CASE REPORT

Successful Local Thrombolytic Therapy in Subacute Budd-Chiari Syndrome: Case Report and Review

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Abstract

Introduction: Management of Budd-Chiari syndrome (BCS) includes different interventions and surgical procedures. There is limited data regarding catheter-directed thrombolysis when treating this condition but it appears to be helpful in the case illustrated below. **Case report:** A 29 year-old woman was referred to our center with one month history of right upper abdominal pain, progressive abdominal distension and intermittent fever not associated with rigors. There was no history of oral contraceptive use. She had mild right upper quadrant tenderness and abdominal distention with moderate elevation of liver enzymes. Her serology was negative for viral hepatitis, autoimmune or cholestatic liver disease. Computed tomography (CT) angiogram of the abdomen showed a large amount of ascites with extensive thrombosis of the inferior vena cava (IVC) involving the hepatic and left renal veins. There was also complete occlusion of the left common iliac vein confirmed by venogram. An infusion catheter was placed through the thrombosed segment of the IVC and right hepatic artery. Thrombolytic therapy was started with the injection of 5 mg of recombinant tissue plasminogen activator (t-PA) as a loading dose followed by 0.3 mg per hour. Enoxaparin and oral warfarin were started simultaneously and once the target INR was reached, enoxaparin was stopped and warfarin continued indefinitely. Ascites was well controlled with diuretics and large-volume paracentesis. A follow up venogram showed partial recanalization of IVC and hepatic veins. A repeat CT scan after 14 weeks showed complete resolution of the thrombus. After 28 months, she is asymptomatic with normal liver function tests and total resolution of the ascites. **Conclusions:** The data on local thrombolysis is limited and the agents and doses are not uniform among reported cases. This case report shows that it can be considered in acute BCS with partial obstruction, followed by angioplasty or TIPS if unsuccessful.

Key words: Subacute Budd-Chiari Syndrome, Thrombolysis, Liver, Venous disease

Introduction

Budd–Chiari syndrome (BCS) results from obstruction of the hepatic venous outflow independent of the level or mechanism of obstruction and in the absence of right heart failure or constrictive pericarditis (1). Obstruction may occur in the hepatic veins and/or in the supra-hepatic portion of the inferior vena cava (IVC) (2). BCS is further divided into primary and secondary BCS. Primary BCS relates to a primarily venous disease (thrombosis or phlebitis) and secondary BCS relates to

compression or invasion by a lesion originating outside the veins (benign or malignant tumor, abscess, cyst, etc.). BCS has been related to myeloproliferative disorders in the majority of patients when the diagnosis has been based on sensitive criteria, regardless of whether peripheral blood cell counts were suggestive or not (3). Membranous occlusion of the IVC and/or hepatic veins is a common cause of hepatic venous outflow obstruction in Asian populations and may be congenital or represent sequelae of thrombosis (2,4). It is also more likely to cause chronic BCS which is unlikely to respond to thrombolysis alone and may require a balloon dilatation or stent placement (5). Hepatic venous outflow obstruction leads to centrilobular congestion and hepatocyte necrosis, which leads to liver failure or cirrhosis if not relieved in time.
The clinical presentation of BCS ranges from asymptomatic up to fulminant hepatic failure (6). In a large series of patients with BCS, the median age was 35, female to male ratio was 2:1, myeloproliferative disorder was overt in 23%, and the main presentations were ascites and hepatomegaly (7). The presentation can be classified as acute which includes fulminant hepatic failure (26%), subacute (54%) and chronic (20%) (8).

Treatment of BCS can be divided into three categories; medical treatment (supportive care, anticoagulation and systemic thrombolysis), radiologic procedure (local thrombolysis, angioplasty, stenting and transjugular intrahepatic portosystemic shunt (TIPS)) or surgery (shunt or liver transplantation). The choice of specific approach is related to the clinical and anatomical feature of the BCS patient as well as the center experience. The goal of therapy is to prevent clot progression, restore the patency of the thrombosed vein decompressing the liver congestion and resolve the related complications (ascites, portal hypertension and malnutrition). There is limited data about the role of catheter-directed thrombolysis in this condition (9). In acute Budd–Chiari syndrome, the role of local thrombolytic therapy remains unclear but appeared to be helpful in the case illustrated here.

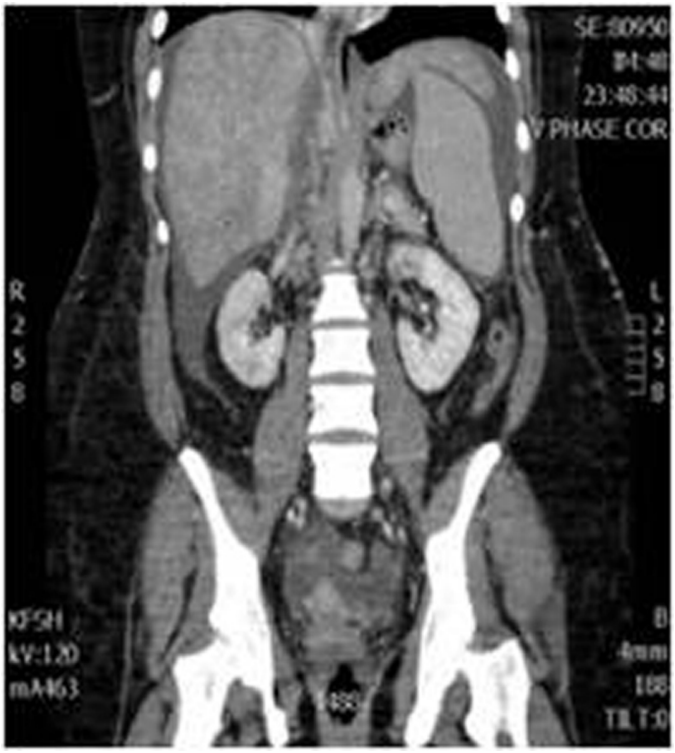
Case Report

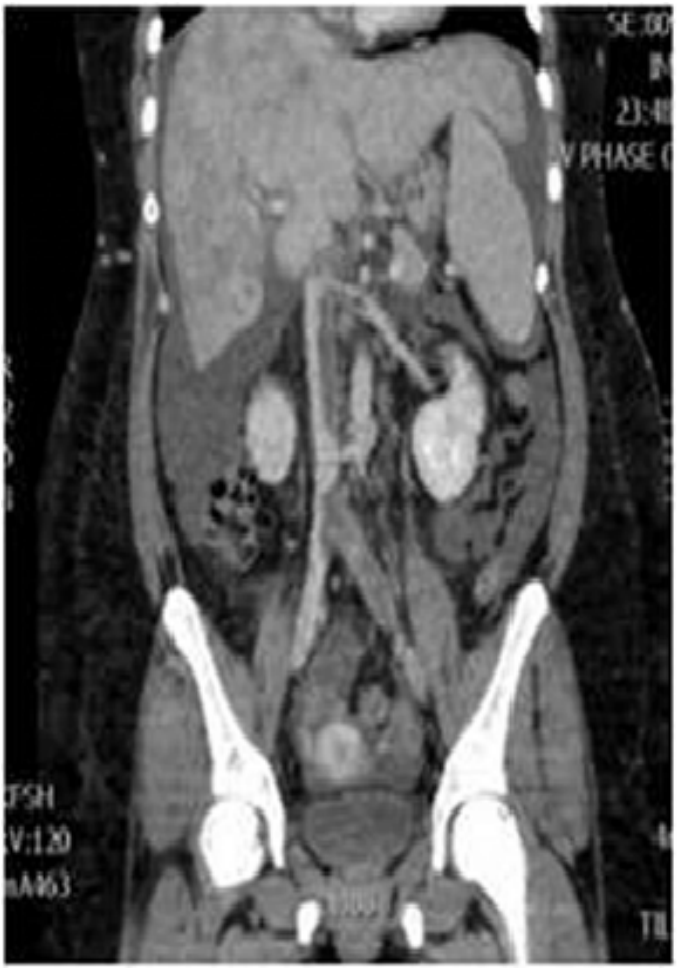
History: A 29 year-old female was referred to King Faisal Specialist Hospital and Research Center (KFSH&RC), Riyadh, Saudi Arabia with one month's history of right upper quadrant dull aching abdominal pain and progressive abdominal distension associated with swelling of both lower limbs. She had an intermittent fever not associated with rigors. There was no history of skin rash, mouth ulcers, joint pain, weight loss or bleeding tendency. She has been married for 2 years, has no children and no history of abortion. She has regular periods for 5 days. She has no history of oral contraceptive pills intake. She is a non-smoker and does not use alcohol or illicit drugs. She had no history of blood transfusions and no family history of rheumatic or liver disease.

Physical examination: Her temperature was 36.8°C, blood pressure 110/78 mm Hg, and heart rate 90 beats per minute. Skin examination revealed no rash or spider angiomas. She did not have any jaundice, lymphadenopathy or thyroid mass. Chest and cardiac examinations were normal. On abdominal examination, she had active bowel sounds and mild right upper quadrant tenderness on deep palpation. Her abdomen was distended with ascites. On percussion, the liver measured 16 cm in mid-clavicular line with a smooth edge. There was no splenomegaly. Neurologic examination was normal with no hyperreflexia or asterixis. There was bilateral pitting edema of both lower limbs.

Investigations: Laboratory investigations revealed a moderate elevation of liver enzymes. Total bilirubin was 83, albumin 29, ALT 44, AST 107, and serum alkaline phosphatase 174. Hepatitis B surface antigen (HBs Ag) and anti-hepatitis C antibody were both negative. Homocystein level was 10.4 μmol/L. JAK2 mutation was not detected. Lupus anticoagulant antibodies, anticardiolipin and beta2-glycopnotein 1 antibodies were positive. ANA was strongly positive. Other tests of thrombophilia screening were within the reference ranges. Abdominal ultrasound showed heterogonous echo pattern of the liver. Liver span was 17 cm in MCL. A contrast-enhanced computed tomography (CT) angiogram of the abdomen (Figures 1A &1B) showed heterogonous enhancement of the liver with hypertrophied caudate lobe. There was extensive thrombosis of the inferior vena cava involving the hepatic and left renal veins with complete occlusion of the left common iliac vein. Venogram through the left femoral vein revealed partial occlusion of the left common iliac vein and infrarenal segment of IVC combined with total occlusion of the suprarenal part of IVC.

Management and progress: An infusion catheter with side holes was placed through the thrombosed segment of the IVC. Thrombolytic therapy was started with the injection of 5 mg of recombinant tissue plasminogen activator (t-PA) as a loading dose, followed by 0.3 mg per hour. Another catheter was placed in the right hepatic artery after cannulation of the right femoral artery and the same regimen of thrombolytic therapy was given for one day. Anticoagulation was started with subcutaneous enoxaparine (Clexane, Sanofi) at a dose of 130 mg daily x5 days along with oral warfarin





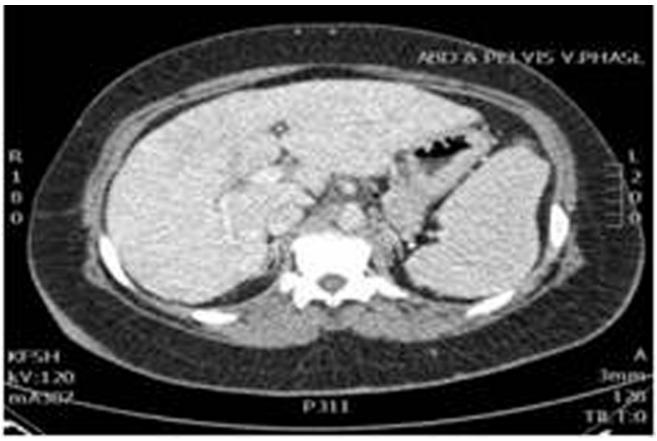


Figure 1: CT Angiogram showing thrombosis of the intrahepatic inferior vena cava involving the hepatic veins (A: Left upper) and left renal veins with complete occlusion of the common and IVC (B: Left Lower), left iliac veins (B), CT angiogram of the abdomen showing complete recanalization of IVC (image C: Above).

sodium (10 mg/day for 5 days; then the dose was adjusted and maintained according to INR). Oral anticoagulation was continued indefinitely. The ascites was managed with diuretics and by large-volume paracentesis under intravenous albumin therapy. Response was monitored by clinical and biochemical parameters with Doppler ultrasounds daily.

A follow up venogram showed partial recanalization of the IVC as well as appreciable opacification of the hepatic veins seen at delayed images of hepatic angiogram. A repeat CT scan after 14 weeks confirmed resolution of the thrombus in the inferior vena cava and common iliac veins (Figure 1C). The heterogeneous attenuation of the hepatic parenchyma was significantly improved and total resolution of the ascites occured. She has been followed for 28 months and is currently asymptomatic with normal liver function tests and total resolution of the ascites.

Discussion

BCS can be classified according to the etiology (primary or secondary), site of obstruction (small hepatic veins, large hepatic veins, IVC or combined), manifestation of the disease (fulminant or non-fulminant) or duration of the disease (acute, subacute or chronic) (1). Therefore, management of BCS depends on manifestation and duration of disease as well as the site and extent of obstruction. Medical treatment (including supportive care. anticoagulation, and systemic thrombolysis) has a limited role as a primary treatment but long term anticoagulation in conjunction with the definitive treatment is required for patients with underlying hypercoagulable state

Table 1. Summary of reported cases of local thrombolytic therapy for 44 cases if Budd Chiari syndrome.

First author (reference)	#	Age/ sex	Primary etiology	Disease onset	Agent & regimen	Infusion site	Outcome	Procedure's complications	Follow-up duration	Assisted procedure
Zhang (4)	14	15-55 8F 6M	Membranous or segmental obstruction (13)	Acute 8; subacute 6	Urokinase at 100,000 every 3-6 hours for 3-8 days.	Local: (HV)	Succsessfu 1 (13)	None	25 months	5 cases balloon+ stent 8 balloons
Sharma (15)	7	23-40/ 1M, 6F	Myeloproliferative, polycythemia vera, thrombocythemia, protein C deficiency	3-4 weeks	tPA	Local:(HA x1; HV and/or IVC x 4; within TIPSS/ PV in x2	Successful in 5 patients	None	Mean follow-up was 4-5 years	Adjunctive balloon angioplasty and/or stent insertion
Greenwood (16)	1	41/M	Unknown	Unknown	Urokinase: Bolus 4400 U/kg, then 4400 U/kg/h for 55 h	Local (IVC)	Successful	Intraperitoneal hemorrhage	Died 18 mo later due to recurrence	Nil
Ilan (17)	1	29/F	Post-partum	Few days	Streptokinase: for 72 h (dose?)	Local (IVC)	Partially successful	None	Died 9 months later	IVC and HV Angioplasty
Ishiguchi (18)	1	42/F	PNH	Chronic (several months)	Urokinase: 10,000 U/min for 35 min; then 240,000 U/day for 7 days	Local (IVC)	Successful	None	14 months	IVC angioplasty and stenting
Raju (19)	1	59/M	Unknown	Few hours	Urokinase: 300,000 U bolus 300,000 U/h for 72 h	Local (IVC)	Successful	None	12 months	Nil
Leebek (20)	1	27/F	Factor V Leiden mutation	2 weeks	10 mg bolus of tPA followed by 4 mg/hr for 24 hr	Local through TIPSS	Partially successful	Minor bleeding at the site of puncture	9 months	-
Alioglu (21)	1	13/M	Membranous web	Unknown	rh-tPA for local thrombolysis (2 mg/h) for 72 h.	Local through percutaneous hepatic vein puncture	Thrombosis recurred	None	Died after 5 months	Balloon angioplasty, surgical embranectomy
Kuo (22)	3	27/M 34/M 14/F	PNH		Urokinase at 125,000 u/h per vein treated. The patient received a total dose of 5 million units of urokinase over 36 hours.	Local (HV)	Successful	None	Nil	Nil
Sholar (23)	1	33/F	PNH	5 days	First time: Streptokinase: 7500 U/h, then 5000 U/h (total 72 h); Second time (2 months after): Urokinase: 250,000 U/40 min, then 250,000 U/2 h	Once local (HV) and once systemic	Successful	None	2 years	Nil
Ding (24)	13	39-70 9M/4F	Membrane obstruct (11); memranous stenosis (2)	Chronic	Urokinase at 150,000 for 30 min; Urokinase at 300,000 for 12 hours, 9-30 days	IVC	Successful	None	17 months	IVC balloon dilation

HV: Hepatic vein; IVC: Inferior vena cava; PNH: Paroxysmal nocturnal hemoglobinuria; TIPSS: Transjugular intrahepatic portosystemic shunt; HA: Hepatic artery; PV: Portal vein; tPA: Recombinant tissue plasminogen activator ; # : number of cases reported. Mo: months; h: hours.

Interventional radiology procedures are playing a major role in the management of patients with recent onset BCS, using angioplasty either alone or in combination with the placement of stent or TIPS (2).

Thrombolytic therapy can be considered in patients with the acute or subacute forms of BCS in which blood clots are younger than three to four weeks (10). Thrombolysis has been used through either systemic or local direct infusion in the treatment of BCS (9). Although few case reports suggested a benefit from systemic thrombolysis (11-15), success was more likely when local thrombolysis was infused into a partially thrombosed vessel. Direct infusion to an affected vein could theoretically lead to a higher concentration and greater efficacy (9,15).

Published experience with local thrombolytic therapy in this setting is limited to small case series and individual reports, which have documented successful treatment in many cases (Table 2) (14-22). In these reported cases therapy was successful in more than 75% of the cases. Various centers have tried different agents (streptokinase, urokinase or t-PA), different treatment regimens and different duration. These agents have been used on an empirical basis as there have been no specific clinical trials. Only a few cases have reported local thrombolysis as a sole therapy without concomitant balloon dilatation or angioplasty (16,19,22,23). This has been shown to be successful for acute or subacute BCS with partial obstruction and absence of membranous obstruction or stenosis. Patients with membranous obstruction or stenosis, even if they present with acute or subacute BCS, will need additional predilatation or stent placement (4,21,24). Ding et al used balloon dilatation prior to catheter directed thrombolysis (predilatation) in 13 cases and all were successful without complication. This series involved patients with chronic IVC thrombosis with membranous obstruction in 11 cases and stenosis in 2 cases (24). Zhang et al also used predilatation prior to thrombolysis in 6 of the 14 cases reported. The purpose of predilatation is to partially recanalize the obstructed hepatic veins and restore the blood flow to the hepatic veins with thrombosis, which helps to improve the efficacy of thrombolytic therapy (4). Wang et al prospectively evaluated predilation in 26 patients versus stent placement in 33 patients with chronic BCS along with local thrombolysis. The predilation approach yielded better intermediate-term results than those with the stent filter approach (25). In our case, success of local thrombolysis as a monoterapy may have been due to the subacute onset thrombosis with partial obstruction. Direct infusion into the hepatic artery, as in our case, can help to achieve a high concentration of the thrombolytic agent in the hepatic veins.

In conclusion, management of patients with BCS needs to be individualized after critical appraisal of the site and extent of block of the hepatic venous outflow tract, as well as the evaluation of synthetic liver function. Even though the data on local thrombolysis is limited and the agents and doses are not uniform among reported cases, it can be considered within the right clinical setting in acute BCS with partial obstruction. It has the advantage of restoring the flow physiologically without the need for a stent or TIPS insertion that may develop stenosis or complicate future liver transplantation. There is not enough clinical data to recommend it, but it appears to be a useful initial step in the acute setting where it can be followed by balloon dilatation, angioplasty or TIPS if unsuccessful. Thrombolysis is best employed in a patient who presents early and has a thrombus that is not completely occlusive. Close clinical, imaging and laboratory follow ups along with appropriate treatment of any underlying disorders can improve long-term venous patency and ultimately patient survival.

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