

Portal vein thrombosis as the first sign of nephrotic syndrome

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SUMMARY

Background A 52-year-old man presented to hospital having experienced abdominal pain, abdominal distention and oliguria for 1 week.

An abdominal CT scan revealed thrombosis in the superior mesenteric vein and in the right branch and the trunk of the portal vein.

Investigations Physical examination, blood and urine analyses, color Doppler ultrasonography and abdominal CT scan.

Diagnosis Nephrotic syndrome complicated by portal vein thrombosis.

Management Treatment with batroxobin, low-molecular-weight heparin, prostaglandin E, dipyridamole and methylprednisolone.

KEYWORDS batroxobin, nephrotic syndrome, portal vein thrombosis, proteinuria, venous thrombosis

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Competing interests

The authors declared no competing interests.

THE CASE

A 52-year-old male was admitted to hospital having experienced abdominal pain, abdominal distention and oliguria for 1 week.

Physical examination on admission revealed a blood pressure of 145/90 mmHg, no heart or lung abnormalities, an abdominal bulge and positive shifting dullness in the abdomen, mild pain on percussion of the hepatic region, active bowel sounds, and mild pitting edema in the lower limbs.

Results of blood tests on admission are presented in Table 1. Measurements of blood tumor markers were as follows: alpha-fetoprotein 10.72 µg/l (normal 0–20 µg/l); carcinoembryonic antigen 2.10 µg/l (normal 0–8 µg/l); and tissue prostate-specific antigen 0.59 µg/l (normal 0–4 µg/l). Serum samples were negative for hepatitis B markers, hepatitis C antibodies, anti-nuclear antibodies, anticardiolipin antibodies, double-stranded DNA antibodies, and Smith antibodies. The patient's coagulation profile was as follows: prothrombin time 13.5 s; activated partial thromboplastin time 39.5 s; thrombin time 16.5 s; and serum fibrinogen level 4.8 g/l. Urinalysis revealed grade 4+ proteinuria and 0–1 red blood cells per high-power field, and a 24-hour urine collection showed 3,467 mg of protein. Color Doppler ultrasonography revealed that the inner diameter of the sagittal part of the left branch of the portal vein was approximately 14 mm; the inner diameter of the right branch of the portal vein was about 15 mm and the inner diameter of the trunk was about 18 mm. Sound transmission through the cavities of these three veins was poor, the veins were hypoechoic, and no blood flow could be detected. The hepatic

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artery had an inner diameter of 7.9 mm, and blood flow was good. Blood perfusion in the hepatic vein and the inferior vena cava was also good. An abdominal CT scan showed thrombosis in the superior mesenteric vein and in the right branch and the trunk of the portal vein, while the right and left renal veins showed no signs of thrombosis (Figure 1A–D). The CT scan also revealed mesenteric edema, a thickened mesentery, edema in the intestinal wall, and abdominal effusion. The patient was diagnosed with nephrotic syndrome complicated by portal vein thrombosis.

On the day of hospital admission, the patient was started on batroxobin (DF-521, Tobishi Pharmaceutical Co., Tokyo, Japan; first dose of 10 IU given by intravenous injection followed by 5 IU via intravenous injection every other day), low-molecular-weight heparin (5,000 IU every 12 hours), prostaglandin E (20 µg every day) and dipyridamole (50 mg three times a day), and he received intravenous methylprednisolone at a dose of 80 mg per day. On admission, the patient's 24-hour urine volume was 300–500 ml. After 5 days of treatment, his 24-hour urine volume had increased to 1,500–2,500 ml, his abdominal distention was obviously relieved, and his abdominal circumference had decreased. On hospital day 12, a urine protein dipstick test was negative and a 24-hour urine collection contained 116 mg of protein. Prothrombin time at this point was 12.5 s, activated partial thromboplastin time was 21.6 s, and serum fibrinogen level was 1.4 g/l. Batroxobin was discontinued on hospital day 12, and low-molecular-weight heparin, prostaglandin E and dipyridamole were continued; methylprednisolone was continued by oral administration. On hospital day 25, another urine protein dipstick test was negative, blood albumin concentration was within the normal range, and color Doppler ultrasonography confirmed complete recanalization of the portal vein. Low-molecular-weight heparin and prostaglandin E were discontinued and dipyridamole and methylprednisolone were continued. After 5 months of treatment with oral methylprednisolone and oral dipyridamole, further laboratory tests revealed that all laboratory parameters had returned to normal levels; therefore, all medications were discontinued. Twenty months after initial presentation, the patient was healthy and remission from nephrotic syndrome had been maintained.

Table 1 Results of blood analyses on presentation.

Laboratory parameter	Value
Hemoglobin level	161 g/l (16.1 g/dl)
White blood cell count	$7.8 \times 10^9/l$
Red blood cell count	$4.96 \times 10^{12}/l$
Platelet count	$163 \times 10^9/l$
Total serum protein	42 g/l
Serum albumin	17 g/l
Serum globulin	25 g/l
Blood urea nitrogen	5.7 mmol/l (16.0 mg/dl)
Serum creatinine	96 µmol/l (1.1 mg/dl)
Serum uric acid	332 µmol/l
Serum cholesterol	13.02 mmol/l (502 mg/dl)
Serum triglycerides	1.78 mmol/l (157.5 mg/dl)
Serum high-density lipoprotein	1.62 mmol/l
Serum IgA	4.3 g/l
Serum IgG	3.38 g/l
Serum IgM	0.99 g/l
Serum complement component C ₃	1.0 g/l
Serum complement component C ₄	0.145 g/l
Serum κ-light chain	1.08 g/l
Serum γ-light chain	1.06 g/l
Serum M protein	0 g/dl

DISCUSSION OF DIAGNOSIS

Common complications of nephrotic syndrome include infections, development of a hypercoagulable state, and venous thrombosis.¹ Venous thrombosis occurs most often in the renal veins and in the veins of the lower limbs. Thrombosis in the mesenteric vein and the femoral vein has also been reported.² Portal vein thrombosis, however, has a relatively low incidence in patients with nephrotic syndrome and usually occurs during treatment or recurrence of the condition, not as the first sign. Portal vein thrombosis as the first sign of nephrotic syndrome is very rare.

The patient presented in this Case Study had hypoproteinemia and severe proteinuria accompanied by an obvious hypercoagulable state and portal vein thrombosis. Routine examinations such as an abdominal CT scan and tumor marker tests excluded the possibility of tumorous changes in the liver and the portal venous system, and excluded secondary options such as abdominal trauma and abdominal cavity

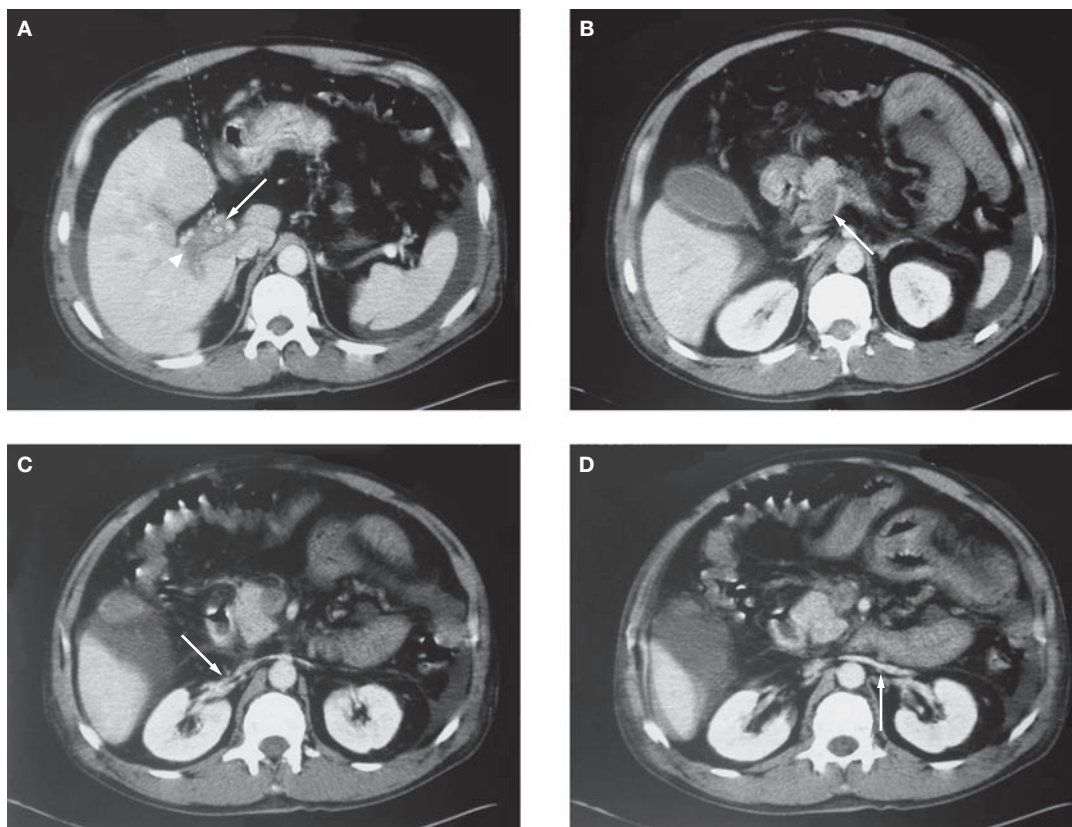


Figure 1 Abdominal CT scans on admission to hospital. (A) CT scan showing thrombosis in the trunk (arrow) and in the right branch of the portal vein (arrowhead). (B) CT scan showing thrombosis in the superior mesenteric vein (arrow). (C) CT scan showing the absence of thrombosis in right renal vein (arrow). (D) CT scan showing the absence of thrombosis in left renal vein (arrow).

infection. The diagnosis of nephrotic syndrome complicated by portal vein thrombosis was established on the basis of these results.

TREATMENT AND MANAGEMENT

Asymptomatic patients with portal vein thrombosis and patients with incomplete occlusions of the portal vein can remain untreated as long as they are followed up regularly (e.g. every 2–4 weeks). All other patients with portal vein thrombosis, however, must be treated. Low-molecular-weight heparin alone might be sufficient in mild cases of portal vein thrombosis, but more-severe cases require thrombolysis and/or thrombectomy. Thrombolysis involves the systemic administration and/or the local application of thrombolytic agents such as urokinase.^{3,4} There are a number of different thrombectomy techniques.

Thrombectomy was contraindicated in the patient described here, as his symptoms had already been present for 1 week. Low-molecular-weight

heparin and batroxobin were administered instead. At present, urokinase is the most commonly used thrombolytic agent for venous thrombosis, but the most appropriate time for urokinase thrombolysis is within 6 hours after symptom onset.⁵

Batroxobin, a serine protease derived from the venom of the pit viper *Bothrops atrox*, is a potent thrombolytic agent approved in China and Japan. The drug's mechanism of action is different to that of urokinase. Batroxobin's primary effects are to reduce fibrinogen levels,⁶ decrease blood viscosity and inhibit platelet aggregation (without affecting platelet count and function), while not prolonging bleeding time. In addition, batroxobin promotes the release of tissue type 1 plasminogen activator from endothelial cells and enhances its activity, reduces the amount of type 1 plasminogen activator inhibitor and inhibits its activity, and transforms plasminogen into active plasmin. Batroxobin can lower whole blood viscosity and inhibit red cell

agglutination, thereby reducing vascular resistance and improving microcirculation. These effects can reduce red blood cell transit time and result in the dredging of blood vessels and the dissolving of the thrombus. The window of opportunity for administering batroxobin is longer than that for urokinase, and batroxobin can be given at different stages of venous thrombosis. As 1 week had passed between the onset of symptoms and the patient's admission to hospital, urokinase was not suitable for this individual and batroxobin was the more-appropriate thrombolytic treatment.

Anticoagulant therapy with heparin was also very important in the patient presented here,⁷ for the treatment of both the portal vein thrombosis and the hypercoagulable state that resulted from the nephrotic syndrome.⁸ Heparin might restore the charge-selective properties of the glomerular basement membrane and can relieve proteinuria.⁹ Low-molecular-weight heparin is easy to use, and is associated with a lower risk of secondary bleeding and a lower recurrence rate of venous thromboembolism than is unfractionated heparin.¹⁰

The patient in this Case Study did not undergo renal biopsy as thrombolytic and anticoagulant therapy had already been given on admission. The patient probably had minimal-change disease, however, as he had a very rapid response to steroid treatment. The use of steroid hormones and other immunosuppressants was critical in the patient presented here, as was the long duration of therapy. Steroid hormones were given to the patient together with thrombolytic and anticoagulant therapy. No obvious adverse effects of the hormones were observed. After 1 week of treatment, the patient's proteinuria had disappeared, his nephrotic syndrome had been relieved, his hypoproteinemia was corrected and his hypercoagulable state had improved. All these factors contributed to the resolution of the portal vein thrombosis and the prevention of thrombus recurrence. Steroid hormones can affect blood coagulation and increase blood viscosity, however, and should therefore be used with caution in patients in whom a pathological confirmation of the diagnosis is not available.

CONCLUSIONS

The possibility of portal vein thrombosis should be considered in patients who have nephrotic syndrome together with abdominal pain or abdominal distention of unknown

etiology, or in those with nephrotic syndrome and other abdominal symptoms—such as ascites, ileus or intestinal necrosis—that cannot be explained.¹¹

After a diagnosis of portal vein thrombosis has been established, thrombolytic therapy or thrombectomy should be applied according to the severity and location of the thrombus and the time since symptom onset. Urokinase or batroxobin can be used for thrombolysis, heparin for anticoagulation, and dipyridamole for the inhibition of further thrombus formation.¹²

If thrombolytic or anticoagulant therapy is delayed because a renal biopsy is performed, the timeliness of treatment might be lost and worse outcomes might occur (e.g. the portal vein obstruction might become irreversible). Thus, the advantages and disadvantages of each treatment option must be weighed up to ensure that the most appropriate therapeutic regimen is provided. If necessary, glucocorticoids can be administered empirically to treat the primary disease (nephrotic syndrome in the patient presented here).

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Competing interests

The authors declared no competing interests.