56] but it has never been explored well in other brain tumours such as medulloblastoma.

The current role of TAMs in the prognosis of MB is still controversial. Despite of the molecular insights provided by MB subgroups, less information were reported about the role of TAMs in MBs[33]. The genetic alterations and the disease risk would make diverse effects on immune microenvironment [57]. Because TAMs are composed of variable amounts of microglia and macrophages, the composition of TAMs are different in all MB subgroups. Margol *et al*[58] and Zhang *et al*[59] reported that TAMs were significantly higher in SHH-MB compared to other MB subgroups. This may be due to the high expression of monocyte chemotactic protein-1 (MCP-1], which helps in TAM recruitment and M2 polarization[60]. Another possibility, SHH-MB may exhibit molecular signatures predictive for fibroblast, T-cells, and macrophage infiltration[34]. Nevertheless, the role of TAMs in this era is not clear and the previous reported studies did not reveal the prognostic connotations of TAMs in SHH-MBs[58].

CD163 expression was observed in the small number of SHH-MBs, which suggested that TAMs may play a dynamic role in SHH-MB formation[58,61]. Another study done by Crotty *et al*[62], revealed that less TAMs in microenvironment was associated with a low recurrence and low risk of metastasis. Lee *et al*[63] suggested that a large number of M1-polarized TAMs was associated with worsening outcome in SHH-MB patients. Lee and his group has also investigated the correlation between TAM recruitment and outcome, and they revealed that expressed M1-polarized TAMs predicted better progression-free survival but, TAMs showed no significant effect on OS[59]. Few studies showed that the immunoreactivity in MB microenvironment, regardless the subtype, is age-related[64]. In a study done by Zhang *et al*, they divided the patients into three age groups. They found that the group between 0-3 years of age and the group between 11-18 year of age had more TAMs than the group aged between 4-10 years. It implies that TAMs in MBs are crucial in different age groups[59]. Zhang *et al*[59] also found that TAMs, mainly M1-polarized type, are prevalent in MBs with metastatic disease.

Tumour recurrence and metastases are the major obstacle for treatment success, and the disease recurrence is responsible for 90% of MB mortality[65]. Group 3 and 4 patients develop spinal metastases regardless of the type of chemotherapy given after resection[2]. The presence of *TP53-MYCN*-alteration in these groups is associated with rapid tumour progression[66]. The ability of Group 3 and 4 to metastasize indicates that these tumor cells participate in the epithelial-to-mesenchymal transition (EMT), thus warranting additional investigations into EMT[67]. It is not yet known why tumor cells enter the EMT phase. A study done by Bonde *et al*[68] showed that TGFβ triggers the EMT phase, shifting the cancer cells to gain a mesenchymal phenotype. The lack of local nutrients, loss of supportive cells in microenvironment, and repeated mutations can all be reasons for this aggressive behavior. Funakoshi *et al*[69] found that loss of CDH1 allows tumour cells to detach from each other and can invade and metastasize.

Tumour infiltrating lymphocyte in immune microenvironment

Generally, increased T-cells trafficking in the brain has been reported in some neurological diseases. The activated T-cells have the role to alter the BBB, allowing for immune cells recruitment and entry to the brain parenchyma[70]. Tumour infiltrating lymphocytes (TIL) are considered signaling interacted cells

between TAMs and tumour cells in the tumour microenvironment (Figure 3). The number of T-cells present in MB was found to be not significantly high compared to other control tissues[33]. Small amount of CD8 cytotoxic T-cells and NK cells suggest a less antitumor activity in MB[34]. However, a small percentage of helper T-cells (Th17) cells was also found at the site of the tumor but with uncertain significance[11]. Some experimental trials revealed that MB cells stimulate the release of the T-cells attractant (RANTES) from the endothelium, causing T-cell immigration[71]. Hence, increasing numbers of T-helper lymphocytes correlate with favourable prognosis in MB patients receiving chemotherapy [44].

T-regulatory cells (Tregs) control the activity of immune cells by releasing some anti-inflammatory cytokines such interleukin-10 (IL-10), and CTLA4-mediated trogocytosis[44]. Treg infiltration in MB microenvironment has been described by Gate *et al*[44]. Consequently, TGFβ drives the CD4 helper T-cells to Tregs, which in turn releases high levels of TGFβ. This process generates a feeding circuit to support immunosuppression. Elevated Treg in MBs can be therapy-induced, as Treg has been detected in the peripheral blood of some treated patients[38].

Interaction between TAMs and TILs in MB microenvironment

The interaction between TAMs and TILs were not scientifically explored in MB microenvironment (Figure 3). Kurdi *et al*[54] has explained the crosstalk between tumour cells, TAM sand TILs in glioblastoma. TAMs encircle cancer cells and supresses the killing action of T-cell thus, T-cells will not be able to help tumour cells against immune evasion. The TAMs accumulate in the microenvironment with less T-cells evolution[54]. Salsman *et al*[71] revealed that MB cell lines can interact with tumor endothelium to recruit T-cells to MB microenvironment, in particular macrophage migration inhibitory factor (MIF). MIF is the key molecule released by MB to stimulate the endothelial cells in the microenvironment to release more potent T-lymphocyte attractants[71].

Current immunotherapy in MB and possible targeted receptors

Immune checkpoints represent a family of proteins on T-cells surface that interact with some ligands on APCs or tumour cells while they inhibit TCR-mediated ligands. Certain cancers (colorectal, ovarian and brain cancers) are resistant to immune checkpoint inhibitor[72]. The number of studies utilizing immunotherapy in the treatment approach of MB is limited. The approach had few selected options. Most of studies were observational and contained a small sample size. There are two clinical trials currently investigating the blockade of inhibitory checkpoint pathways in MB including pembrolizumab and nivolumab (NCT02359565) (NCT03173950). CD276, another immune check point inhibitor on T-cell, is also under investigation[73]. CD40 [a TNF receptor] expressed by antigen presenting cells and B-cells expresses cytokines, activates T-cells, and in turn timulate programmed cell death[74]. CD40 has a significant cytotoxic effect on tumor cells. APX005M, a humanized IgG1κ monoclonal antibody agonist of CD40 is currently evaluated in a phase I trial (NCT03389802) in patients with recurrent MBs. The recent actively recruiting clinical trials are summarized in (Table 1).

Numerous studies revealed that TAMs may interfere with some anti-tumor treatments such as chemotherapies and other antibody-based immunotherapies targeting some molecules such as PD-1/PD-1[50,72]. These findings emphasize that TAMs might be a promising target of novel anti-tumor treatment particularly in patient not responding to the standard treatment. The ability of TAMs to limit the efficacy of immune check point blockade has been previously investigated in several cancers[75,76]. TAMs express multiple ligands for checkpoint receptors, such as PD-L1/2, CD80/86, and CD204/CD206, and the current checkpoint inhibitors are different from the targeted receptors as they maintain a state of effective immunosuppression[77] (Figure 3). These legends, representing M2-polarized TAMs, have not been investigated in MB microenvironment. Martin *et al*[78] showed that MBs expressing reduced levels of PD-L1 can help tumour cells to evade from the immunity, suggesting that an inflamed tumor microenvironment is necessary for PD-1 pathway stimulation. However, the efficacy of PD-PD-L1 inhibitor has not been yet proven to be formally used in MB treatment.

Trogocytosis is a process involved in immune microenvironment concerned with the transfer of membrane fragments and cell surface proteins between cells. It is not known if induced iTregs can undergo trogocytosis. The trogocytosis of CD80/CD86 occurring in CTLA-4 or PDL1-independent approach plays a significant role in the immune suppression[79]. CD80/86 expression and trogocytosis have never been explored in MB microenvironment. As a key mechanism, Treg-linked CTLA-4 inhibits the CD80/CD86 molecules expression on APCs. Tekguc *et al*[80] revealed that blockade of CTLA-4 and PD-1/PD-L1 pathways may impede Treg-mediated immunosuppression, which in turn enhances anti tumour activity response. This novel exploration has not been investigated in MB. Several investigations have demonstrated that activation of PI3Kγ signaling in macrophages suppresses NF-κB, thereby stimulating immunosuppression. TAMs in cancers treated with chemotherapies are often responsible for chemoresistance as they are more susceptible to the cytotoxic effect of macrophages[81]. This process occurs when there is excessive recruitment of anti-apoptotic process in tumour microenvironment[82].

Understanding the molecular events in the mechanism of TAMs activation allows for the development of anti-tumor treatment strategies. TAMs can be targeted to inhibit their infiltration in microenvironment through direct killing or through a TAM-polarization reprogramming. TAMs accumulate in tumour microenvironment because of the continuous recruitment of monocytes from the blood

circulation to TAMs through multiple tumour derived mediators. These mediators play a connection role between macrophages and tumour cells. CCL2 has been described as the main mediator involved in TAM recruitment. Indeed, the blockage of this pathway would cause less TAMs accumulation in tumour microenvironment[83]. Another pathway involved in monocytic recruitment into TAMs is the CXCL12/CXCR4 pathway[84]. It has been used in different trials of different cancers such as myeloid leukemia but never been tried in brain cancers.

CSF-1, a colony stimulating factor involved in the proliferation and the recruitment of monocytes-macrophages, is an essential target against TAM in tumour microenvironment. The expression of CSF-1 in tumour microenvirment was proven to be a poor prognosticator in multiple body cancers[85]. After treatment with CSF-1 inhibitor in one of clinical trials, the number of TAMs have depleted and there was an infiltration of CD8 cytotoxic T-cells in the tumor[86,87].

Reprogramming of TAM is another possible strategy to inhibit TAM activity. Several approaches attempted to switch M2-polarized TAMs into antitumor M1-like macrophages through monoclonal antibody inhibitors and Toll-like receptor (TLR) blockers. Alvarez-Arellano *et al*[88] revealed that TLR7 is a prognostic factor of survival in MB. Resiquimod, an agonist to TLR7/8, has shown an attention couple years ago for its efficacy to reprogram macrophages[89]. The CD47–SIRPα, involved in the regulation of phagocytosis, has never been used to reprogram TAMs. CD47 is expressed by tumor cells and interacts with the signal regulatory protein-α. Substantial evidence assumed that overexpression of CD47 in many cancers had a role in the phagocytic resistance[90]. However, this investigation has never been investigated in MB patients. Promising results were obtained in lymphoma patients in a combination of anti-CD47 with anti-CD20. Despite these results, the *in vivo* application of CD47 for the treatment of cancer is still limited.

CONCLUSION

Medulloblastoma is the most common malignant pediatric tumour in CNS that are subclassified into four distinguishing molecular subgroups. The current treatments failed to improve the patient's survival significantly while the serious complications associated with these cytotoxic therapies warrant for exploring new therapeutic approaches targeting different immune receptors. The identification of tumour microenvironment has facilitated the scientists understanding how tumor growth and progression are regulated. TAMs and TILs, the main dominant immune cells in microenvironment, seem to have a major role in immune mechanism and tumor progression. Their infiltration in microenvironment has prompted researchers to evaluate the interaction of new targeted immune receptors with the current signaling pathways. Their infiltration in microenvironment may also be targeted through different reprogramming mechanisms. However, the ability of TAMs to limit the efficacy of immune check point blockade in MB requires further investigations. These strategic thoughts emphasize that TAMs might be a promising targeted treatment particularly in patients with recurrent or progressive MB. Further studies to explore new targeted receptors in tumour microenvironment and understanding the conventional relationship between TAMs, TILs and tumour cells are essential to develop new therapeutic approaches.

FOOTNOTES

Author contributions: All authors shared in writing the review.

Conflict-of-interest statement: All the author declare no conflict of interests for this article.

Country/Territory of origin: Saudi Arabia

ORCID number: Maher Kurdi 0000-0002-8979-3849.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 **Pollack IF**, Boyett JM, Yates AJ, Burger PC, Gilles FH, Davis RL, Finlay JL; Children's Cancer Group. The influence of central review on outcome associations in childhood malignant gliomas: results from the CCG-945 experience. *Neuro Oncol* 2003; **5**: 197-207 [PMID: 12816726 DOI: 10.1215/S1152851703000097]

2 **Ramaswamy V**, Remke M, Bouffet E, Bailey S, Clifford SC, Doz F, Kool M, Dufour C, Vassal G, Milde T, Witt O, von Hoff K, Pietsch T, Northcott PA, Gajjar A, Robinson GW, Padovani L, André N, Massimino M, Pizer B, Packer R, Rutkowski S, Pfister SM, Taylor MD, Pomeroy SL. Risk stratification of childhood medulloblastoma in the molecular era: the current consensus. *Acta Neuropathol* 2016; **131**: 821-831 [PMID: 27040285 DOI: 10.1007/s00401-016-1569-6]

3 **Ning MS**, Perkins SM, Dewees T, Shinohara ET. Evidence of high mortality in long term survivors of childhood medulloblastoma. *J Neurooncol* 2015; **122**: 321-327 [PMID: 25557108 DOI: 10.1007/s11060-014-1712-y]

4 **Altman J**, Bayer SA. The generation, movements, and settling of cerebellar granule cells and the formation of parallel fibers in development of the cerebellar system in relation to its evolution structure and function. CRC Press 1997; New York pp. 334-361

5 **Louis DN**, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 2016; **131**: 803-820 [PMID: 27157931 DOI: 10.1007/s00401-016-1545-1]

6 **Taylor MD**, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, Eberhart CG, Parsons DW, Rutkowski S, Gajjar A, Ellison DW, Lichter P, Gilbertson RJ, Pomeroy SL, Kool M, Pfister SM. Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol* 2012; **123**: 465-472 [PMID: 22134537 DOI: 10.1007/s00401-011-0922-z]

7 **Thompson MC**, Fuller C, Hogg TL, Dalton J, Finkelstein D, Lau CC, Chintagumpala M, Adesina A, Ashley DM, Kellie SJ, Taylor MD, Curran T, Gajjar A, Gilbertson RJ. Genomics identifies medulloblastoma subgroups that are enriched for specific genetic alterations. *J Clin Oncol* 2006; **24**: 1924-1931 [PMID: 16567768 DOI: 10.1200/JCO.2005.04.4974]

8 **Ellison DW**, Dalton J, Kocak M, Nicholson SL, Fraga C, Neale G, Kenney AM, Brat DJ, Perry A, Yong WH, Taylor RE, Bailey S, Clifford SC, Gilbertson RJ. Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. *Acta Neuropathol* 2011; **121**: 381-396 [PMID: 21267586 DOI: 10.1007/s00401-011-0800-8]

9 **Northcott PA**, Buchhalter I, Morrissy AS, Hovestadt V, Weischenfeldt J, Ehrenberger T, Gröbner S, Segura-Wang M, Zichner T, Rudneva VA, Warnatz HJ, Sidiropoulos N, Phillips AH, Schumacher S, Kleinheinz K, Waszak SM, Erkek S, Jones DTW, Worst BC, Kool M, Zapatka M, Jäger N, Chavez L, Hutter B, Bieg M, Paramasivam N, Heinold M, Gu Z, Ishaque N, Jäger-Schmidt C, Imbusch CD, Jugold A, Hübschmann D, Risch T, Amstislavskiy V, Gonzalez FGR, Weber UD, Wolf S, Robinson GW, Zhou X, Wu G, Finkelstein D, Liu Y, Cavalli FMG, Luu B, Ramaswamy V, Wu X, Koster J, Ryzhova M, Cho YJ, Pomeroy SL, Herold-Mende C, Schuhmann M, Ebinger M, Liau LM, Mora J, McLendon RE, Jabado N, Kumabe T, Chuah E, Ma Y, Moore RA, Mungall AJ, Mungall KL, Thiessen N, Tse K, Wong T, Jones SJM, Witt O, Milde T, Von Deimling A, Capper D, Korshunov A, Yaspo ML, Kriwacki R, Gajjar A, Zhang J, Beroukhim R, Fraenkel E, Korbel JO, Brors B, Schlesner M, Eils R, Marra MA, Pfister SM, Taylor MD, Lichter P. The whole-genome landscape of medulloblastoma subtypes. *Nature* 2017; **547**: 311-317 [PMID: 28726821 DOI: 10.1038/nature22973]

10 **Robinson G**, Parker M, Kranenburg TA, Lu C, Chen X, Ding L, Phoenix TN, Hedlund E, Wei L, Zhu X, Chalhoub N, Baker SJ, Huether R, Kriwacki R, Curley N, Thiruvenkatam R, Wang J, Wu G, Rusch M, Hong X, Becksfort J, Gupta P, Ma J, Easton J, Vadodaria B, Onar-Thomas A, Lin T, Li S, Pounds S, Paugh S, Zhao D, Kawauchi D, Roussel MF, Finkelstein D, Ellison DW, Lau CC, Bouffet E, Hassall T, Gururangan S, Cohn R, Fulton RS, Fulton LL, Dooling DJ, Ochoa K, Gajjar A, Mardis ER, Wilson RK, Downing JR, Zhang J, Gilbertson RJ. Novel mutations target distinct subgroups of medulloblastoma. *Nature* 2012; **488**: 43-48 [PMID: 22722829 DOI: 10.1038/nature11213]

11 **Zhao F**, Ohgaki H, Xu L, Giangaspero F, Li C, Li P, Yang Z, Wang B, Wang X, Wang Z, Ai L, Zhang J, Luo L, Liu P. Molecular subgroups of adult medulloblastoma: a long-term single-institution study. *Neuro Oncol* 2016; **18**: 982-990 [PMID: 27106407 DOI: 10.1093/neuonc/now050]

12 **Cavalli FMG**, Remke M, Rampasek L, Peacock J, Shih DJH, Luu B, Garzia L, Torchia J, Nor C, Morrissy AS, Agnihotri S, Thompson YY, Kuzan-Fischer CM, Farooq H, Isaev K, Daniels C, Cho BK, Kim SK, Wang KC, Lee JY, Grajkowska WA, Perek-Polnik M, Vasiljevic A, Faure-Conter C, Jouvet A, Giannini C, Nageswara Rao AA, Li KKW, Ng HK, Eberhart CG, Pollack IF, Hamilton RL, Gillespie GY, Olson JM, Leary S, Weiss WA, Lach B, Chambless LB, Thompson RC, Cooper MK, Vibhakar R, Hauser P, van Veelen MC, Kros JM, French PJ, Ra YS, Kumabe T, López-Aguilar E, Zitterbart K, Sterba J, Finocchiaro G, Massimino M, Van Meir EG, Osuka S, Shofuda T, Klekner A, Zollo M, Leonard JR, Rubin JB, Jabado N, Albrecht S, Mora J, Van Meter TE, Jung S, Moore AS, Hallahan AR, Chan JA, Tirapelli DPC, Carlotti CG, Fouladi M, Pimentel J, Faria CC, Saad AG, Massimi L, Liau LM, Wheeler H, Nakamura H, Elbabaa SK, Perezpeña-Diazconti M, Chico Ponce de León F, Robinson S, Zapotocky M, Lassaletta A, Huang A, Hawkins CE, Tabori U, Bouffet E, Bartels U, Dirks PB, Rutka JT, Bader GD, Reimand J, Goldenberg A, Ramaswamy V, Taylor MD. Intertumoral Heterogeneity within Medulloblastoma Subgroups. *Cancer Cell* 2017; **31**: 737-754.e6 [PMID: 28609654 DOI: 10.1016/j.ccell.2017.05.005]

13 **Pugh TJ**, Weeraratne SD, Archer TC, Pomeranz Krummel DA, Auclair D, Bochicchio J, Carneiro MO, Carter SL, Cibulskis K, Erlich RL, Greulich H, Lawrence MS, Lennon NJ, McKenna A, Meldrim J, Ramos AH, Ross MG, Russ C, Shefler E, Sivachenko A, Sogoloff B, Stojanov P, Tamayo P, Mesirov JP, Amani V, Teider N, Sengupta S, Francois JP, Northcott PA, Taylor MD, Yu F, Crabtree GR, Kautzman AG, Gabriel SB, Getz G, Jäger N, Jones DT, Lichter P, Pfister SM, Roberts TM, Meyerson M, Pomeroy SL, Cho YJ. Medulloblastoma exome sequencing uncovers subtype-specific somatic mutations. *Nature* 2012; **488**: 106-110 [PMID: 22820256 DOI: 10.1038/nature11329]

14 **Schröder M**. Human DEAD-box protein 3 has multiple functions in gene regulation and cell cycle control and is a prime target for viral manipulation. *Biochem Pharmacol* 2010; **79**: 297-306 [PMID: 19782656 DOI: 10.1016/j.bcp.2009.08.032]

15 **Trubicka J**, Szperl M, Grajkowska W, Karkucińska-Więckowska A, Tarasińska M, Falana K, Dembowska-Bagińska B, Łastowska M. Identification of a novel inherited ALK variant M1199L in the WNT type of medulloblastoma. *Folia Neuropathol* 2016; **54**: 23-30 [PMID: 27179218 DOI: 10.5114/fn.2016.58912]

16 **Gajjar AJ**, Robinson GW. Medulloblastoma-translating discoveries from the bench to the bedside. *Nat Rev Clin Oncol*

2014; **11**: 714-722 [PMID: 25348790 DOI: 10.1038/nrclinonc.2014.181]

17 **Cho YJ**, Tsherniak A, Tamayo P, Santagata S, Ligon A, Greulich H, Berhoukim R, Amani V, Goumnerova L, Eberhart CG, Lau CC, Olson JM, Gilbertson RJ, Gajjar A, Delattre O, Kool M, Ligon K, Meyerson M, Mesirov JP, Pomeroy SL. Integrative genomic analysis of medulloblastoma identifies a molecular subgroup that drives poor clinical outcome. *J Clin Oncol* 2011; **29**: 1424-1430 [PMID: 21098324 DOI: 10.1200/JCO.2010.28.5148]

18 **Rutkowski S**, Gerber NU, von Hoff K, Gnekow A, Bode U, Graf N, Berthold F, Henze G, Wolff JE, Warmuth-Metz M, Soerensen N, Emser A, Ottensmeier H, Deinlein F, Schlegel PG, Kortmann RD, Pietsch T, Kuehl J; German Pediatric Brain Tumor Study Group. Treatment of early childhood medulloblastoma by postoperative chemotherapy and deferred radiotherapy. *Neuro Oncol* 2009; **11**: 201-210 [PMID: 18818397 DOI: 10.1215/15228517-2008-084]

19 **Kool M**, Jones DT, Jäger N, Northcott PA, Pugh TJ, Hovestadt V, Piro RM, Esparza LA, Markant SL, Remke M, Milde T, Bourdeaut F, Ryzhova M, Sturm D, Pfaff E, Stark S, Hutter S, Seker-Cin H, Johann P, Bender S, Schmidt C, Rausch T, Shih D, Reimand J, Sieber L, Wittmann A, Linke L, Witt H, Weber UD, Zapatka M, König R, Beroukhim R, Bergthold G, van Sluis P, Volckmann R, Koster J, Versteeg R, Schmidt S, Wolf S, Lawerenz C, Bartholomae CC, von Kalle C, Unterberg A, Herold-Mende C, Hofer S, Kulozik AE, von Deimling A, Scheurlen W, Felsberg J, Reifenberger G, Hasselblatt M, Crawford JR, Grant GA, Jabado N, Perry A, Cowdrey C, Croul S, Zadeh G, Korbel JO, Doz F, Delattre O, Bader GD, McCabe MG, Collins VP, Kieran MW, Cho YJ, Pomeroy SL, Witt O, Brors B, Taylor MD, Schüller U, Korshunov A, Eils R, Wechsler-Reya RJ, Lichter P, Pfister SM; ICGC PedBrain Tumor Project. Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. *Cancer Cell* 2014; **25**: 393-405 [PMID: 24651015 DOI: 10.1016/j.ccr.2014.02.004]

20 **Smith MJ**, Beetz C, Williams SG, Bhaskar SS, O'Sullivan J, Anderson B, Daly SB, Urquhart JE, Bholah Z, Oudit D, Cheesman E, Kelsey A, McCabe MG, Newman WG, Evans DG. Germline mutations in SUFU cause Gorlin syndrome-associated childhood medulloblastoma and redefine the risk associated with PTCH1 mutations. *J Clin Oncol* 2014; **32**: 4155-4161 [PMID: 25403219 DOI: 10.1200/JCO.2014.58.2569]

21 **Northcott PA**, Jones DT, Kool M, Robinson GW, Gilbertson RJ, Cho YJ, Pomeroy SL, Korshunov A, Lichter P, Taylor MD, Pfister SM. Medulloblastomics: the end of the beginning. *Nat Rev Cancer* 2012; **12**: 818-834 [PMID: 23175120 DOI: 10.1038/nrc3410]

22 **Sursal T**, Ronecker JS, Dicpinigaitis AJ, Mohan AL, Tobias ME, Gandhi CD, Jhanwar-Uniyal M. Molecular Stratification of Medulloblastoma: Clinical Outcomes and Therapeutic Interventions. *Anticancer Res* 2022; **42**: 2225-2239 [PMID: 35489737 DOI: 10.21873/anticanres.15703]

23 **Menyhárt O**, Giangaspero F, Győrffy B. Molecular markers and potential therapeutic targets in non-WNT/non-SHH (group 3 and group 4) medulloblastomas. *J Hematol Oncol* 2019; **12**: 29 [PMID: 30876441 DOI: 10.1186/s13045-019-0712-y]

24 **Zhou P**, Sha H, Zhu J. The role of T-helper 17 (Th17) cells in patients with medulloblastoma. *J Int Med Res* 2010; **38**: 611-619 [PMID: 20515574 DOI: 10.1177/147323001003800223]

25 **Waszak SM**, Northcott PA, Buchhalter I, Robinson GW, Sutter C, Groebner S, Grund KB, Brugières L, Jones DTW, Pajtler KW, Morrissy AS, Kool M, Sturm D, Chavez L, Ernst A, Brabetz S, Hain M, Zichner T, Segura-Wang M, Weischenfeldt J, Rausch T, Mardin BR, Zhou X, Baciu C, Lawerenz C, Chan JA, Varlet P, Guerrini-Rousseau L, Fults DW, Grajkowska W, Hauser P, Jabado N, Ra YS, Zitterbart K, Shringarpure SS, De La Vega FM, Bustamante CD, Ng HK, Perry A, MacDonald TJ, Hernáiz Driever P, Bendel AE, Bowers DC, McCowage G, Chintagumpala MM, Cohn R, Hassall T, Fleischhack G, Eggen T, Wesenberg F, Feychting M, Lannering B, Schüz J, Johansen C, Andersen TV, Röösli M, Kuehni CE, Grotzer M, Kjaerheim K, Monoranu CM, Archer TC, Duke E, Pomeroy SL, Shelagh R, Frank S, Sumerauer D, Scheurlen W, Ryzhova MV, Milde T, Kratz CP, Samuel D, Zhang J, Solomon DA, Marra M, Eils R, Bartram CR, von Hoff K, Rutkowski S, Ramaswamy V, Gilbertson RJ, Korshunov A, Taylor MD, Lichter P, Malkin D, Gajjar A, Korbel JO, Pfister SM. Spectrum and prevalence of genetic predisposition in medulloblastoma: a retrospective genetic study and prospective validation in a clinical trial cohort. *Lancet Oncol* 2018; **19**: 785-798 [PMID: 29753700 DOI: 10.1016/S1470-2045(18)30242-0]

26 **Wolden SL**, Dunkel IJ, Souweidane MM, Happersett L, Khakoo Y, Schupak K, Lyden D, Leibel SA. Patterns of failure using a conformal radiation therapy tumor bed boost for medulloblastoma. *J Clin Oncol* 2003; **21**: 3079-3083 [PMID: 12915597 DOI: 10.1200/JCO.2003.11.140]

27 **Schwalbe EC**, Lindsey JC, Nakjang S, Crosier S, Smith AJ, Hicks D, Rafiee G, Hill RM, Iliasova A, Stone T, Pizer B, Michalski A, Joshi A, Wharton SB, Jacques TS, Bailey S, Williamson D, Clifford SC. Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma: a cohort study. *Lancet Oncol* 2017; **18**: 958-971 [PMID: 28545823 DOI: 10.1016/S1470-2045(17)30243-7]

28 **Kann BH**, Park HS, Lester-Coll NH, Yeboa DN, Benitez V, Khan AJ, Bindra RS, Marks AM, Roberts KB. Postoperative Radiotherapy Patterns of Care and Survival Implications for Medulloblastoma in Young Children. *JAMA Oncol* 2016; **2**: 1574-1581 [PMID: 27491009 DOI: 10.1001/jamaoncol.2016.2547]

29 **Northcott PA**, Korshunov A, Witt H, Hielscher T, Eberhart CG, Mack S, Bouffet E, Clifford SC, Hawkins CE, French P, Rutka JT, Pfister S, Taylor MD. Medulloblastoma comprises four distinct molecular variants. *J Clin Oncol* 2011; **29**: 1408-1414 [PMID: 20823417 DOI: 10.1200/JCO.2009.27.4324]

30 **Hoff KV**, Hinkes B, Gerber NU, Deinlein F, Mittler U, Urban C, Benesch M, Warmuth-Metz M, Soerensen N, Zwiener I, Goette H, Schlegel PG, Pietsch T, Kortmann RD, Kuehl J, Rutkowski S. Long-term outcome and clinical prognostic factors in children with medulloblastoma treated in the prospective randomised multicentre trial HIT'91. *Eur J Cancer* 2009; **45**: 1209-1217 [PMID: 19250820 DOI: 10.1016/j.ejca.2009.01.015]

31 **Franceschi E**, Giannini C, Furtner J, Pajtler KW, Asioli S, Guzman R, Seidel C, Gatto L, Hau P. Adult Medulloblastoma: Updates on Current Management and Future Perspectives. *Cancers (Basel)* 2022; **14** [PMID: 35954372 DOI: 10.3390/cancers14153708]

32 **Quail DF**, Joyce JA. The Microenvironmental Landscape of Brain Tumors. *Cancer Cell* 2017; **31**: 326-341 [PMID: 28292436 DOI: 10.1016/j.ccell.2017.02.009]

33 **Griesinger AM**, Birks DK, Donson AM, Amani V, Hoffman LM, Waziri A, Wang M, Handler MH, Foreman NK.

Characterization of distinct immunophenotypes across pediatric brain tumor types. *J Immunol* 2013; **191**: 4880-4888 [PMID: 24078694 DOI: 10.4049/jimmunol.1301966]

34 **Bockmayr M**, Mohme M, Klauschen F, Winkler B, Budczies J, Rutkowski S, Schüller U. Subgroup-specific immune and stromal microenvironment in medulloblastoma. *Oncoimmunology* 2018; **7**: e1462430 [PMID: 30228931 DOI: 10.1080/2162402X.2018.1462430]

35 **Eisemann T**, Wechsler-Reya RJ. Coming in from the cold: overcoming the hostile immune microenvironment of medulloblastoma. *Genes Dev* 2022; **36**: 514-532 [PMID: 35680424 DOI: 10.1101/gad.349538.122]

36 **Weiss N**, Miller F, Cazaubon S, Couraud PO. The blood-brain barrier in brain homeostasis and neurological diseases. *Biochim Biophys Acta* 2009; **1788**: 842-857 [PMID: 19061857 DOI: 10.1016/j.bbamem.2008.10.022]

37 **Voskuhl RR**, Peterson RS, Song B, Ao Y, Morales LB, Tiwari-Woodruff S, Sofroniew MV. Reactive astrocytes form scar-like perivascular barriers to leukocytes during adaptive immune inflammation of the CNS. *J Neurosci* 2009; **29**: 11511-11522 [PMID: 19759299 DOI: 10.1523/JNEUROSCI.1514-09.2009]

38 **Gururangan S**, Reap E, Schmittling R, Kocak M, Reynolds R, Grant G, Onar-Thomas A, Baxter P, Pollack IF, Phillips P, Boyett J, Fouladi M, Mitchell D. Regulatory T cell subsets in patients with medulloblastoma at diagnosis and during standard irradiation and chemotherapy (PBTC N-11). *Cancer Immunol Immunother* 2017; **66**: 1589-1595 [PMID: 28825123 DOI: 10.1007/s00262-017-2051-6]

39 **Rizvi NA**, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, Miller ML, Rekhtman N, Moreira AL, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander C, Garon EB, Merghoub T, Wolchok JD, Schumacher TN, Chan TA. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015; **348**: 124-128 [PMID: 25765070 DOI: 10.1126/science.aaa1348]

40 **Colegio OR**, Chu NQ, Szabo AL, Chu T, Rhebergen AM, Jairam V, Cyrus N, Brokowski CE, Eisenbarth SC, Phillips GM, Cline GW, Phillips AJ, Medzhitov R. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. *Nature* 2014; **513**: 559-563 [PMID: 25043024 DOI: 10.1038/nature13490]

41 **Mundt S**, Mrdjen D, Utz SG, Greter M, Schreiner B, Becher B. Conventional DCs sample and present myelin antigens in the healthy CNS and allow parenchymal T cell entry to initiate neuroinflammation. *Sci Immunol* 2019; **4** [PMID: 30679199 DOI: 10.1126/sciimmunol.aau8380]

42 **Raffaghello L**, Nozza P, Morandi F, Camoriano M, Wang X, Garrè ML, Cama A, Basso G, Ferrone S, Gambini C, Pistoia V. Expression and functional analysis of human leukocyte antigen class I antigen-processing machinery in medulloblastoma. *Cancer Res* 2007; **67**: 5471-5478 [PMID: 17545629 DOI: 10.1158/0008-5472.CAN-06-4735]

43 **Smith C**, Santi M, Rajan B, Rushing EJ, Choi MR, Rood BR, Cornelison R, MacDonald TJ, Vukmanovic S. A novel role of HLA class I in the pathology of medulloblastoma. *J Transl Med* 2009; **7**: 59 [PMID: 19594892 DOI: 10.1186/1479-5876-7-59]

44 **Haberthur K**, Brennan K, Hoglund V, Balcaitis S, Chinn H, Davis A, Kreuser S, Winter C, Leary SE, Deutsch GH, Ellenbogen RG, Crane CA. NKG2D ligand expression in pediatric brain tumors. *Cancer Biol Ther* 2016; **17**: 1253-1265 [PMID: 27834580 DOI: 10.1080/15384047.2016.1250047]

45 **Dehne N**, Mora J, Namgaladze D, Weigert A, Brüne B. Cancer cell and macrophage cross-talk in the tumor microenvironment. *Curr Opin Pharmacol* 2017; **35**: 12-19 [PMID: 28538141 DOI: 10.1016/j.coph.2017.04.007]

46 **Feng X**, Szulzewsky F, Yerevanian A, Chen Z, Heinzmann D, Rasmussen RD, Alvarez-Garcia V, Kim Y, Wang B, Tamagno I, Zhou H, Li X, Kettenmann H, Ransohoff RM, Hambardzumyan D. Loss of CX3CR1 increases accumulation of inflammatory monocytes and promotes gliomagenesis. *Oncotarget* 2015; **6**: 15077-15094 [PMID: 25987130 DOI: 10.18632/oncotarget.3730]

47 **Fridman WH**, Zitvogel L, Sautès-Fridman C, Kroemer G. The immune contexture in cancer prognosis and treatment. *Nat Rev Clin Oncol* 2017; **14**: 717-734 [PMID: 28741618 DOI: 10.1038/nrclinonc.2017.101]

48 **Gieryng A**, Pszczolkowska D, Walentynowicz KA, Rajan WD, Kaminska B. Immune microenvironment of gliomas. *Lab Invest* 2017; **97**: 498-518 [PMID: 28287634 DOI: 10.1038/labinvest.2017.19]

49 **Ye XZ**, Xu SL, Xin YH, Yu SC, Ping YF, Chen L, Xiao HL, Wang B, Yi L, Wang QL, Jiang XF, Yang L, Zhang P, Qian C, Cui YH, Zhang X, Bian XW. Tumor-associated microglia/macrophages enhance the invasion of glioma stem-like cells *via* TGF-β1 signaling pathway. *J Immunol* 2012; **189**: 444-453 [PMID: 22664874 DOI: 10.4049/jimmunol.1103248]

50 **Mantovani A**, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. *Nat Rev Clin Oncol* 2017; **14**: 399-416 [PMID: 28117416 DOI: 10.1038/nrclinonc.2016.217]

51 **Wenes M**, Shang M, Di Matteo M, Goveia J, Martín-Pérez R, Serneels J, Prenen H, Ghesquière B, Carmeliet P, Mazzone M. Macrophage Metabolism Controls Tumor Blood Vessel Morphogenesis and Metastasis. *Cell Metab* 2016; **24**: 701-715 [PMID: 27773694 DOI: 10.1016/j.cmet.2016.09.008]

52 **Hussain SF**, Yang D, Suki D, Aldape K, Grimm E, Heimberger AB. The role of human glioma-infiltrating microglia/macrophages in mediating antitumor immune responses. *Neuro Oncol* 2006; **8**: 261-279 [PMID: 16775224 DOI: 10.1215/15228517-2006-008]

53 **Engler JR**, Robinson AE, Smirnov I, Hodgson JG, Berger MS, Gupta N, James CD, Molinaro A, Phillips JJ. Increased microglia/macrophage gene expression in a subset of adult and pediatric astrocytomas. *PLoS One* 2012; **7**: e43339 [PMID: 22937035 DOI: 10.1371/journal.pone.0043339]

54 **Kurdi M**, Alghamdi B, Butt NS, Baeesa S. The relationship between CD204 (M2)-polarized tumour-associated macrophages (TAMs), tumour-infiltrating lymphocytes (TILs), and microglial activation in glioblastoma microenvironment: a novel immune checkpoint receptor target. *Discov Oncol* 2021; **12**: 28 [PMID: 35201470 DOI: 10.1007/s12672-021-00423-8]

55 **Noman MZ**, Desantis G, Janji B, Hasmim M, Karray S, Dessen P, Bronte V, Chouaib S. PD-L1 is a novel direct target of HIF-1α, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. *J Exp Med* 2014; **211**: 781-790 [PMID: 24778419 DOI: 10.1084/jem.20131916]

56 **Bloch O**, Crane CA, Kaur R, Safaee M, Rutkowski MJ, Parsa AT. Gliomas promote immunosuppression through induction of B7-H1 expression in tumor-associated macrophages. *Clin Cancer Res* 2013; **19**: 3165-3175 [PMID: 23613317 DOI: 10.1158/1078-0432.CCR-12-3314]

57 **Gordon SR**, Maute RL, Dulken BW, Hutter G, George BM, McCracken MN, Gupta R, Tsai JM, Sinha R, Corey D, Ring AM, Connolly AJ, Weissman IL. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. *Nature* 2017; **545**: 495-499 [PMID: 28514441 DOI: 10.1038/nature22396]

58 **Margol AS**, Robison NJ, Gnanachandran J, Hung LT, Kennedy RJ, Vali M, Dhall G, Finlay JL, Erdreich-Epstein A, Krieger MD, Drissi R, Fouladi M, Gilles FH, Judkins AR, Sposto R, Asgharzadeh S. Tumor-associated macrophages in SHH subgroup of medulloblastomas. *Clin Cancer Res* 2015; **21**: 1457-1465 [PMID: 25344580 DOI: 10.1158/1078-0432.CCR-14-1144]

59 **Zhang J**, Yuan X, Wang Y, Liu J, Li Z, Li S, Liu Y, Gong X, Sun Y, Wu W, Sun L, Du S, Wang T. Tumor-Associated Macrophages Correlate With Prognosis in Medulloblastoma. *Front Oncol* 2022; **12**: 893132 [PMID: 35860588 DOI: 10.3389/fonc.2022.893132]

60 **O'Connor T**, Heikenwalder M. CCL2 in the Tumor Microenvironment. *Adv Exp Med Biol* 2021; **1302**: 1-14 [PMID: 34286437 DOI: 10.1007/978-3-030-62658-7_1]

61 **Maximov V**, Chen Z, Wei Y, Robinson MH, Herting CJ, Shanmugam NS, Rudneva VA, Goldsmith KC, MacDonald TJ, Northcott PA, Hambardzumyan D, Kenney AM. Tumour-associated macrophages exhibit anti-tumoural properties in Sonic Hedgehog medulloblastoma. *Nat Commun* 2019; **10**: 2410 [PMID: 31160587 DOI: 10.1038/s41467-019-10458-9]

62 **Crotty EE**, Smith SMC, Brasel K, Pakiam F, Girard EJ, Connor YD, Zindy F, Mhyre AJ, Roussel MF, Olson JM. Medulloblastoma recurrence and metastatic spread are independent of colony-stimulating factor 1 receptor signaling and macrophage survival. *J Neurooncol* 2021; **153**: 225-237 [PMID: 33963961 DOI: 10.1007/s11060-021-03767-x]

63 **Lee C**, Lee J, Choi SA, Kim SK, Wang KC, Park SH, Kim SH, Lee JY, Phi JH. M1 macrophage recruitment correlates with worse outcome in SHH Medulloblastomas. *BMC Cancer* 2018; **18**: 535 [PMID: 29739450 DOI: 10.1186/s12885-018-4457-8]

64 **Patt S**, Zimmer C. Age-related immunoreactivity pattern in medulloblastoma. *Childs Nerv Syst* 1992; **8**: 326-331 [PMID: 1382852 DOI: 10.1007/BF00296563]

65 **Pizer BL**, Clifford SC. The potential impact of tumour biology on improved clinical practice for medulloblastoma: progress towards biologically driven clinical trials. *Br J Neurosurg* 2009; **23**: 364-375 [PMID: 19637007 DOI: 10.1080/02688690903121807]

66 **Hill RM**, Kuijper S, Lindsey JC, Petrie K, Schwalbe EC, Barker K, Boult JK, Williamson D, Ahmad Z, Hallsworth A, Ryan SL, Poon E, Robinson SP, Ruddle R, Raynaud FI, Howell L, Kwok C, Joshi A, Nicholson SL, Crosier S, Ellison DW, Wharton SB, Robson K, Michalski A, Hargrave D, Jacques TS, Pizer B, Bailey S, Swartling FJ, Weiss WA, Chesler L, Clifford SC. Combined MYC and P53 defects emerge at medulloblastoma relapse and define rapidly progressive, therapeutically targetable disease. *Cancer Cell* 2015; **27**: 72-84 [PMID: 25533335 DOI: 10.1016/j.ccell.2014.11.002]

67 **Yang J**, Weinberg RA. Epithelial-mesenchymal transition: at the crossroads of development and tumor metastasis. *Dev Cell* 2008; **14**: 818-829 [PMID: 18539112 DOI: 10.1016/j.devcel.2008.05.009]

68 **Bonde AK**, Tischler V, Kumar S, Soltermann A, Schwendener RA. Intratumoral macrophages contribute to epithelial-mesenchymal transition in solid tumors. *BMC Cancer* 2012; **12**: 35 [PMID: 22273460 DOI: 10.1186/1471-2407-12-35]

69 **Funakoshi Y**, Sugihara Y, Uneda A, Nakashima T, Suzuki H. Recent advances in the molecular understanding of medulloblastoma. *Cancer Sci* 2022 [PMID: 36520034 DOI: 10.1111/cas.15691]

70 **Engelhardt B**, Ransohoff RM. Capture, crawl, cross: the T cell code to breach the blood-brain barriers. *Trends Immunol* 2012; **33**: 579-589 [PMID: 22926201 DOI: 10.1016/j.it.2012.07.004]

71 **Salsman VS**, Chow KK, Shaffer DR, Kadikoy H, Li XN, Gerken C, Perlaky L, Metelitsa LS, Gao X, Bhattacharjee M, Hirschi K, Heslop HE, Gottschalk S, Ahmed N. Crosstalk between medulloblastoma cells and endothelium triggers a strong chemotactic signal recruiting T lymphocytes to the tumor microenvironment. *PLoS One* 2011; **6**: e20267 [PMID: 21647415 DOI: 10.1371/journal.pone.0020267]

72 **Quaranta V**, Schmid MC. Macrophage-Mediated Subversion of Anti-Tumour Immunity. *Cells* 2019; **8** [PMID: 31331034 DOI: 10.3390/cells8070747]

73 **Picarda E**, Ohaegbulam KC, Zang X. Molecular Pathways: Targeting B7-H3 (CD276) for Human Cancer Immunotherapy. *Clin Cancer Res* 2016; **22**: 3425-3431 [PMID: 27208063 DOI: 10.1158/1078-0432.CCR-15-2428]

74 **Vonderheide RH**. Prospect of targeting the CD40 pathway for cancer therapy. *Clin Cancer Res* 2007; **13**: 1083-1088 [PMID: 17317815 DOI: 10.1158/1078-0432.CCR-06-1893]

75 **Arlauckas SP**, Garris CS, Kohler RH, Kitaoka M, Cuccarese MF, Yang KS, Miller MA, Carlson JC, Freeman GJ, Anthony RM, Weissleder R, Pittet MJ. In vivo imaging reveals a tumor-associated macrophage-mediated resistance pathway in anti-PD-1 therapy. *Sci Transl Med* 2017; **9** [PMID: 28490665 DOI: 10.1126/scitranslmed.aal3604]

76 **Gordon S**, Plüddemann A. Tissue macrophages: heterogeneity and functions. *BMC Biol* 2017; **15**: 53 [PMID: 28662662 DOI: 10.1186/s12915-017-0392-4]

77 **Winograd R**, Byrne KT, Evans RA, Odorizzi PM, Meyer AR, Bajor DL, Clendenin C, Stanger BZ, Furth EE, Wherry EJ, Vonderheide RH. Induction of T-cell Immunity Overcomes Complete Resistance to PD-1 and CTLA-4 Blockade and Improves Survival in Pancreatic Carcinoma. *Cancer Immunol Res* 2015; **3**: 399-411 [PMID: 25678581 DOI: 10.1158/2326-6066.CIR-14-0215]

78 **Martin AM**, Nirschl CJ, Polanczyk MJ, Bell WR, Nirschl TR, Harris-Bookman S, Phallen J, Hicks J, Martinez D, Ogurtsova A, Xu H, Sullivan LM, Meeker AK, Raabe EH, Cohen KJ, Eberhart CG, Burger PC, Santi M, Taube JM, Pardoll DM, Drake CG, Lim M. PD-L1 expression in medulloblastoma: an evaluation by subgroup. *Oncotarget* 2018; **9**: 19177-19191 [PMID: 29721192 DOI: 10.18632/oncotarget.24951]

79 **Gu P**, Gao JF, D'Souza CA, Kowalczyk A, Chou KY, Zhang L. Trogocytosis of CD80 and CD86 by induced regulatory T cells. *Cell Mol Immunol* 2012; **9**: 136-146 [PMID: 22307040 DOI: 10.1038/cmi.2011.62]

80 **Tekguc M**, Wing JB, Osaki M, Long J, Sakaguchi S. Treg-expressed CTLA-4 depletes CD80/CD86 by trogocytosis, releasing free PD-L1 on antigen-presenting cells. *Proc Natl Acad Sci U S A* 2021; **118** [PMID: 34301886 DOI: 10.1073/pnas.2023739118]

81 **Colotta F**, Peri G, Villa A, Mantovani A. Rapid killing of actinomycin D-treated tumor cells by human mononuclear cells. I. Effectors belong to the monocyte-macrophage lineage. *J Immunol* 1984; **132**: 936-944 [PMID: 6690624]

82 **Anfray C**, Ummarino A, Andón FT, Allavena P. Current Strategies to Target Tumor-Associated-Macrophages to Improve Anti-Tumor Immune Responses. *Cells* 2019; **9** [PMID: 31878087 DOI: 10.3390/cells9010046]

83 **Canè S**, Ugel S, Trovato R, Marigo I, De Sanctis F, Sartoris S, Bronte V. The Endless Saga of Monocyte Diversity. *Front Immunol* 2019; **10**: 1786 [PMID: 31447834 DOI: 10.3389/fimmu.2019.01786]

84 **Sánchez-Martín L**, Estecha A, Samaniego R, Sánchez-Ramón S, Vega MÁ, Sánchez-Mateos P. The chemokine CXCL12 regulates monocyte-macrophage differentiation and RUNX3 expression. *Blood* 2011; **117**: 88-97 [PMID: 20930067 DOI: 10.1182/blood-2009-12-258186]

85 **Koh YW**, Park C, Yoon DH, Suh C, Huh J. CSF-1R expression in tumor-associated macrophages is associated with worse prognosis in classical Hodgkin lymphoma. *Am J Clin Pathol* 2014; **141**: 573-583 [PMID: 24619759 DOI: 10.1309/AJCPR92TDDFARISU]

86 **DeNardo DG**, Brennan DJ, Rexhepaj E, Ruffell B, Shiao SL, Madden SF, Gallagher WM, Wadhwani N, Keil SD, Junaid SA, Rugo HS, Hwang ES, Jirström K, West BL, Coussens LM. Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. *Cancer Discov* 2011; **1**: 54-67 [PMID: 22039576 DOI: 10.1158/2159-8274.CD-10-0028]

87 **Stafford JH**, Hirai T, Deng L, Chernikova SB, Urata K, West BL, Brown JM. Colony stimulating factor 1 receptor inhibition delays recurrence of glioblastoma after radiation by altering myeloid cell recruitment and polarization. *Neuro Oncol* 2016; **18**: 797-806 [PMID: 26538619 DOI: 10.1093/neuonc/nov272]

88 **Alvarez-Arellano L**, Eguía-Aguilar P, Piña-Sánchez P, González-García N, Palma-Guzman A, Perezpeña-Diazconti M, Maldonado-Bernal C. High expression of Toll-like receptor 7 is a survival factor in pediatric medulloblastoma. *Childs Nerv Syst* 2021; **37**: 3743-3752 [PMID: 34480601 DOI: 10.1007/s00381-021-05347-w]

89 **Thauvin C**, Widmer J, Mottas I, Hocevar S, Allémann E, Bourquin C, Delie F. Development of resiquimod-loaded modified PLA-based nanoparticles for cancer immunotherapy: A kinetic study. *Eur J Pharm Biopharm* 2019; **139**: 253-261 [PMID: 30981947 DOI: 10.1016/j.ejpb.2019.04.007]

90 **Murata Y**, Kotani T, Ohnishi H, Matozaki T. The CD47-SIRPα signalling system: its physiological roles and therapeutic application. *J Biochem* 2014; **155**: 335-344 [PMID: 24627525 DOI: 10.1093/jb/mvu017]

91 **Luzzi S**, Giotta Lucifero A, Brambilla I, Semeria Mantelli S, Mosconi M, Foiadelli T, Savasta S. Targeting the medulloblastoma: a molecular-based approach. *Acta Biomed* 2020; **91**: 79-100 [PMID: 32608377 DOI: 10.23750/abm.v91i7-S.9958]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2023 March 24; 14(3): 131-137

DOI: 10.5306/wjco.v14.i3.131

ISSN 2218-4333 (online)

CASE REPORT

Unusual breast metastasis of gastrointestinal stromal tumor: A case report and literature review

Daria Filonenko, Nikolay Karnaukhov, Gurami Kvetenadze, Lyudmila Zhukova

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Guo F, China; Machaku D, Tanzania; Wang Z, China; Zhao G, China

Received: September 21, 2022
Peer-review started: September 21, 2022
First decision: November 14, 2022
Revised: November 27, 2022
Accepted: February 21, 2023
Article in press: February 21, 2023
Published online: March 24, 2023

Daria Filonenko, Department of Oncology Chemotherapy, SBIH Moscow Clinical Scientific and Practical Center Named After A.S.Loginov of DHM Moscow, Moscow 111123, Russia

Nikolay Karnaukhov, Department of Pathomorphology, SBIH "Moscow Clinical Scientific and Practical Center Named After A.S. Loginov" DHM, Moscow 111123, Russia

Gurami Kvetenadze, Department of Surgery, SBIH "Moscow Clinical Scientific and Practical Center Named After A.S. Loginov" DHM, Moscow 111123, Russia

Lyudmila Zhukova, Department of Oncology, SBIH "Moscow Clinical Scientific and Practical Center Named After A.S. Loginov" DHM, Moscow 111123, Russia

Corresponding author: Daria Filonenko, PhD, Chief Physician, Department of Oncology Chemotherapy, SBIH Moscow Clinical Scientific and Practical Center Named After A.S.Loginov of DHM Moscow, Shosse Enthuziastov 86, Moscow 111123, Russia.
shubina_d@mail.ru

Abstract

BACKGROUND

Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal tumors of gastrointestinal tract. The most common sites of metastases are the liver and the peritoneum, whereas breast metastases from GIST are extremely rare. We present a second case of GIST breast metastasis.

CASE SUMMARY

We found a case of breast metastasis from rectum GIST. A 55-year-old female patient presented with rectum tumor with multiply liver lesions and metastasis in the right breast. Abdominal-perineal extirpation of rectum was performed, histology and immunohistochemistry study showed GIST, mixed type with CD117 and DOG-1 positive staining. The patient was taking imatinib 400 mg for 22 mo with stable disease. Because of growth of the breast metastasis the treatment was changed twice: The dose of imatinib was doubled with further progression in the breast lesion and then the patient was receiving sunitinib for 26 mo with partial response in the right breast and stable disease in the liver lesions. The breast lesion increased and right breast resection was done – surgery on local progression, the liver metastases were stable. Histology and immunohisto-chemistry studies revealed GIST metastasis, CD 117 and DOG 1 positive with KIT exon 11 mutation. After surgery the patient resumed imatinib. Until now the patient has been taking imatinib 400 mg for 19 mo without progression, last

follow up was in November 2022.

CONCLUSION
GISTs breast metastases are extremely rare, we described the second case. At the same time second primary tumors have been reported frequently in patients diagnosed with GISTs and breast cancer is one of the most common second primary tumors in patients with GISTs. That is why it is very important to distinguish primary from metastatic breast lesions. Surgery on local progression made it possible to resume less toxic treatment.

Key Words: Gastrointestinal stromal tumors; Metastases; Breast; Limited progression; Case report

Core Tip: We presented the second case of gastrointestinal stromal tumor (GIST) metastasis to the breast, which is a very extraordinary condition. The most common metastatic sites of GIST are the liver and the peritoneum and at the same time metastasis to the breast from extramammary carcinomas is extremely rare and in this clinical situation it is obligatory to exclude breast cancer. Our patient received two lines of treatment due to metastatic disease and had a local progression on imatinib and sunitinib therapy, growth only lesion in the breast, we removed increased metastasis (surgery on local progression), that allowed to return to less toxic treatment, the patient resumed imatinib until now.

Citation: Filonenko D, Karnaukhov N, Kvetenadze G, Zhukova L. Unusual breast metastasis of gastrointestinal stromal tumor: A case report and literature review. *World J Clin Oncol* 2023; 14(3): 131-137
URL: https://www.wjgnet.com/2218-4333/full/v14/i3/131.htm
DOI: https://dx.doi.org/10.5306/wjco.v14.i3.131

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare tumors, with an incidence 1%-2% and at the same time are the most frequent mesenchymal tumors of gastrointestinal tract[1]. Approximately 10% to 20% of patients present with metastatic disease[2]. Many evidences showed that gastrointestinal tumors can metastasize to other parts of the body[3]. The most common metastatic sites of GISTs are the liver (60%-70%) and the peritoneum (20%-30%)[4]. Lung metastases (2%-9%), bone and soft tissue (1%-6%) and skin (1%) can occur but very rare. Casuistic bizzare cases of GISTs metastasis to brain[5], core[6], ovary [7,8], and breast[9] are described in the literature. We made a literature review, breast metastases from GIST have been previously described only in one case.

Breast tumors are usually primary. The incidence of metastatic spread from extramammary sites to the breast varies between 0.4% and 1.5% of all breast malignancies. The breast is considered to be resistant to metastasis because it contains large areas of fibrous tissue with a relatively low supply of blood. Most common malignancies that metastasize into the breast are lymphoma, leukemia, melanoma and carcinomas of stomach, ovary, lung, kidney and others[10-12].

In the article we report a second case of GIST patient presenting breast metastasis, highlighting the pathological/molecular features of this unusual site of metastatic presentation and the clinical implications.

CASE PRESENTATION

Chief complaints

The 55-year-old female complained of the tumor in her right breast.

History of present illness

In April 2016 55-year-old female patient presented with recurrent rectum tumor. Abdominal-perineal extirpation of rectum was performed, histology and immunohistochemistry study showed GIST, mixed type with CD117 and DOG-1 positive staining. After the surgery computer tomography (CT) revealed multiply cystic liver lesions that were estimated as metastases, biopsy was not done. At the same time, the patient found lesion in her right breast 30 mm, biopsy was not performed. The patient was taking imatinib 400 mg from June 2016 until August 2018 for 22 mo with stable disease.

In September 2018 Lesion in the right breast increased, liver lesions were stable and the dose of imatinib was doubled, the patient received imatinib 800mg from September until December 2018 with further growth of breast lesion. From December 2018 until March 2020 for 15 mo the patient was receiving sunitinib 50 mg 4/2 regiment. In March 2020 the dose of sunitinib was reduced to 25 mg every day without a break because of hand–food skin reaction grade 2 and then until February 2021 for 11 mo the patient continued the treatment with partial response lesion in the right breast and stable disease in the liver lesions. The toxicity of modified regiment was acceptable. The patient became hypothyroid and received levothyroxine 25 mcg.

In August 2020 breast ultrasound and magnetic resonance imaging were done at the first time and revealed heterogeneous lesion 47 mm on the border of the upper quadrants of the right breast with central zone of necrosis and peripheral vascularization, BIRADS 5 (Figure 1). The biopsy of the right breast was done to exclude primary breast cancer, histology and immunohistochemistry showed metastasis of GIST, mixed type, 10 mitoses with CD117 and DOG -1 positive staining.

In February 2021 control positron emission tomography-computed tomography (PET-CT) in comparison with September 2020 was obtained and demonstrated progression in the right breast lesion, size increased from 39 mm to 48 mm and FDG uptake increased from 7 to 12 and invasion to the large pectoral muscle was detected (Figure 2). The multiply liver metastases were stable.

History of past illness

The patient had a rectum leiomyoma resection twice in 2012 and 2013 then the patient was on follow up until April 2016.

Personal and family history

The patient's other medical history was not noteworthy.

Physical examination

In the right breast on the border of the upper quadrants the solid lesion was revealed, 50 mm in size.

Laboratory examinations

Laboratory testing showed any clinically significant abnormalities.

Imaging examinations

In April 2021, histology and immunohistochemistry studies showed tumor macroscopical size 50 mm with thick fibrous capsule, with histologically negative margins (Figure 3); microscopic examination showed predominantly epithelioid type with focuses of spindle cell that occupied 15% of the square, with prominent hyperchromatic nuclei, high mitotic index (72 mitoses per 50 HPF), small foci of necrosis and large hemorrhagic areas; immunohistochemistry study showed immunophenotype typical for GIST: Strong cytoplasmic expression CD34, membrane-cytoplasmic expression CD117 and DOG-1 (Figure 4).

MULTIDISCIPLINARY EXPERT CONSULTATION

The clinical situation was estimated as local progression: increase of breast lesion and stable of the liver lesions. Because of growth of the breast metastasis the treatment was changed twice: The patient received double dose of imatinib and sunitinib. Taking into account that the patient had local progression we decided to remove increasing lesion.

FINAL DIAGNOSIS

The final diagnosis was local progression: Increase of breast lesion and stable of the liver lesions.

TREATMENT

In April 2021 right breast resection with partial resection of large pectoral muscle was done. The patient had undergone surgery in 2012, 2013 and 2016 in different clinics, unfortunately histology materials were lost and we had no opportunity to compare histological specimens.

Molecular analysis was performed on the breast metastasis by direct Sanger sequencing and revealed a KIT exon 11 mutation, with a consequent 557-559 deletion.

After surgery we decided to resume imatinib. Previously we changed treatment because of the growth of breast lesion (increased imatinib dose, prescribed sunitinib) and then we removed increased

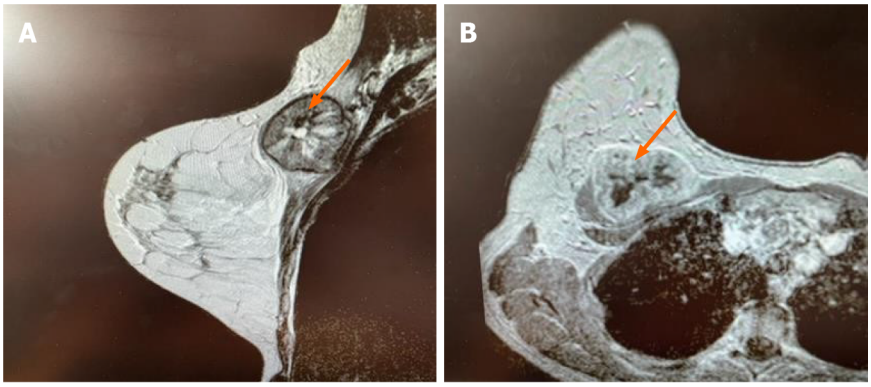


Figure 1 Breast magnetic resonance imaging. Heterogeneous lesion 47 mm (orange arrows) on the border of the upper quadrants of the right breast with central zone of necrosis and peripheral vascularization. A: Axial; B: Frontal.

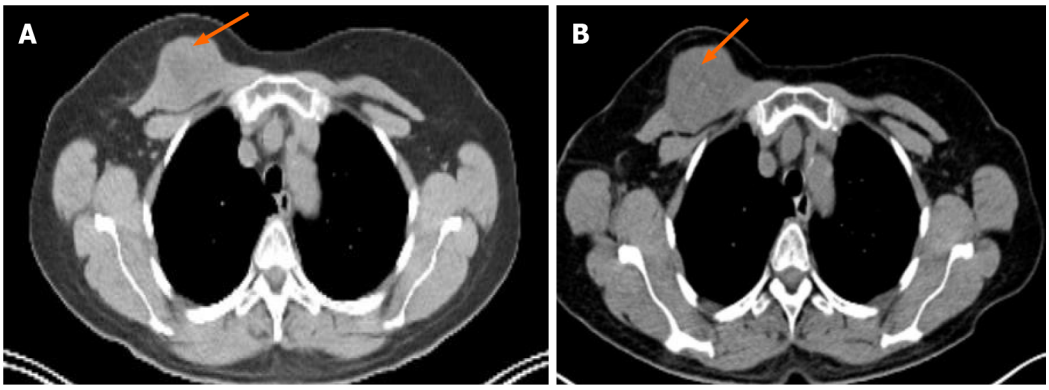


Figure 2 Positron emission tomography-computed tomography. A: Computed tomography (CT) on September 2020; B: CT on February 2021 demonstrated progression in the right breast lesion (orange arrows), size increased from 39 mm to 48 mm.

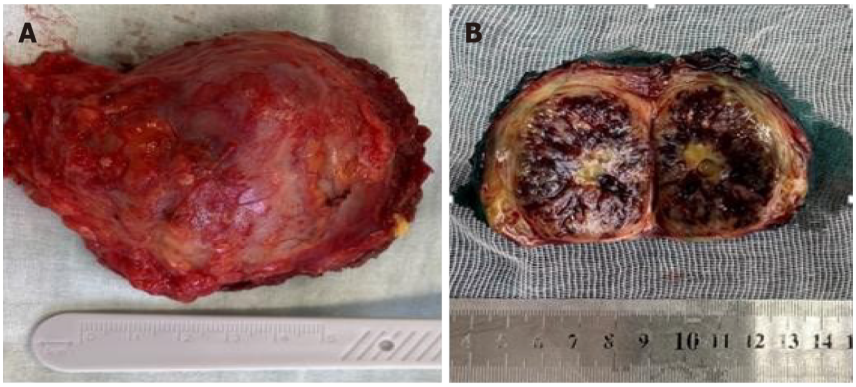
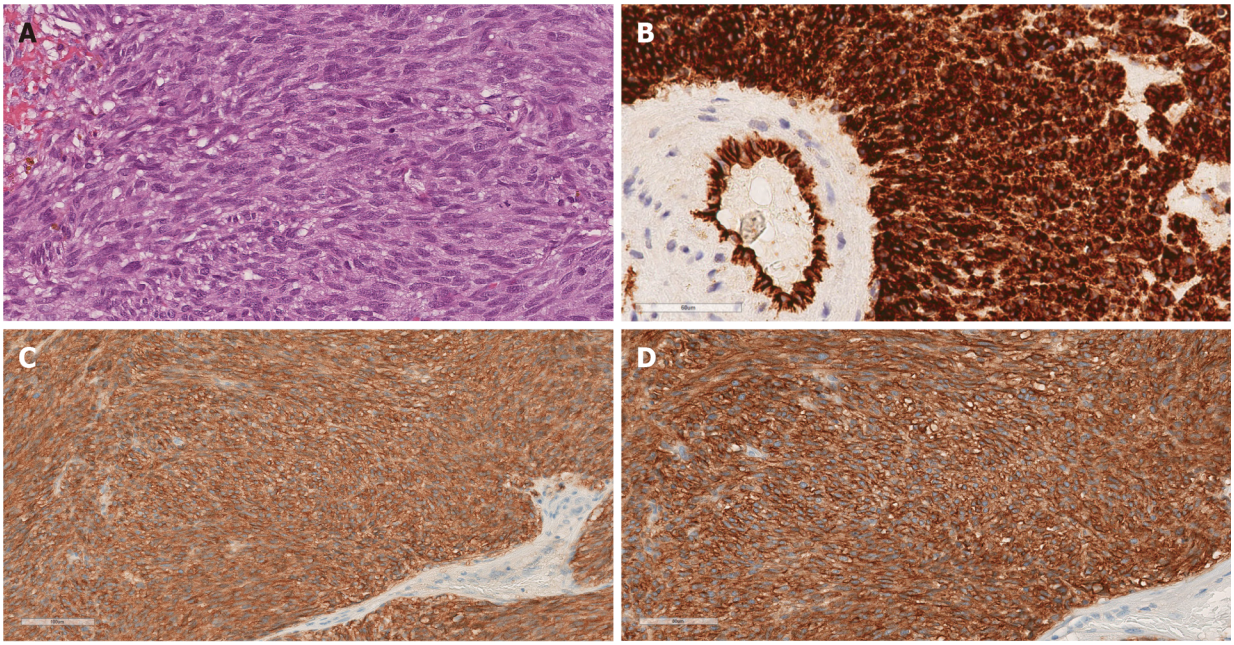


Figure 3 Macroscopic examination. A, B: Macroscopical size 50 mm, thick fibrous capsule.

metastasis that is why we decided to return to less toxic treatment.

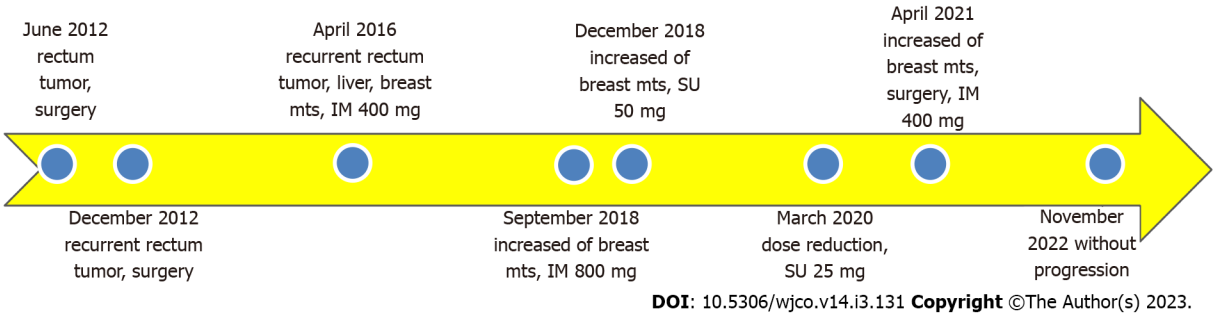
OUTCOME AND FOLLOW-UP

From April 2021 until now patient has been taking imatinib for 19 mo without progression, PET-CT was done in November 2022. By November 2022 the live duration with metastatic GIST is 77 mo (Figure 5).



DOI: 10.5306/wjco.v14.i3.131 **Copyright** ©The Author(s) 2023.

Figure 4 Microscopic examination. A: Histology, original magnification ×200, hematoxylin-eosin stain; B: Immunohistochemistry original magnification ×200, CD34 positive stain; C: Immunohistochemistry ×200, CD117 positive stain, D: Immunohistochemistry original magnification×200, DOG-1 positive stain.



DOI: 10.5306/wjco.v14.i3.131 **Copyright** ©The Author(s) 2023.

Figure 5 Treatment timeline.

DISCUSSION

We made a literature review, breast metastases from GIST have been previously described only in one case[9]. Hasbay *et al*[9] reported the clinical case of 46-year-old women with metastases of GIST to liver, bone, abdominal lymph nodes and left breast. We reported the second case of GIST metastases to the breast.

In this case we came across with diagnostic challenges because the most common metastatic sites of GIST are the liver and the peritoneum and at the same time metastasis to the breast from extra-mammary carcinomas is extremely rare and varies between 0.4% and 1.5% of all breast malignancies [10]. We usually deal with primary breast cancer because that is the most common female malignancies [13].

Recently, there is an increasing evidence regarding the association of sporadic GISTs with second neoplasia. In a systematic review and meta-analysis conducted the rate of secondary tumors with GISTs was reported to be 20%[14]. Breast cancers are the most common malignancies together with GISTs.

Taking into account that breast metastasis from GISTs are extremely rare and that second tumors including breast cancer are common, at first in this clinical situation it is obligatory to exclude breast cancer that we have done.

Our patient had a local progression, growth only lesion in the breast, we removed increased metastasis that allowed us to return to less toxic treatment, the patient resumed imatinib. The critical question of whether surgery provides additional benefit over remaining on tyrosine kinase inhibitors (TKIs) therapy alone without surgical resection is unanswered. Randomized trials failed to recruit quickly enough to meet target accrual. In the absence of randomized trials, single-institution and multi-institutional retrospective studies document long-term disease control and longer overall survival for

selected patients who undergo metastasectomy of increased lesions while other lesions under control (local progression) on imatinib therapy. Removal of increased metastases let to continue imatinib therapy and not to change the TKIs that have less efficacy and not so favorable profile of toxicity. The median time to progression on sunitinib therapy is 6 mo, on regorafenib only 4 mo. Fairweather *et al*[15] published the largest series of patients with metastatic GIST treated with TKI undergoing surgical resection (n = 323). The median time to progression during imatinib therapy on local progression was 47 mo from the start of imatinib and 11 mo from cytoreductive surgery, removal increasing lesions[15]. These data are consistent with the result of treatment of our patient; the duration of imatinib therapy after surgery is 19 mo that is more than four times higher than the median PFS on regorafenib therapy.

CONCLUSION

In conclusion, breast metastases from GISTs are very rare, but it is clinically very important to distinguish primary from metastatic breast lesions.

FOOTNOTES

Author contributions: Filonenko D has been treating the patient, developing the treatment strategy of the patient; made the literature review, analyzed the data and wrote the text of the article and revised the article according to editor's revisions; Karnaukhov N is pathologist who made the morphology, histology and immunohistochemistry investigations, take a photo of these investigations; Kvetenadze G is a surgeon who performed resection of the right breast; Zhukov L is developing the treatment strategy of the patient, made the literature review, analyzed the data and correct the text of the article and revised the article according to editor's revisions.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to report.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Russia

ORCID number: Daria Filonenko 0000-0002-7224-3111; Nikolay Karnaukhov 0000-0003-0889-2720; Lyudmila Zhukova 0000-0003-4848-6938.

S-Editor: Wang JL
L-Editor: A
P-Editor: Wang JL

REFERENCES

1 **Miettinen M**, Lasota J. Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch* 2001; **438**: 1-12 [PMID: 11213830 DOI: 10.1007/s004280000338]
2 **Miettinen M**, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. *Hum Pathol* 1999; **30**: 1213-1220 [PMID: 10534170 DOI: 10.1016/s0046-8177(99)90040-0]
3 **Tulsi R**, Ul Haque MM, Hanif FM, Devi A, Mubarak M, Hassan Luck N. Metastasis of Duodenal Adenocarcinoma to the Urinary Bladder Presenting as Hematuria. *J Transl Int Med* 2021; **9**: 143-145 [PMID: 34497753 DOI: 10.2478/jtim-2021-0010]
4 **Liu P**, Tan F, Liu H, Ge J, Liu S, Lei T, Zhao X. Skin Metastasis of Gastrointestinal Stromal Tumors: A Case Series and Literature Review. *Cancer Manag Res* 2020; **12**: 7681-7690 [PMID: 32904396 DOI: 10.2147/CMAR.S261823]
5 **Wong CS**, Chu YC. Intra-cranial metastasis of gastrointestinal stromal tumor. *Chin Med J (Engl)* 2011; **124**: 3595-3597 [PMID: 22340184 DOI: 10.3760/cma.j.issn.0366-6999.2011.21.029]
6 **Bashir U**, Qureshi A, Khan HA, Uddin N. Gastrointestinal stromal tumor with skeletal muscle, adrenal and cardiac metastases: an unusual occurrence. *Indian J Pathol Microbiol* 2011; **54**: 362-364 [PMID: 21623091 DOI:

10.4103/0377-4929.81638]
7 **De Leo A**, Nannini M, Dondi G, Santini D, Urbini M, Gruppioni E, De Iaco P, Perrone AM, Pantaleo MA. Unusual bilateral ovarian metastases from ileal gastrointestinal stromal tumor (GIST): a case report. *BMC Cancer* 2018; **18**: 301 [PMID: 29548310 DOI: 10.1186/s12885-018-4204-1]
8 **Irving JA**, Lerwill MF, Young RH. Gastrointestinal stromal tumors metastatic to the ovary: a report of five cases. *Am J Surg Pathol* 2005; **29**: 920-926 [PMID: 15958857 DOI: 10.1097/01.pas.0000155161.55915.c3]
9 **Hasbay B**, Aytaç HÖ, Kayaselçuk F, Torun N. An Unusual Gastrointestinal Stromal Tumor Presentain: Breast, Liver and Lymph Node Metastasis. *Eur J Breast Health* 2017; **13**: 216-218 [PMID: 29082381 DOI: 10.5152/ejbh.2017.3492]
10 **McFarlane ME**. Metastasis to the breast: a rare site for secondary malignancy. *Int J Surg* 2006; **4**: 204-205 [PMID: 17462351 DOI: 10.1016/j.ijsu.2005.10.008]
11 **Klingen TA**, Klaasen H, Aas H, Chen Y, Akslen LA. Secondary breast cancer: a 5-year population-based study with review of the literature. *APMIS* 2009; **117**: 762-767 [PMID: 19775345 DOI: 10.1111/j.1600-0463.2009.02529.x]
12 **Wang Y**, Hou K, Jin Y, Bao B, Tang S, Qi J, Yang Y, Che X, Liu Y, Hu X, Zheng C. Lung adenocarcinoma-specific three-integrin signature contributes to poor outcomes by metastasis and immune escape pathways. *J Transl Int Med* 2021; **9**: 249-263 [PMID: 35136724 DOI: 10.2478/jtim-2021-0046]
13 **Siegel RL**, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin* 2021; **71**: 7-33 [PMID: 33433946 DOI: 10.3322/caac.21654]
14 **Petrelli F**, Tomasello G, Barni S, Varricchio A, Costanzo A, Rampulla V, Cabiddu M, Turati L, Russo A, Seghezzi S, Passalacqua R, Ghidini M. Risk of second primary tumors in GIST survivors: A systematic review and meta-analysis. *Surg Oncol* 2019; **29**: 64-70 [PMID: 31196495 DOI: 10.1016/j.suronc.2019.03.001]
15 **Fairweather M**, Balachandran VP, Li GZ, Bertagnolli MM, Antonescu C, Tap W, Singer S, DeMatteo RP, Raut CP. Cytoreductive Surgery for Metastatic Gastrointestinal Stromal Tumors Treated With Tyrosine Kinase Inhibitors: A 2-institutional Analysis. *Ann Surg* 2018; **268**: 296-302 [PMID: 28448384 DOI: 10.1097/SLA.0000000000002281]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com