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An Unusual Clinical Presentation of Budd–Chiari Syndrome in an Adolescent Boy

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Abstract

We report an unusual case of massive splenomegaly with pancytopenia without ascites, which was referred to us with suspicion of a myeloproliferative disorder in an adolescent boy. The work-up done was noncontributory to a hematological disorder. On further work-up, liver biopsy depicted sinusoidal congestion, with Doppler study suggestive of nonvisualization of hepatic veins. There was hypertrophy of the right lobe and the presence of venovenous collaterals. Janus kinase 2 (JAK2) V617F mutation was negative, which confirmed the absence of unidentified myeloproliferative disorder. This was an atypical presentation of Budd–Chiari syndrome (BCS) in children. The absence of ascites could be due to more efficient collateral formation in adolescent age groups due to angiogenesis. Underlying thrombophilia was detected as methylenetetrahydrofolate reductase mutation 677C > T with raised serum homocysteine levels. It is imperative to be aware of the diverse clinical manifestations in children for early detection and appropriate intervention to prevent catastrophic results in pediatric BCS.

Keywords

- Budd–Chiari syndrome
- hypersplenism
- myeloproliferative disorder
- children
- thrombophilia

Introduction

Budd–Chiari syndrome (BCS) is a rare disorder caused due to hepatic venous outflow obstruction with variable underlying conditions. BCS has a low incidence worldwide (1/100,000).[1] It is fairly uncommon in children, with a study showing only 5% incidence in ages below 12 years, whereas more than one-half of the classical cases occurred in the third and fourth decades of life.[2] There are limited data on the clinical profile and underlying prothrombotic conditions in children. BCS can cause severe portal hypertension, negatively affecting life expectancy when the diagnosis and treatment are not done at an early stage. We present a case with an atypical presentation, which was evaluated as a suspected myeloproliferative disorder but was confirmed to be BCS with a heterozygous methylenetetrahydrofolate reductase (MTHFR) 677C > T mutation and raised homocysteine levels.

Case Presentation

A previously healthy 12-year-old boy was referred to the outpatient department of our hospital, a tertiary care teaching hospital, for a suspected myeloproliferative disorder. He had presented with a 6-month history of gradually progressive abdominal distention and loss of appetite. There was no history of jaundice or generalized edema. There was no loss of weight, bleeding from any site, or history of recurrent infections. On examination, a slightly distended abdomen was present with firm hepatomegaly and massive nontender firm splenomegaly. There was no free fluid on clinical examination.

Investigations

On evaluation, initial blood investigations demonstrated a hemoglobin level of 12.1 g/dL, total leucocyte count of

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Table 1 Laboratory investigation of the patient

Test	Result	Normal values
Hb (g/dL)	12.1	11.5–15.5
TLC ($\times 10^3$/μL)	2	4.5–13.5
DLC	N 39%	33–61%
	L 52%	28–48%
	M 5%	4–10%
	E 3%	0–3%
	B 0.3%	0–1%
Platelet count ($\times 10^3$/μL)	38	150–450
Peripheral smear	RBCs are normocytic normochromic with occasional microcytosis Platelet count reduced, normal in size WBC count reduced. No blasts or abnormal cells seen	–
Total serum bilirubin (mg/dL)	0.6	<1.5
Serum protein (g/dL)	4.3	6.3–7.9
AST (U/L)	75	10–40
ALT (U/L)	83	5–55
ALP (U/L)	467	100–495
PT (s)	14	11–13.5
INR	1.04	0.8–1.2
Serum creatinine (mg/dL)	0.7	0.5–1
Lactate dehydrogenase (IU/L)	225	100–330
Serum homocysteine level (μmol/L)	29.7	5 - 15

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; DLC, differential leukocyte count; Hb, hemoglobin; INR, international normalized ratio; PT, prothrombin time; RBC, red blood cell; TLC, total leukocyte count; WBC, white blood cell.

2,000/μL, and platelet count of 38,000/μL. Liver function tests measured the total serum bilirubin (0.6 mg/dL), alanine transaminase (75 U/L), aspartate transaminase (83 U/L), total serum protein (5.3 g/dL), albumin (3.1 g/dL), and international normalized ratio (1.02). The child was admitted to the pediatric ward and managed on the lines of evaluation of a possible underlying myeloproliferative disorder. Serum lactate dehydrogenase and uric acid were within the normal range. The peripheral smear did not show any blasts. Serum lactate was within the normal range. Renal functions were preserved. A bone marrow examination was done, which revealed a normal study (normocellular, normoblastic erythroid reaction, myeloid:erythroid ratio of 4:1, adequate megakaryocytes showing maturation). A comprehensive work-up was initiated for other causes of massive splenomegaly. The investigations have been detailed in ►**Table 1**. The presence of hyperreactive malarial syndrome was ruled out. Viral markers and RK39 strip test for *Leishmania* antibody were negative. There was no clinical evidence of ascites or portal hypertension. Keeping a possibility of portal vein thrombosis, an ultrasound abdomen and liver biopsy were planned. The ultrasound depicted a normal liver echotexture with partial left lobe agenesis with normal caliber of portal vein and splenic enlargement. Liver biopsy revealed sinusoidal congestion (►**Fig. 1**). A color Doppler study of the liver was then performed, which revealed the diagnosis. It showed an atrophied left lobe of the liver with hypertrophied right lobe. There was a narrowing of the right hepatic vein, dilation of the middle hepatic vein, and no visualization of the left hepatic vein with normal portal vein flow. The hepatic venous waveform was altered and a radiological diagnosis of BCS was given. Triphasic contrast-enhanced computed tomography showed attenuated caliber with the presence of thrombus in the left hepatic vein with multiple intrahepatic venovenous collaterals, a dilated splenoportal axis, and multiple submucosal gastric and esophageal

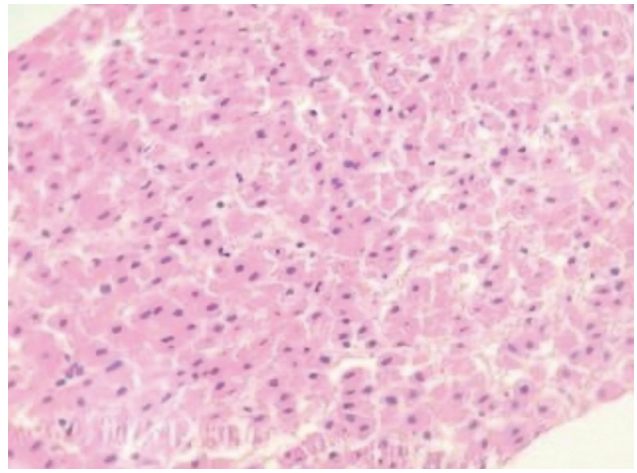

Fig. 1 Photomicrograph showing histopathologic features of BCS with sinusoidal congestion (hematoxylin and eosin stain, ×400).

Table 2 Second line-investigations and prothrombotic work-up of the patient

Test	Result
ANA	Negative
PNH work-up (by flow cytometry) – CD59, FLAER CD24, FLAER CD14	All normal, not suggestive of PNH
Protein C functional assay	Normal
Protein S functional assay	Normal
Antithrombin activity	Normal
Prothrombin mutation assay	No mutation detected
Factor V Leiden mutation	No mutation detected
MTHFR mutation 677C > T	Heterozygous mutation detected
Serum homocysteine level	Elevated
JAK2 V617F	No mutation detected

Abbreviations: ANA, antinuclear antibody; FLAER, fluorescent aerolysin; JAK, Janus kinase; MTHFR, methylenetetrahydrofolate reductase; PNH, paroxysmal nocturnal hemoglobinuria.

varices. An evaluation for the primary underlying prothrombotic state was performed, which has been detailed in ►**Table 2**. Janus kinase 2 (JAK2) V617F mutation was negative, which confirmed the absence of unidentified myeloproliferative disorder. Investigations depicted raised serum homocysteine levels (29.5 µmol/L; normal: 5.5–16.4 µmol/L). A heterozygous MTHFR mutation 677C > T was detected. He was started on anticoagulants and extended release β blockers and sent for radiological endovascular intervention to another specialized center after which he did not follow up.

Discussion

BCS is a rare disorder characterized by hepatomegaly, abdominal pain, and ascites, occasionally with jaundice.[3] BCS was initially not suspected in our case as the child had presented with hepatomegaly and massive splenomegaly without ascites. We ruled out myeloproliferative disorders and other possible etiological causes of massive splenomegaly. Approximately 8% of patients with BCS have onset of symptoms during adolescence. Data on the diverse clinical course and genetic disorders leading to thrombophilia in this unique group are scarce.[4]

Very little data are available about hepatic venous outflow tract obstruction in children. It has a variable clinical presentation in different age groups. A diagnosis of BCS was suggested by ultrasound Doppler examination. Venovenous collaterals are the important clue to the radiological diagnosis of BCS, which have been reported in 80 to 94% of cases by others.[5,6] The presence of massive splenomegaly and platelet count above 200×109 cells/L has been associated with underlying myeloproliferative neoplasms with high specificity but low sensitivity in BCS.[7]

A recent study has demonstrated that ascites is less commonly seen in adolescent children compared with younger children or adults. It could be postulated that in adolescent patients with BCS, the reason for mild disease and low prevalence of ascites could be more efficient collateral formation in the adolescent age group due to angiogenesis. Further evaluation of the exact pathophysiological mechanism would need further research in this age group. Vascular endothelial growth factor and hypoxia-inducing factor expression facilitate angiogenesis. The factors are high in young and tend to decrease with increase in age.[8] It is hence important to consider BCS in the differential diagnosis in adolescents presenting with hepatosplenomegaly without ascites.

The response to therapy is better in adolescents. In adults, medical treatment including anticoagulation had a success rate of 20% or less[9] and was largely limited to cases with mild disease with lower Child–Pugh scores.[10] There are no published data on the safety and efficacy of anticoagulation without radiological intervention in children with BCS.[11]

BCS is often associated with a hypercoagulable state (75% of cases),[1] membranes, trauma, neoplasia, and infections leading to obstruction of hepatic venous flow. We did a complete prothrombotic profile assessment and found elevated homocysteine levels with an underlying heterozygous MTHFR mutation. MTHFR is an enzyme that breaks down the amino acid homocysteine and folate, and the C677T mutation in 5,10-MTHFR leads to increased plasma homocysteine, which predisposes individuals to thrombosis. A study comparing 41 patients of BCS to 80 sex- and age-matched healthy controls concluded that the relative risk among carriers of 677C > T was 1.6 and that hyperhomocysteinemia and homozygous C677T mutation in the MTHFR gene were important risk factors.[12] One of the limitations of our report is the failure to conclusively prove the role of heterozygous MTHFR mutation as the cause of BCS.

In conclusion, our report highlights an atypical presentation of BCS in an adolescent. This case recapitulates the importance of a complete clinical assessment and evaluation by a Doppler ultrasound in all cases of unexplained asymptomatic hepatosplenomegaly. This necessitates a high index of suspicion to avoid missing this life-threatening diagnosis. Early and appropriate intervention to mitigate the damage can essentially restore hepatic function and thus prevent catastrophic results.

Authors' Contributions

S. A. and G. P. supported in data collection, data analysis, and preparing the first draft of the manuscript. R. M. and S. M. contributed in editing and preparing the second draft of the manuscript. A. S. dedicated to supervision and editing. All authors approved of the final manuscript.

Note

All authors have substantial contributions to the conception and design of the work and preparing and revising the draft critically for important intellectual content. All authors have approved the final version of the manuscript and are accountable for all aspects of the work.

Conflict of Interest
None declared.

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