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Case Report

Evaluation of Pathophysiological Characteristics in the Setting of Budd Chiari Syndrome and Renal Artery Stenosis Induced by Polycythemia Vera

Juna Musa[1]*, Ali Guy[2], Elton Cekaj[3], Erisa Kola[4], Edlira Horjeti[5], Ina Kola[6], Carlos Rivera[7] and Belinda Bejtja[1]

[1]*General Practitioner, Tirana, Albania*

[2]*Clinical Instructor of Physical Medicine and Rehabilitation, New York University, School of Medicine, NYU Medical Center, USA*

[3]*Radiologist, Regional Hospital of Durres, Albania*

[4]*Pathologist, Department of Pathology and Forensic Medicine, Albania*

[5]*Family Doctor, Primary Care Center Nr. 2, Tirana, Albania*

[6]*Plastic Surgery Resident, Tirana, Albania*

[7]*Research Fellow, General Surgery Department, Metabolic and Bariatric Institute, Cleveland Clinic, Florida, USA*

***Corresponding Author:** Juna Musa, General Practitioner, Tirana, Albania

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Abstract

Budd-Chiari syndrome is a rare life-threatening disorder caused most frequently as a complication of Polycythemia Vera [1]. BDS is caused by an obstruction of the hepatic vein outflow at the level of either the hepatic veins or the sub-diaphragmatic segment of the inferior vena cava [2]. Myeloproliferative neoplasms and chronic inflammatory diseases are the most common causes of BCS [2]. The precise location and size of the obstruction is clinically and prognostically significant as it dictates the patient's symptoms and guides through the appropriate therapeutic management [3]. A 54-year-old female presented with Primary Erythrocytosis from Polycythemia Vera and refractory hypertension secondary to renal arterial stenosis (RAS), findings of Reno vascular occlusive disease may be primarily due to underlying PV. Radiological assessments (CT scan with IV contrast) and the clinical presentation were consistent with the diagnosis of BCS. Along with literature review; we discussed the pathological events that take place in such rare associations.

Keywords: Budd-Chiari syndrome (BCS); Inferior Vena Cava (IVC); Polycythemia Vera; Renal Artery Stenosis

Introduction and Background Information

Historically Budd-Chiari syndrome (BCS) was defined as a rare condition characterized by hepatic venous outflow obstruction, usually located at the level of the hepatic vein and inferior vena cava (IVC) [1]. However, the precise location of the obstruction(s) was of a clinical and prognostic importance. The most recent accepted definition of primary BCS is hepatic outflow obstruction regardless of the cause or level of obstruction [2].

Classical BCS typically presents with an acute onset of symptoms although they depend on the extension and rapidity of venous occlusion as well as on the development of collateral circulation that decompresses the hepatic sinusoids' is considered primary or secondary depending on the origin of the obstructive lesion [3]. If obstruction is the result of endoluminal venous lesion-like thrombosis, primary BCS is considered. In secondary BCS, the cause originates from neighboring structures like extrinsic compression or tumor invasion [2].

The main conditions which cause BCS are: conditions accompanied by hypercoagulable states, neoplasms, oral contraceptives use, hormonal therapy, pregnancy, inflammatory bowel disease, celiac disease and trauma. Polycythemia Vera is considered to be the most frequent condition causing the BCS (10 - 40%) [4]. BCS are classified as being fulminant, acute, subacute or chronic [5]. Since BCS is rare, both classification and management are empirical and not evidence- based and follow opinion leaders' suggestions [6-9].

Treatment and prognosis of BCS depends on the severity of the symptoms, etiology and the level and extent of the obstruction including complementary management of the underlying cause [3].

Case Presentation

A 54-year-old female patient was admitted to the hospital because of shortness of breath, headache, and fatigue and right upper abdominal quadrant pain. Objective examination revealed firm hepatomegaly, splenomegaly and bilateral papilledema in the fundus oculi examination. Her past medical history includes hypertension diagnosed 12 years back regularly controlled with Atenolol and Enalapril. However, during the last year prior to this episode, she has had other episodes with hypertension requiring an increase in the dose of the antihypertensive drugs. Despite all these efforts, her BP was still high. Her BP was 180/110 mmHg

without significant difference in BP between all limbs and without postural fall. During the last week before being admitted, she had several episodes of increased BP up to 230/110. Laboratory results showed elevated creatinine [estimated glomerular filtration rate (eGFR) 37 mL/min/1.73m2], high uric acid level and +2 proteinuria. A CT scan was performed, revealing a severe stenosis in the proximal portion of the right renal artery, which had resulted in ischemia of the affected kidney with collateral flow. The left kidney appeared atrophic and not enlarged as it is expected due to compensation.

A complete blood count revealed marked pancytosis, consisting of erythrocytosis, mild thrombocytosis and leukocytosis. Bone Marrow biopsy confirmed the diagnosis of PV, showing hypercellularity. Genetic analysis for JAK2F V617F mutation further supported the diagnosis of PV. Patient was aware of diagnosis and treated with low dose aspirin and phlebotomies but refused treatment with hydroxyurea.

Hematology	Blood chemistry and serology	Urine analysis
WBC= 11800/mm^3	PT= 26.1 sec	Glucose (-)
RBC= 6100000/mm^3	INR= 1.44 %	Protein (++)
Hb= 17.5 g/dl Hct= 52% PLT= 517000/ mm^3	APTT= 28 sec AST= 42 U/L, ALT=21 U/L ALP=165 U/L, GGT=114 U/L Creatinine = 2.1 mg/dl, BUN= 171 mg/dl	24-hour urine protein= 4 gr/ day
	Uric acid= 8.1 mg/dl HbsAg (-)	

Table

Abdominal ultrasonography showed enlargement of the caudate hepatic lobe, moderate ascites and thrombosis of the hepatic veins. Other findings were: collateral vessels between the tributary territory to the hepatic vein and those tributary to the left and right lobes, multiple vascular tracks in the caudate lobe which led to the inferior vena cava, congestive splenomegaly with important collateral circulation at the hilum, and a small quantity of ascites in the pelvis. The hepatic veins were thin and tortuous, suggesting flow through collateral circulation. Color Doppler ultrasound studies showed absent or flat flow in the hepatic veins, inferior vena cava and intrahepatic collateral pathways. It revealed an enlarged portal vein diameter of 15 mm with reversed hepato- portal flow and a slow hepato-jugular flow at the level of the portal vein. Enlargement of caudate vein of 3 mm in diameter strongly suggests the diagnosis of Budd-Chiari syndrome in the appropriate clinical setting. The sonographic findings also suggested long-standing thrombosis. Stenosis of right renal artery of more than 90% was detected on visualization of the renal vessels. The contralateral kidney was atrophic. We don't have any other prior ultrasound imaging of the kidney to confirm if the left kidney was atrophic due to a congenital presentation or the left kidney, due to longstanding right kidney stenosis is not able to compensate anymore.

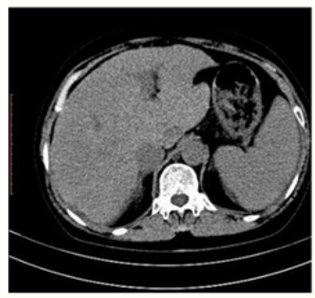

Figure 1: Axial CT scan without contrast media. Note the missing supra-hepatic veins cause of Budd Chiari Syndrome.

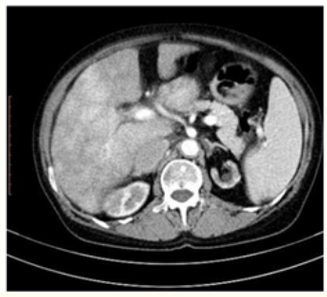

Figure 2: Axial CT scan, arterial phase showing a mosaic pattern of the liver.

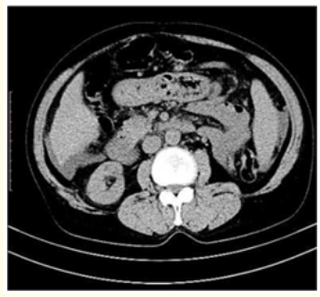

Figure 3: Axial CT without contrast media. Ascites is seen perihepatic, in morrison pouch and perisplenic.

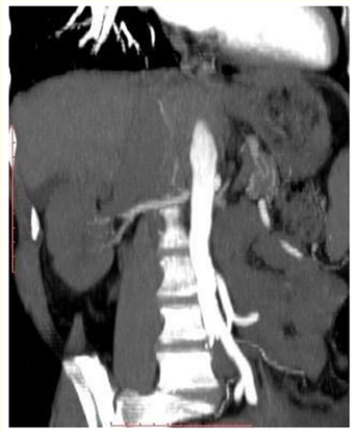

Figure 4: Coronal CT scan. Note the missing right artery origin due to stenosis.

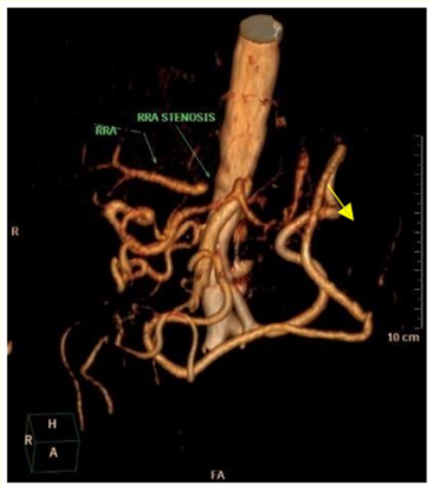

Figure 5: Volume rendering CT scan view identifies right renal artery stenosis.

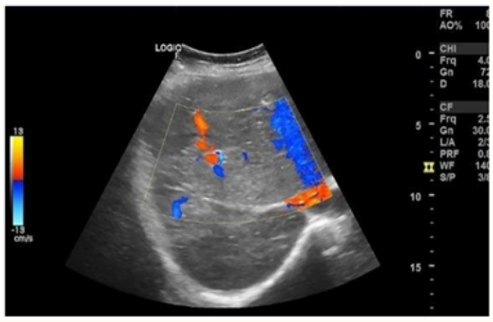

Figure 6: Ultrasound view, to be noted thrombosis of right prehepatic vein, hyperechogenic without doppler signal.

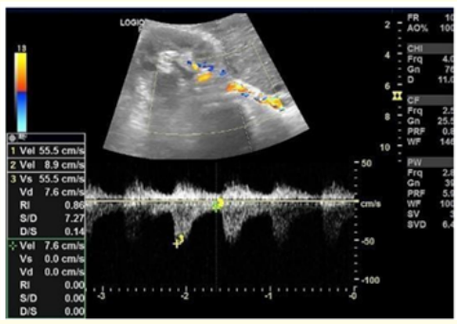

Figure 7: Right renal artery high resistance index cause.

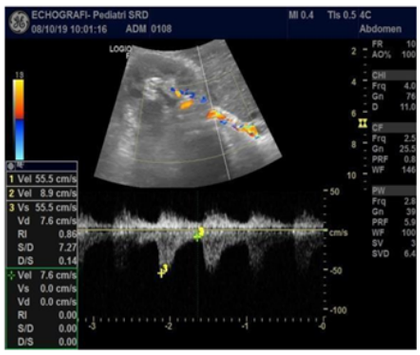

Figure 8: High RI values cause of hypertensive renal ischemia (proximal artery stenosis).

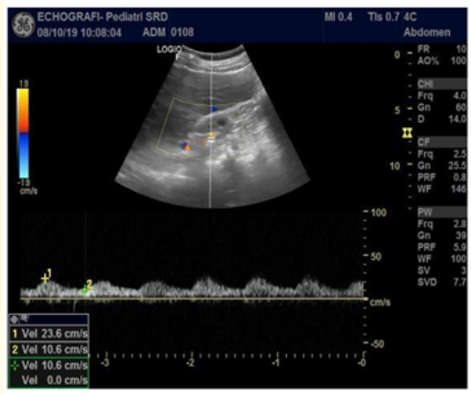

Figure 9: Low peak systolic and low diastolic velocities cause of chronic renal hypertensive ischemia.

Endoscopic examination revealed varices extending above the mucosal level up to one third of the luminal diameter, consistent with esophageal varices grade 2.

The defining features of BCS are: the nodular aspect of the liver, compensatory hypertrophy of the caudate lobe (vascularized by vessels that directly open into the inferior vena cava), the absence of the vascular signal in the suprahepatic veins, intralumenal echogenic fill at this level and the development of collateral circulation [1,6,7].

In establishing the diagnosis in our patient, we excluded other causes of liver cirrhosis like viral hepatitis, alcohol abuse, autoimmune liver disease, Wilson disease, hemochromatosis, and alfa-1-antitrypsin deficiency. The patient did not use oral contraceptives.

Discussion

Our case represents a rare coexistence of renal artery stenosis combined with PV and Budd-Chiari Syndrome and severe hypertension in a 54-year-old female. To our knowledge, only a few cases of PV combined with renal artery stenosis (RAS) have been reported, and we do not know whether these two disease entities have a causal relationship [11].

For the exploration of secondary hypertension with an elevated EPO level, we performed CT angiography covering the adrenal glands and renal arteries and found irregular severe stenosis of the right renal artery and an atrophic left kidney. Although RAS is known to impair renal perfusion and chronic hypoxia subsequently increases erythropoietin secretion and leads to secondary erythrocytosis, it is not evident whether the elevated EPO level caused by RAS could induce an acquired mutation [11,12].

The two most common causes of renal artery stenosis are: atherosclerosis, which commonly occurs at the origin of the proximal portion of the artery in older patients with typical cardiovascular risk factors [13-17]. In contrast, Fibro muscular dysplasia occurs in the middle or distal arterial segments in younger patients

without cardiovascular risk factors. Fibro muscular dysplasia is a non-atherosclerotic, non-inflammatory vascular disease that most predominantly affects the renal artery in women at middle aged. We do not know the exact underlying mechanism that caused renal artery stenosis, because we did not perform a histopathologic evaluation of the patient's renal artery due to high risk of bleeding. Although we assume FMD to be the main mechanism because of the patient's middle age and excluding the atherosclerosis plaque explanation because Except for the Hypertension, she had no risk factors for atherosclerotic disease, such as smoking, diabetes, severe dyslipidemia, obesity, or past family history of cardiovascular diseases [12-17].

Damage to the full thickness of the vascular structure in large vessels from atherosclerosis, such as the renal artery, has not been recognized as major complication of PV due to its impact is limited to the vascular endothelium [11]. On the other hand, the most probable hypothesis is that the extreme renal artery stenosis in this patient with PV is due to proliferation of erythrocytes, leukocytes, or platelets could damage vascular endothelial cells, and this damage could lead to fibro muscular intimal proliferation of the artery without thrombotic occlusion. PV can lead to intraluminal thrombus formation and arterial intimal proliferation via multiple mechanisms such as hyper viscosity from increased Hematocrit, activation of leukocytes and platelets, and abnormalities in coagulation systems and vascular endothelial function [18]. The possible relationship could be explained by the over stimulation of the JAK2/STAT5 system, a known promoter of angiogenesis, promoting the activation of platelets and leukocytes accelerating vascular endothelium and intima hyperplasia of the atherosclerotic plaque [19].

Still, it's not clear if progressive intimal and medial wall proliferation can be caused by endothelial irritation and edema due to repeated microvascular thrombosis and hypertension [19].

Another study showed that the most common characteristics of Myeloproliferative neoplasm associated Renal vascular hypertension manifesting primarily in women, is associated with untreated PV and essential thrombocytosis, leukocytosis and JAK2 mutation positive just like in our case [18-20].

In the pathophysiology of Renal vascular hypertension, the primary cause of blood pressure elevation is excessive activation of the renin-angiotensin-aldosterone system. Normally when we have severe stenosis of renal artery, we expect the contralateral kidney to be enlarged due to hyper perfusion and glomerular hyper filtration associated with an activated renin-angiotensin- aldosterone system, leading to proteinuria. In our case, we found out that the contralateral kidney is not enlarged, but atrophic. This raises several hypotheses that maybe the atrophic left kidney was congenital, or the left kidney is not able to compensate anymore, due to longstanding right kidney stenosis. However, this leads to hypertension being refractory and secondary to the severe renal artery stenosis [18-20].

Potential hypotheses that can explain the underlying mechanism of our presentation are:

1. RAS with secondary refractory hypertension giving rise to secondary PV which on the other hand induced BCS as a complication.
2. PV causing primary erythrocytosis and renal artery stenosis with secondary hypertension possible due to an increased thrombotic risk secondary to hyper viscosity.

The gold standard to distinguish primary polycythemia from secondary polycythemia is the measurement of EPO levels [22]. In our patient; we noticed hypo perfusion of the kidney caused by significant unilateral Renal artery stenosis, which is a well-known cause of Renal-vascular hypertension. Chronic hypoxia triggers Erythropoietin release by the kidney. It may be assumed that in the case of one-sided renal artery stenosis, ipsilateral increased Erythropoietin production may be due to compensatory reduction in the contralateral kidney.

In spite of that further prospective studies are needed to evaluate the possible associations between PV and RAS and to address gaps in knowledge and understand more the Physiopathological mechanisms of the interaction factors.

Conclusions

Bud Chiari syndrome is a rare syndrome with a wide array of symptoms but not uncommon complication in the setting of an untreated PV patient.

Co-existence of renal artery stenosis along with contralateral kidney atrophy that is presented in our patient, it can either be congenital, or due to long standing of hypertension.

In conclusion, our case report demonstrates that there is a possible association between PV and RAS. Therefore, elevated EPO levels and hypertension in patients with *JAK2* mutation should not be neglected or underestimated in clinical practice.

Therefore, because of the complications, patients with Polycythemia Vera should be aware of the importance of early treatment and periodic follow-up, especially in the setting of impaired renal function.

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