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Original Research Article **Gastroenterology**

Budd Chiari syndrome (BCS) and Myeloproliferative Neoplasms (MPN): A Moroccan Experience Center

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Abstract

Background and Objectives*:** Budd–Chiari syndrome is a vascular disorder of the liver which can cause fulminant liver injury and lethal portal hypertension-related complications. It is a rare disease and can be primary or secondary. The objective of our work is to detail evolution, treatment of patients with BCS and MPN according to the experience of a Moroccan center. ***Patients and Methods*:** This is a retrospective and descriptive study in the university hepato-gastroenterology department including all patients with BCS and MPN with portal hypertension (PH) over a period of 29 years. All our patients benefited from an etiological work-up and morphological explorations. ***Results*:** Out of a total 29 patients had BCS, 4 had MPN with a prevalence of 10%. Clinically, the signs of decompensated PH were predominant. Imaging confirmed BCS. The etiological work-up showed that all our patients had essential thrombocytemia. We had also association of other prothrombotic factors in 50 % of cases and a portal thrombosis in 25% of cases**.** Our patients had received treatment for the causative disease and treatment of thrombosis associated with the treatment of PH complications. The evolution was marked by the death of 2 patients (50%). ***Conclusion: The strong association between MPN and BCS is well established. The knowledge of the molecular mutations underlying MPN has dramatically improved in the last decade, allowing early diagnosis of MPN in a significant portion of BCS patient.

Keywords: Budd Chiari Syndrome- Myeloproliferative Neoplasms – Treatment-Evolution.

INTRODUCTION

Budd-Chiari syndrome (BCS) is a vascular disease of the liver, characterized by partial or total obstruction of hepatic venous flow in the vascular space between the hepatic veins and the junction between the inferior vena cava and the right atrium. It can be primary or secondary. The objective of our work is to detail the etiological, therapeutic and evolutionary profile in patients with BCS.

MATERIALS AND METHODS

This is a retrospective and descriptive study in the university hepato-gastroenterology department including all patients with BCS and MPN with portal hypertension (PH) over a period of 29 years from 1991 to 2024.

All our patients benefited from a biological work-up including a blood count, a complete liver work-up including transaminases, alkaline phosphatases, gamma glutamyl transferase, bilirubin, prothrombin level (TP), international normalized ratio (INR), albumin, etc.

Morphologically, all our patients benefited from abdomino-pelvic ultrasound coupled with Doppler, abdominal angioscanner and hepatic MRI angiography, depending on the context.

RESULTS

Out of a total of 364 cases of vascular liver disease, 29 patients had BCS, with a prevalence of 8%, and 4 patients with BCS and MPN disease, 29 patients had BCS, with a prevalence of 10 %. The mean age of our patients was 31 years. All our patients were females.

The table below shows the prevalence of BCS in vascular liver disease:

Table 1: prevalence of BCS UN vascular liver disease

	Portal vein thrombosis	Porto-Sinusoidal Vascular Disorders (PSVD)	BCS
Prevalence	57.69%(n=210)	35.44%(n=129)	8%(n=29)

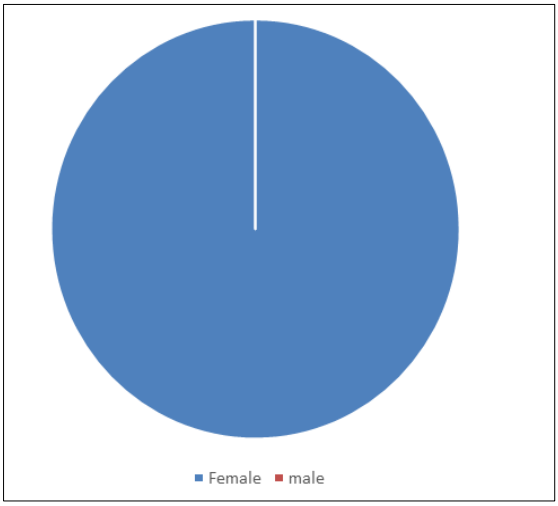

Figure 1: Gender distribution of our patients

Clinically, the signs of decompensated PH were predominant with ascites in 58% of cases (n=17), upper gastrointestinal bleeding in 31% of cases (n=9), jaundice in 13% of cases (n=4) and hepatocellular insufficiency in one case. Hepatic colic in 31% of cases (n=8).

The table below summarizes all the functional signs seen in our patients:

Table 2: Functional signs in our patients

	Number of patients	**Percentage in %**
Increased abdominal volume	3	75%
Jaundice	3	75%
Pruritus	3	75%
Atypical abdominal pain	2	50%
Anorexia	2	50%
Clinical anemia syndrome	1	25%
Hepatic colic	1	25%
Profound asthenia	1	25%
Hematemesis	1	25%

Imaging confirmed BCS with thrombosis of the two or three hepatic veins alone in 25% of cases each one (n=1), and thrombosis of the hepatic veins (HV) and the inferior vena cava (IVC) at the same time in 50 % of cases (n=2). Chronic portal thrombosis was associated with 01 patients.

The table below show the results the different levels of thrombosis on Doppler ultrasound in our series:

Table 3: Showing the different levels of thrombosis on Doppler ultrasound in our series.

	2 HV	**3 HV**	**2 HV et IVC**	**Portal thrombosis**
Number of patients	1+	1+	2	01
percentage in %	25%	25%	50.%	25%

The table below shows the results of Doppler ultrasound and angioscanner(CT) in our patient:

Table 4: Doppler ultrasound and angio CT findings in our patients

	Thrombosis of HV alone	**Thrombosis of HV and IVC**	**Associated portal vein thrombosis**
Abdominal ultrasound with Doppler	25 % (n=1)	50% (n=2)	25% (n=1)
Abdominal angioscan	25% (n=1)	50% (n=2)	25% (n=1)

A liver biopsy was performed in 50% of cases (n=2) and showed cirrhosis in 50% of cases (n=1), and sever fibrosis F3 in 50% of cases (n=1). The table below shows the results of liver biopsy in our patients:

Table 5: the results of liver biopsy in our patients

Diagnostic	Number of patients	Percentage in %
Severe fibrosis: F3	1	50%
Cirrhosis	1	50%

The etiological work-up showed that all our patients had essential thrombocythemia (ET)
The table below shows the associations of prothrombotic factors in our patients:

Table 6: Showing the associations of prothrombotic factors in our series.

	Number of patients	Percentage
Protein C+protein S deficiency+ AT	1	25%
Antithrombin III+protein C deficiency	1	25 %

The table below shows the prevalence of prothrombotic factors:

Table 7: Prevalence of prothrombotic factors

	At least one factor	Several factors
Prevalence	50% (n=19)	50% (n=5)

Our patients had received treatment for the causative disease and treatment of thrombosis associated with the treatment of MPN and PH complications. The evolution was marked by the death of 2 patients (50%), a repermeabilization of the HV by medical treatment in one case.

DISCUSSION

I-Introduction

Budd-Chiari syndrome (BCS) is a vascular disease of the liver, characterized by partial or total obstruction of hepatic venous flow in the vascular space between the hepatic veins (minimum two veins), and the junction between the inferior vena cava and the right atrium. The updated WHO classification of Philadelphia-negative MPNs includes polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), the latter including prefibrotic/early primary myelofibrosis [6]. These disorders are characterized by stem cell-derived clonal myeloproliferation with mutually exclusive JAK2, CALR, and MPL mutations [1-3].

II-Epidemiology

In two population-based studies, MPN emerged as the condition more frequently associated with BCS, accounting for 38–48% of cases. A metaanalysis carried out on 555 patients with BCS demonstrated that the prevalence of overt MPN diagnosed after a complete diagnostic work-up was 31.8% in the patients without cirrhosis and hepatobiliary cancers. Another meta-analysis conducted according to the same criteria in 1062 patients with BCS reported a prevalence of overt MPN as high as 40.9% [4, 5].

Reference	Type of SVT	*n* patients	JAK2 V617F, (*n*, %)	Overt MPN (*n*, %[a])	JAK2 V617F (*n*, %[a])		
					All patients[a]	MPN patients[a]	Non-MPN patients[a]
Qi et al., 2011 [20], Meta-analysis	BCS	555	177/555 31.8%	77/242 31.8%	106/242 43.8%	62/77 80.5%	44/165 26.6%
	EHPVO	858	250/858 29.1%	86/532 16.1%	136/532 25.5%	75/86 87.2%	61/446 13.6%
Smalberg et al.,2012 [21] Meta-analysis	BCS	1062	159/401 41.1%	180/440 40.9%	188/440 42.7%	144/180 80.3%	44/260 17.1%
	EHPVO	855	166/595 27.7%	188/615 31.5%	228/615 37.0%	162/188 86.6%	66/427 15.4%

Prevalence of myeloproliferative neoplasms (MPN) and the JAK2 V617F mutation in patients with splanchnic vein thrombosis (SVT): Budd-Chiari syndrome. (BCS) and extra-hepatic portal vein obstruction (EHPVO). Modified from De Stefano *et al.*,

III-Molecular Diagnosis of MPN-Related Budd–Chiari Syndrome

Given the high rate of MPN as an underlying cause of BCS and SVT, the current practice guidelines recommend the routine screening for MPN. However, the diagnosis of MPN in this setting is somewhat difficult, because splenomegaly is mistakenly associated with the occurrence of portal hypertension,

hypercythemia is often masked by portal hypertension-related hypersplenism and hemodilution or gastrointestinal bleeding, and hepatic ischemia in BCS patients can produce an inappropriately elevated level of erythropoietin. Therefore, a deep diagnostic work-up should apply either molecular and histological tools to unravel underlying diseases [6].

Until the mid-1990s, the spontaneous endogenous erythroid colonies (EEC) (growth of erythroid colonies in the absence of exogenous erythropoietin) assay was employed as a diagnostic tool to recognize MPN at overt and early stages; in the seminal studies, the EEC assay was positive in 78% of idiopathic BCS.

However, this assay requires special technical facilities and lacks standardization, with a specificity of less than 80% . [6]. [7]. In the last decade, the capacity of diagnosing Philadelphia-negative MPN has been dramatically improved due to the knowledge of the somatic mutations associated with MPN. Almost all patients with PV harbor the somatic activating mutation JAK2 V617F in the exon 14 (approximately 96%) or additional mutations in the JAK2 exon 12 (approximately 3%). JAK2 V617F also occurs in ET and PMF, with mutational frequencies of 55% and 65%, respectively. CALR is a multi-functional calcium-binding protein mostly localized in the endoplasmic reticulum.

CALR mutations are rare in PV but are present in 25–35% of PMF patients and 15–24% of ET patients. Mutations in the MPL gene are present in approximately 4% of ET patients, 8% of PMF patients, and rarely in PV [8].

A. JAK2 V617F Mutation

In the meta-analysis mentioned above conducted by Qi *et al.*, on 555 patients with BCS, the pooled prevalence of JAK2 V617F mutation was 43.8% in the patients with a complete diagnostic work-up for MPN. However, the rate of the mutation was as high as 80.5% in the patients who fulfilled the WHO diagnostic criteria for MPN, and 26.6% in the patients who did no. Consistently, in the meta-analysis conducted by Smalberg *et al.*, the JAK2 V617F mutation was positive in 42.7% of the BCS patients, 87.2% in those with overt MPN, and 13.6% in those without typical hematologic features of MPN However, the negative predictive value of the JAK2 V617F marker for diagnosis of MPN is low, being the mutation absent in approximately 40% of ET or PMF patients. The JAK2 V617F mutation is rare in Chinese patients with BCS, suggesting a difference in the causes of BCS between Western countries and China [6, 7].

B. Carl Mutation

The prevalence of the CALR exon 9 mutations in patients with BCS and EHPVO has been recently reviewed. The data of 1492 patients with SVT reported in 11 papers were analyzed; 580 of them had BCS. The pooled proportion of CALR mutations was 1.21% in all SVT patients regardless of JAK2 V16F mutation and MPN status, and the pooled proportion of CALR mutations was 1.41% and 1.59% in BCS and EHPVO patients, respectively. The pooled proportion of CALR mutations in SVT, BCS, and EHPVO patients without JAK2 V617F mutation was 1.52%, 1.03%, and 1.82%, respectively. Accordingly, regular screening for CALR mutations in unselected SVT patients might be of little use. Another finding was that the prevalence of CALR mutations was relatively higher in SVT, BCS, and EHPVO patients with MPN than in those without MPN (SVT: 3.71% vs. 1.21%; BCS: 2.79% vs. 1.41%; EHPVO: 7.87% vs. 1.59%), but the absolute value remained low [7].

Iv. Diagnostic Strategy

Investigation of the JAK2 V617F mutation and a complete laboratory work-up for thrombophilia is mandatory in patients with non-cirrhotic and non-malignant BCS. Bone marrow biopsy is recommended in SVT patients. This procedure aims to refine the diagnosis of MPN according to the WHO criteria in the patients JAK2 V617-positive and to capture additional cases of MPN in the JAK2 V617F-negative patients. In those latter, a complete molecular work-up including CALR, MPL, and exon 12 mutation should be reserved only for those with bone marrow biopsy highly suggestive of MPN [9].

V. Treatment at Diagnosis

In the acute phase, the treatment of patients with BCS and with Philadelphia-negative MPN does not differ from that of patients without MPN. A prompt treatment with low molecular or unfractionated heparin followed by vitamin K antagonists (VKA) should start promptly. A step-wise approach is suggested. In the case of clinical deterioration despite anticoagulation, a second-line based on invasive procedures, such as angioplasty with or without stenting, transjugular intrahepatic portosystemic shunt (TIPS), or surgical portosystemic shunt, should be considered.

Systemic thrombolytic therapy with tissue plasminogen activator is scarcely effective, whereas catheter-directed thrombolysis may be useful for the treatment of acute and partially occlusive thrombosis [10, 11].

Recently TIPS has been proposed as the treatment of choice for patients with BCS with signs of portal hypertension. Angioplasty/stenting should be the second-line treatment in the subgroup of patients if TIPS is ineffective or unsuitable.

Surgical shunts should be the treatment of choice when both TIPS and angioplasty/ stenting are

ineffective or unsuitable. Liver transplantation should be considered as a salvage treatment [12, 13].

VI. Prognosis

The prognosis of BCS has significantly improved with time. In a large series of 104 BCS patients with a median follow-up of 3.9 years, overall survival did not differ according to the presence or absence of JAK2 V617F (p = 0.29) or of diagnosis of MPN (p = 0.961). However, event-free survival was shorter in patients with JAK2 V617F (p = 0.07) and significantly reduced in those with MPN (p = 0.0145) [14].

CONCLUSION

The strong association between MPN and BCS is well established. The knowledge of the molecular mutations underlying MPN has dramatically improved in the last decade, allowing early diagnosis of MPN in a significant portion of BCS patients

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