Case Report

DOI: 10.5582/ddt.2019.01014

Acute mesenteric vein thrombosis after endoscopic injection sclerotherapy for esophageal varices in a patient with liver cirrhosis

Le Wang[1,2], Xiangbo Xu[1], Yue Hou[1], Xiaodong Shao[1], Xiaozhong Guo[1,*], Xingshun Qi[1,*]

[1] *Department of Gastroenterology, General Hospital of Northern Theater Command, Shenyang, Liaoning, China;*
[2] *Postgraduate College, Dalian Medical University, Dalian, Liaoning, China.*

Summary **Portal vein thrombosis (PVT) is a common complication of liver cirrhosis. The association between endoscopic injection sclerotherapy (EIS) and PVT is unclear. In this paper, we reported that a male cirrhotic patient developed acute mesenteric vein thrombosis after EIS for secondary prophylaxis of esophageal variceal bleeding. Immediate anticoagulation therapy was effective and safe in this patient.**

Keywords: Portal vein thrombosis, endoscopic therapy, anticoagulation therapy

1. Introduction

Portal vein thrombosis (PVT) is a common complication of liver cirrhosis with a prevalence of 0.6-26% (*1*). Acute PVT refers to recent (< 30 days) formation of thrombosis in the main portal vein or its branches; by comparison, chronic PVT often has multiple collateral vessels around the thrombosed portal vein (*2*). Risk factors for the development of PVT in cirrhotic patients include reduced portal vein flow velocity, liver dysfunction, portosystemic collateral vessels, splenectomy, and thrombophilia, *etc*. (*3*).

Endoscopic variceal ligation (EVL) is the preferred treatment of choice for both controlling esophageal variceal bleeding and secondary prophylaxis, and endoscopic injection sclerotherapy (EIS) may be performed if EVL is technically difficult (*4*). During EIS procedure, sclerosing agents are injected into varices, thereby achieving variceal occlusion. Notably, this procedure may increase the portal vein blood flow, thereby resulting in a sudden increase of portal vein pressure and turbulent blood flow pooling in the portal venous system, which causes PVT (*5*).

In this paper, we reported a case of acute mesenteric vein thrombosis after EIS for esophageal varices in a patient with liver cirrhosis, in whom anticoagulation with low molecular weight heparin (LMWH) achieved partial mesenteric vein recanalization without any bleeding episode.

**Address correspondence to:*
Dr. Xingshun Qi and Dr. Xiaozhong Guo, Department of Gastroenterology, General Hospital of Northern Theater Command, No. 83 Wenhua Road, Shenyang, 110840 Liaoning Province, China.
E-mail: xingshunqi@126.com (XQ); guo_xiao_zhong@126.com (XG)

2. Case report

On May 29, 2017, a 53-year-old male with a 23-year history of liver cirrhosis secondary to hepatitis B virus infection was admitted to our department due to nausea and diarrhea for 5 days. He was accompanied by abdominal distension and intermittent fever with body temperature up to 38.5℃ which was normalized after oral antipyretic. There was neither abdominal pain nor bloody purulent stool. During the past 18 years, he was repeatedly admitted to our department due to the development of ascites, encephalopathy, and/or gastroesophageal variceal bleeding. He underwent splenectomy with devascularization in 2007, EIS in 2012 and 2013, and EVL in 2014 and 2016. Laboratory tests demonstrated that red blood cell (RBC) was 3.6×10^{12}/L (reference range: $4.3\text{-}5.8 \times 10^{12}$/L), hemoglobin (Hb) was 118 g/L (reference range: 130-175 g/L), hematocrit (HCT) was 36.2% (reference range: 40-50%), white blood cell (WBC) was 9.5×10^{9}/L (reference range: $3.5\text{-}9.5 \times 10^{9}$/L), percentage of granulocyte (GR%) was 61.1% (reference range: 40-75%), erythrocyte sedimentation rate (ESR) was 17 mm/h (reference range: 0-15 mm/h), C-reactive protein (CRP) was 25.5 mg/L (reference range: 0-8 mg/L), total bilirubin (TBIL) was

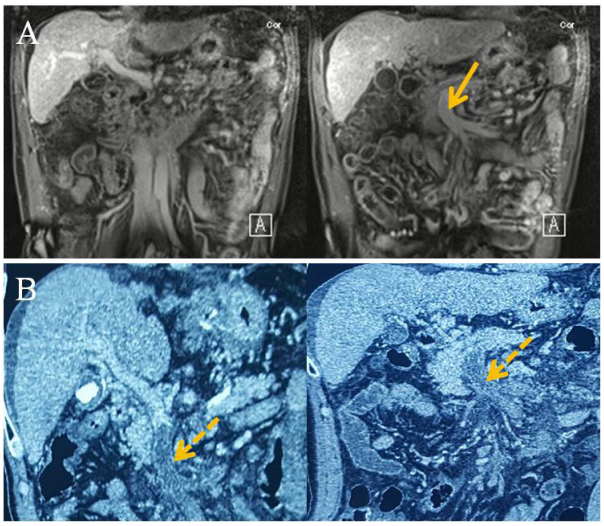

Figure 1. Coronal views. (A) contrast-enhanced magnetic resonance imaging performed on May 29, 2017 showing patent mesenteric vein (solid arrow); **(B)** computed tomography angiography performed on June 13, 2017 showing complete thrombosis in the mesenteric vein (dotted arrow).

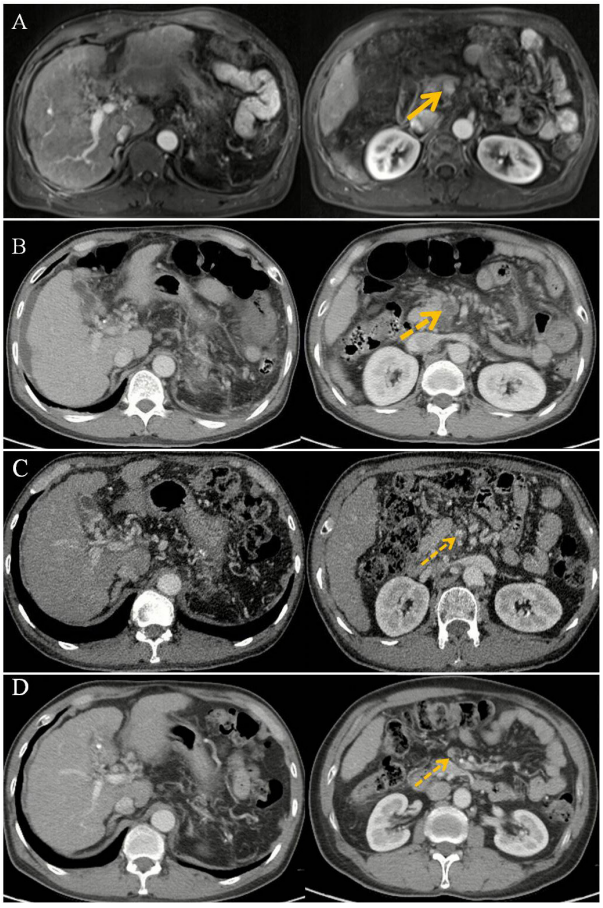

Figure 2. Axial views. (A) contrast-enhanced magnetic resonance imaging performed on May 29, 2017 showing patent mesenteric vein (solid arrow); **(B)** computed tomography angiography performed on June 13, 2017 showing complete thrombosis in the mesenteric vein (dotted arrow); **(C)** computed tomography angiography performed on July 19, 2017 showing partial recanalization of mesenteric vein thrombosis (thin dotted arrow); **(D)** computed tomography angiography performed on June 5, 2018 showing partial recanalization of mesenteric vein (thin dotted arrow) with collateral circulation around the mesenteric vein.

29.4 μmol/L (reference range: 5.1-22.2 μmol/L), direct bilirubin (DBIL) was 10.0 μmol/L (reference range: 0-8.6 μmol/L), alanine amino-transaminase (ALT) was 14.93 U/L (reference range: 9-50 U/L), aspartate amino-transaminase (AST) was 31.55 U/L (reference range: 15-40 U/L), alkaline phosphatase (AKP) was 127.26 U/L (reference range: 45-125 U/L), γ-glutamyl transpeptidase (GGT) was 40.85 U/L (reference range:10-60 U/L), serum albumin (ALB) was 36.2 g/L (reference range: 40-55 g/L), prothrombin time (PT) was 13.9 seconds (reference range: 11.5-14.5 seconds), international normalized ratio (INR) was 1.06, and D-dimer was 2.52 mg/L (reference range: 0.01-0.55 mg/L). Contrast-enhanced axial (Figure 1A) and coronal (Figure 2A) magnetic resonance imaging revealed liver cirrhosis, ascites, and multiple collaterals around the intrahepatic portal vein branch and portal trunk, but patent mesenteric vein. His Child-Pugh score was 6.

On May 30, 2017, the patient developed fever with a body temperature up to 38.8°C and abdominal distension again. Laboratory tests demonstrated that WBC was 13.5 × 10^9/L, GR% was 83.3%, ESR was 33 mm/h, CRP was 42.9 mg/L, and procalcitonin (PCT) was 0.11 ng/mL (reference range: 0-0.05 ng/mL). Blood culture demonstrated the absence of bacteria within 5 days. Cefoperazone sulbactam sodium was given intravenously with a dosage of 1.5 g twice a day. The patient's condition was stable and his body temperature regressed after a 6-day duration of antibiotics.

On June 6, 2017, upper gastrointestinal endoscopy revealed post-ligation scar and mild varices without red color sign at the lower esophagus. Prophylactic EIS was performed.

On June 13, 2017, he developed persistent abdominal pain accompanied by fever. Physical examination showed abdominal softness, mild tenderness in the left upper abdomen, neither rebound tenderness nor muscle tension, negative shifting dullness, and weak borborygmus. Laboratory tests demonstrated that PT was 16.0 seconds, INR was 1.26, fibrinogen degradation product (FDP) was 51.96 mg/L (reference range: 0.01-5.00 mg/L), antithrombin III (ATIII) was 48% (reference range: 80-120 U/L), and D-dimer was 16.05 mg/L. Abdominal X-ray showed that abdominal intestine had gas accumulation and expansion, but no air-fluid level was observed. Computed tomography angiography (CTA) revealed complete thrombosis in the mesenteric vein as well as edematous and thickened small intestine wall (Figures 1B and 2B). Immediately, anticoagulation with LMWH was given subcutaneously with a dosage of 4,250 iu twice a day. Abdominal pain improved gradually.

On June 16, 2017, his upper abdominal pain significantly relieved in the absence of abdominal distension, nausea, or vomiting. The body temperature was gradually normalized. Physical examination

showed soft abdomen, slight tenderness, neither rebound tenderness nor muscle tension, negative shifting dullness, and normal borborygmus.

On June 19, 2017, his body temperature was normal and abdominal pain disappeared. Laboratory tests demonstrated that PT was 15.8 seconds, INR was 1.24, FDP was 18.47 mg/L, ATIII was 52%, and D-dimer was 7.79 mg/L.

On June 22, 2017, the patient was discharged without any complaints. LMWH was recommended after discharge.

On July 19, 2017, CTA revealed partial recanalization of mesenteric vein (Figure 2C).

On January 14, 2018, upper gastrointestinal endoscopy revealed esophageal and gastric varices. Endoscopic treatment was not performed because this patient was receiving anticoagulants at that time.

On April 1, 2018, the patient stopped anticoagulant therapy before prophylactic endoscopic treatment. He did not develop any bleeding episode during the entire 10-month period of anticoagulation therapy.

On June 5, 2018, the CTA revealed partial recanalization of mesenteric vein with collateral circulation around the mesenteric vein (Figure 2D).

On June 8, 2018, the patient underwent EVL for secondary prophylaxis of variceal bleeding. The last follow-up was performed on January 10, 2019 when his general condition was stable without any complaints.

3. Discussion

This patient developed complete thrombosis in the mesenteric vein after EIS for the prophylaxis of esophageal variceal bleeding. His clinical manifestations were abdominal pain and fever. CTA confirmed the diagnosis of PVT. Anticoagulation therapy with LMWH achieved partial recanalization without any bleeding episode.

At present, the first-line choice for secondary prophylaxis of variceal bleeding is a combination of EVL and non-selective beta-blockers (*6*). However, EIS may be performed if EVL was technically difficult or infeasible (*4*). Our endoscopist considered EIS, because EVL was technically difficult in this patient due to post-EVL scars.

Association between EIS and PVT. Incidence of PVT after EIS was heterogeneous among studies. Kawasaki *et al*. observed that none of 22 cirrhotic patients had splenic or portal vein thrombosis during a post-EIS follow-up duration of 26 ± 17 months (*7*). Barsoum *et al*. observed that only 1 of 122 patients had a recent thrombus in the portal vein after EIS, which was confirmed by autopsy (*8*). By comparison, Hou *et al*. observed that 16 of 91 cirrhotic patients had a PVT after cyanoacrylate injection for gastric variceal bleeding (*9*). Amitrano *et al*. observed that 10 of 61 cirrhotic patients developed PVT after EIS for esophageal variceal bleeding (*10*). The difference in the incidence of PVT among studies may be related to the heterogeneity of patient characteristics, date when the imaging was performed, and diagnostic approaches.

Association between EIS and PVT was controversial among comparative studies. Hunter *et al*. found that PVT occurred in 4 of 11 patients who had EIS and only 1 of 10 patients who did not have EIS (4/11 *vs*. 1/10) (*11*). Leach *et al*. retrospectively identified 27 patients who underwent portosystemic shunting after an episode of variceal bleeding. Patients with a history of EIS had a higher incidence of splanchnic vein thrombosis than those without (6/11 *vs*. 2/16) (*12*). By comparison, one prospective controlled study found no significant difference in the incidence of PVT between cirrhotic patients who received EIS for esophageal variceal bleeding and those who did not (8/72 *vs*. 5/52) (*13*).

In our patient, a complete thrombosis in the mesenteric vein was observed on the 7th day after EIS. Therefore, their association should not be ignored. In addition, infection, especially abdominal inflammation, is one of the most frequently acquired prothrombotic states (*2,14*). Our patient might have an intra-abdominal infection manifested as digestive symptoms, fever, and elevated inflammatory indexes at admission. Unfortunately, we did not identify the origin of infection. But antibiotic was potentially effective in our patient.

The cases of portal venous system thrombosis caused by EIS might be extrapolated to other endoscopic variceal therapy, because all types of endoscopic variceal therapy may lead to an increased portal vein pressure and then cause turbulent blood flow pooling in the portal venous system. On the other hand, gastroesophageal varices and variceal rebleeding can be aggravated by PVT (*15*). Thus, endoscopic variceal treatment, PVT, and variceal rebleeding may produce a vicious circle in cirrhotic patients.

Anticoagulation for PVT. Anticoagulation is the major treatment option of PVT (*5*). Baveno VI consensus indicates that systemic anticoagulation with LMWH should be started as soon as a diagnosis of PVT is made (*16*). Guidance for the management of venous thrombosis in unusual sites also indicates that cirrhotic patients with splanchnic vein thrombosis who do not have active bleeding should initiate early anticoagulation with LMWH (*17*). In our patient, anticoagulation with LMWH was started immediately after his diagnosis of PVT.

A systematic review and meta-analysis concluded that anticoagulant therapy increased the rate of portal vein recanalization from 42% in patients who did not receive anticoagulants to 71% in patients who received anticoagulants and reduced the rate of thrombotic progression from 33% to 9%, but did not significantly increase the risk of bleeding, such as variceal bleeding (*18*). Our meta-analysis also supported that anticoagulant therapy increased portal vein recanalization in cirrhotic patients (*19*).

Two recent studies also suggested that anticoagulation therapy could increase the rate of portal recanalization, but not increase the risk of bleeding. A prospective cohort study demonstrated that the recanalization rate was significantly higher in patients treated with anticoagulants than untreated patients (56.8% *vs*. 27.7%). Of the 46 patients who achieved portal recanalization, 67.4% had complete recanalization, but 36% suffered from recurrent thrombosis after stopping anticoagulants. Risk of bleeding complications was similar between the two groups (*20*). Another prospective study also demonstrated that 57.5% of patients treated with anticoagulants achieved complete recanalization, and 25.0% achieved partial recanalization. Of the 40 patients treated with anticoagulants, 37.5% developed bleeding, but none died from bleeding. Notably, 70% of patients had a recurrence or extension of PVT after stopping anticoagulants (*21*). Taken together, both studies indicated that anticoagulation should be maintained in order to avoid recurrence.

In our patient, anticoagulants were started immediately after a diagnosis of PVT. A partial recanalization of mesenteric vein was achieved after anticoagulant therapy for 1 month. Then, anticoagulant therapy was maintained for additional 9 months in order to avoid recurrence. He did not develop any bleeding episode during the entire period of anticoagulation therapy.

In conclusion, EIS may be a risk factor of thrombosis within portal vein system. Once acute thrombus within portal vein system was confirmed, an immediate and continuous treatment with anticoagulants should be effective and safe.

References

1. Fujiyama S, Saitoh S, Kawamura Y, Sezaki H, Hosaka T, Akuta N, Kobayashi M, Suzuki Y, Suzuki F, Arase Y, Ikeda K, Kumada H. Portal vein thrombosis in liver cirrhosis: Incidence, management, and outcome. BMC Gastroenterol. 2017; 17:112.
2. Seedial SM, Mouli SK, Desai KR. Acute portal vein thrombosis: Current trends in medical and endovascular management. Semin Intervent Radiol. 2018; 35:198-202.
3. Qi X, Li H, Liu X, Yao H, Han G, Hu F, Shao L, Guo X. Novel insights into the development of portal vein thrombosis in cirrhosis patients. Expert Rev Gastroenterol Hepatol. 2015; 9:1421-1432.
4. Hwang JH, Shergill AK, Acosta RD, *et al*. The role of endoscopy in the management of variceal hemorrhage. Gastrointest Endosc. 2014; 80:221-227.
5. Stine JG, Northup PG. Management of non-tumoral portal vein thrombosis in patients with cirrhosis. Dig Dis Sci. 2019; 64:619-626.
6. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey WD. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Am J Gastroenterol. 2007; 102:2086-2102.
7. Kawasaki S, Henderson JM, Riepe SP, Brooks WS, Hertzler G. Endoscopic variceal sclerosis does not increase the risk of portal venous thrombosis. Gastroenterology. 1992; 102:206-215.
8. Barsoum MS, Abdel-Wahab Mooro H, Bolous FI, Ramzy AF, Rizk-Allah MA, Mahmoud FI. The complications of injection sclerotherapy of bleeding oesophageal varices. Br J Surg. 1982; 69:79-81.
9. Hou MC, Lin HC, Lee HS, Liao WC, Lee FY, Lee SD. A randomized trial of endoscopic cyanoacrylate injection for acute gastric variceal bleeding: 0.5 mL versus 1.0 mL. Gastrointest Endosc. 2009; 70:668-675.
10. Amitrano L, Brancaccio V, Guardascione MA, Margaglione M, Sacco M, Martino R, De Nucci C, Mosca S, Iannaccone L, Ames PR, Romano L, Balzano A. Portal vein thrombosis after variceal endoscopic sclerotherapy in cirrhotic patients: Role of genetic thrombophilia. Endoscopy. 2002; 34:535-538.
11. Hunter GC, Steinkirchner T, Burbige EJ, Guernsey JM, Putnam CW. Venous complications of sclerotherapy for esophageal varices. Am J Surg. 1988; 156:497-501.
12. Leach SD, Meier GH, Gusberg RJ. Endoscopic sclerotherapy: A risk factor for splanchnic venous thrombosis. J Vasc Surg. 1989; 10:9-13.
13. Politoske D, Ralls P, Korula J. Portal vein thrombosis following endoscopic variceal sclerotherapy. Prospective controlled comparison in patients with cirrhosis. Dig Dis Sci. 1996; 41:185-190.
14. Acuna-Villaorduna A, Tran V, Gonzalez-Lugo JD, Azimi-Nekoo E, Billett HH. Natural history and clinical outcomes in patients with portal vein thrombosis by etiology: A retrospective cohort study. Thromb Res. 2019; 174:137-140.
15. Cagin YF, Atayan Y, Erdogan MA, Dagtekin F, Colak C. Incidence and clinical presentation of portal vein thrombosis in cirrhotic patients. Hepatobiliary Pancreatic Diseases International. 2016; 15:499-503.
16. de Franchis R. Expanding consensus in portal hypertension: Report of the Baveno VI consensus workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015; 63:743-752.
17. Ageno W, Beyer-Westendorf J, Garcia DA, Lazo-Langner A, McBane RD, Paciaroni M. Guidance for the management of venous thrombosis in unusual sites. J Thromb Thrombolysis. 2016; 41:129-143.
18. Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: A systematic review and meta-analysis. Gastroenterology. 2017; 153:480-487.e481.
19. Qi X, De Stefano V, Li H, Dai J, Guo X, Fan D. Anticoagulation for the treatment of portal vein thrombosis in liver cirrhosis: A systematic review and meta-analysis of observational studies. Eur J Intern Med. 2015; 26:23-29.
20. Pettinari I, Vukotic R, Stefanescu H, Pecorelli A, Morelli M, Grigoras C, Sparchez Z, Andreone P, Piscaglia F. Clinical impact and safety of anticoagulants for portal vein thrombosis in cirrhosis. Am J Gastroenterol. 2019; 114:258-266.
21. Bergere M, Erard-Poinsot D, Boillot O, Valette PJ, Guillaud O, Chambon-Augoyard C, Dumortier J. Portal vein thrombosis and liver cirrhosis: Long-term anticoagulation is effective and safe. Clin Res Hepatol Gastroenterol. 2018; pii: S2210-7401(18)30268-7.

(Received March 5, 2019; Revised April 13, 2019; Accepted April 21, 2019)