Splanchnic Venous Thrombosis: Challenges and Opportunities

The status of management choices for this uncommon disease state.

BY MEHRAN MIDIA, MD, FRCP(C), AND MAHMOOD K. RAZAVI, MD, FSIR

Isolated mesenteric venous thrombosis without concomitant extrahepatic portal vein thrombosis or a splenic vein thrombosis is rare. Therefore, we will focus on splanchnic venous thrombosis (SVT), particularly portal and mesenteric vein thrombosis. Comprehensive management of secondary portal hypertension due to chronic SVT is beyond the scope of this article.

BACKGROUND AND CHANGING LANDSCAPE

The lifetime risk of SVT in the general population is approximately 1%. One-third of patients with acute SVT will have bowel infarction. Thirty-day and 1-year mortality rates of SVT are approximately 20% and 5%, respectively, and 5-year mortality associated with occlusion of both the mesenteric and extrahepatic portal veins approaches 62%. Early diagnosis and management have the potential to reduce both morbidity and mortality of this uncommon, at times elusive, and potentially fatal condition.

The prevalence of SVT in patients with cirrhosis varies between 0.6% and 25%, with the highest prevalence occurring in liver transplant candidates. In patients with hepatocellular carcinoma (HCC), reported incidence is as high as 44%. SVT is historically more common in developing countries due to a higher rate of intra-abdominal infections, but this might be changing given the obesity epidemic in the Western world. By one estimate, 34% of the United States population is considered to be obese (BMI > 30). Incidence of symptomatic SVT occurs in 1% of patients undergoing laparoscopic bariatric surgery, with an estimated 180,000 surgeries performed in the United States in 2013 alone.

There are many challenges associated with the diagnosis and management of SVT, which is relatively rare and commonly multifactorial. It is not uncommon for systemic and local causes to occur concurrently in the same patient (30%–40% of cases). SVT’s natural history is not well understood and could have an unpredictable presentation. The evidence for treatment is largely based on retrospective case series and case reports, and many reported outcomes are in the context of underlying disorders, such as cirrhosis or malignancies, which preclude extrapolation of data to a larger population.

Virchow’s triad elements are also applicable in the pathogenesis of SVT (Table 1). In cirrhotic patients, low portal blood flow velocity detected on Doppler exam is the only independent risk factor that has been identified for SVT. Given this, it is not surprising that the creation of a portosystemic shunt (TIPS) is not only effective in treating SVT, but also in securing a long-lasting result in selected patients with and without underlying cirrhosis.
In patients undergoing bariatric surgery, metabolic syndrome resulting in a hypercoagulable state, chronic inflammation, venous stasis from increasing intra-abdominal pressure and CO\textsubscript{2} insufflation, and intraoperative manipulation of splanchnic vasculature are among suggested causative factors for SVT.

In addition, up to 72% of cases of presumed idiopathic SVT are shown to have underlying thrombophilia, and among these, primary myelodysplastic syndrome (MDS) is very common.\textsuperscript{14,23} In the west, latent MDS has been reported in 58% of patients with idiopathic SVT, and 51% of these patients will develop overt MDS on follow-up. Given these facts, routine peripheral blood screening of JAK2 mutation (JAK2V617F) is recommended in all patients with unprovoked SVT.\textsuperscript{23-25}

The clinical course, management, and prognosis of SVT depend on its evolution, extent, and the nature of underlying disease.\textsuperscript{13,26} Although a small percentage of patients are clinically symptomatic, likely due to dual blood supply of the liver and the efficiency of arterial and venous rescue mechanism in splanchnic circulation, a great majority of cases of SVT are incidentally found on imaging, suggesting that its true occurrence is underestimated.\textsuperscript{27} SVT could be classified as acute or chronic (based on a 60-day cutoff), extra- or intrahepatic, occlusive or nonocclusive, and progressive or self-resolving. Spontaneous resolution of SVT is uncommon, with the exception of cases that are due to acute pancreatitis.\textsuperscript{28,29} Complete recanalization of septic splanchnic thrombophlebitis has been described with antibiotic and anticoagulant treatment.\textsuperscript{30} The annual incidence of recurrence of extrahepatic portal vein thrombosis is 5.5%, while this rate is 9.1% for mesenteric venous thrombosis requiring long-term or life-long anticoagulant treatment.\textsuperscript{31,32}

**MANAGEMENT STRATEGIES**

Management strategies for treating SVT include conservative, anticoagulant therapy, pharmacological and mechanical thrombectomy including PTA with and without stenting; TIPS; and surgical interventions (Figure 1). These treatments are usually used stepwise and at times in combination; there are different thresholds for treatment and success as well as complication rates reported in the literature.\textsuperscript{26,33} With the exception of thrombectomy in conjunction with bowel resection for ischemic gut, surgical methods are less commonly used given the safety and efficacy of the less invasive interventions.\textsuperscript{34}

Once the diagnosis of SVT is established, patient care would fall under one or a combination of any of the following: (1) patient with physical, laboratory, or imaging findings of bowel ischemia and peritonitis in whom surgical intervention is indicated; (2) patient with acute, progressive, or extensive mesenteric venous thrombosis and those who failed on systemic therapies who are referred to percutaneous image-guided interventions; (3) patients with a small burden of nonprogressive and nonocclusive disease often require systemic treatment or perhaps no treatment at all based on underlying comorbidities, etiology, and symptomatology. Recanalization with anticoagulant therapy is most successful when initiated within the first week, when the success rate approaches 70% (usually reported in the 30%–40% range), dropping to 25% in the second week.\textsuperscript{35,36} Systemic anticoagulation is generally of limited value in patients with acute and extensive mesenteric venous thrombosis. Presence of ascites and splenic vein thrombosis, likely indicating the chronicity of SVT, have shown to be independently associated with failure of anticoagulant therapy.\textsuperscript{17,36}

Management decisions for SVT are frequently individualized and are based on low-level evidence and local experience and level of expertise.\textsuperscript{34} These limitations are reflected in a set of guidelines that were put forward by the American Association for the Study of Liver Diseases (AASLD) and the American College of Chest Physicians on treatment of acute and chronic SVT.\textsuperscript{37,38}

Heterogeneity in management practices is well shown in

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**TABLE 1. MOST COMMON CAUSES OF SPLANCHNIC VEIN THROMBOSIS IN ADULTS**

<table>
<thead>
<tr>
<th>I. Systemic</th>
<th>II. Local</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloproliferative neoplasms</td>
<td>Abdominal malignancy</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Increased factor VIII level</td>
<td>Abdominal surgery</td>
</tr>
<tr>
<td>Hyperhomocytinemia</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>Abdominal infection</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>III. Idiopathic</td>
</tr>
<tr>
<td>Protein C deficiency</td>
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a recent international registry for antithrombotic treatment of SVT.\textsuperscript{39} Based on prospective observations in 613 patients, (1) despite referral to thrombosis centers, almost one in four patients did not receive any antithrombotic treatment for splanchnic vein thrombosis, although two-thirds of incidentally detected SVT was treated; (2) only a handful of patients underwent more invasive therapeutic management, such as thrombolysis, PTA, or thrombectomy; (3) incidental diagnosis, single vein thrombosis, gastrointestinal bleeding, thrombocytopenia, cancer, and cirrhosis were significantly associated with no treatment; while (4) the decision to start on a vitamin K antagonist after an initial course or parenteral anticoagulant was significantly associated with younger age, symptomatic onset, multiple vein involvement, and unprovoked thrombosis.\textsuperscript{39}

Regardless of etiology and symptomatology, the primary goal of the treatment in SVT is to preserve or restore proper directional flow in splanchnic veins and gut and liver function; the secondary goal is to manage the complications of portal hypertension in patients with chronic SVT.\textsuperscript{40} Elimination of clot and restoration of proper flow in splanchnic veins could serve a different purpose in different settings: to save bowel in patients with extensive or occlusive SVT; to preserve liver functions in patients with cirrhosis; to preserve surgical candidacy, technical feasibility, and to improve short- and long-term outcomes in liver transplant patients; to prevent or treat complications of portal hypertension; to allow completion of systemic treatment in patients with cancer causing extrahepatic portal vein occlusion or stenosis; and to restore bile flow in rare cases of biliary cholangiopathy. However, the benefit of treatment for certain indications is controversial.\textsuperscript{32,36,41-48}

There are recent reports advocating preemptive use of anticoagulants in patients with cirrhosis, although the exact impact of SVT on the natural history of liver cirrhosis remains an open question.\textsuperscript{50-52} In a small nonblinded, single-center study, a 12-month course of enoxaparin was shown to be safe and effective, preventing SMV in patients with cirrhosis and a Child-Pugh score of 7 to 10; further, it appeared to delay occurrence of hepatic decompression and improve survival.\textsuperscript{53}

Apart from commonly used low-molecular-weight heparin, oral direct thrombin inhibitors such as rivaroxaban have been suggested as an attractive therapeutic option for treatment of acute and chronic portal and mesenteric venous thrombosis in patients with compensated cirrhosis and preserved renal function. The predictable pharmacokinetics of this class of anticoagulants allow fixed dosing without a need for coagulation monitoring. Rivaroxaban has been shown to be cost effective compared to warfarin in the prevention of recurrent venous thromboembolism with a similar rate of major and nonmajor bleeding complications (relatively less intracranial and more gastrointestinal bleeding).\textsuperscript{54-57} Furthermore, current concerns about the lack of antidote may be alleviated when the FXa inhibitor antidote, andexanet alfa (Portola Pharmaceutical), gains regulatory approval.\textsuperscript{54}

**PERCUTANEOUS TECHNIQUES**

SVT could be managed percutaneously using an indirect method by intra-arterial infusion of thrombolytic agent via the superior mesenteric artery (SMA) and directly using a transhepatic, transjugular/transfemoral, transsplenic, or transiliocolic vein approach.\textsuperscript{16-19,58-60} Transarterial infusion via the SMA is to preserve or restore proper directional flow in splanchnic veins and gut and liver function; the secondary goal is to manage the complications of portal hypertension in patients with chronic SVT.\textsuperscript{40} Elimination of clot and restoration of proper flow in splanchnic veins could serve a different purpose in different settings: to save bowel in patients with extensive or occlusive SVT; to preserve liver functions in patients with cirrhosis; to preserve surgical candidacy, technical feasibility, and to improve short- and long-term outcomes in liver transplant patients; to prevent or treat complications of portal hypertension; to allow completion of systemic treatment in patients with cancer causing extrahepatic portal vein occlusion or stenosis; and to restore bile flow in rare cases of biliary cholangiopathy. However, the benefit of treatment for certain indications is controversial.\textsuperscript{32,36,41-48}
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in patients with SVT when it involves small mesenteric tributaries. This is easy to perform, but it often calls for a longer infusion time and a larger dose of thrombolytic drug delivery.\textsuperscript{16,41,60} Transarterial infusion is not proven to be effective in patients with extensive and occlusive SVT and also carries risk of thrombosis and embolus on the arterial side.\textsuperscript{41,42,60} The direct methods, in general, are more efficient and less time consuming and allow treatment of patients with extensive thrombus but usually require more involved interventions, which could be associated with devastating intra-abdominal hemorrhage.\textsuperscript{17,42} Compared to pharmacological thrombolysis, mechanical thrombectomy allows expeditious debulking of thrombus burden, and reduction in duration and total dose of thrombolytic needed, but comes with the risk of embolism (if combined with TIPS) or vascular trauma causing bleeding and intimal trauma.\textsuperscript{17,18,40,59,61,62} Regardless of approach, using meticulous technique in puncture, securing access, and navigating through splanchic veins could translate to a lower complication rate, particularly if pharmacological thrombolysis is to be instituted. Risk of hemorrhage is reported to be higher when anticoagulant and thrombolytic infusion are used in combination. Transparenchymal (transhepatic or transsplenic) access for treatment of SVT could cause major bleeding, reported in approximately 6.5\% of cases.\textsuperscript{64,65}

For pharmacological thrombolysis, both urokinase and rt-PA (Activase, Genentech) infusion directly into the SMA or thrombosed splanchic vein with concomitant therapeutic and subtherapeutic intravenous heparin have been used. In addition, concomitant papaverine has also been infused via arterial catheter in some reports to lessen the effect of arterial vasospasm.\textsuperscript{63}

There are many methods and devices used for mechanical thrombectomy alone or in combination with pharmacological thrombolysis.\textsuperscript{18,59,63,64,66,67} Also, the utility of a variety of balloons and stents has been described in restoring splanchic vein patency.

TIPS has been described solo or in combination with other methods in treating SVT in patients with and without cirrhosis, prior to and post-liver transplant.\textsuperscript{17-19,40,63} TIPS is advised in patients with ascites and coagulopathy. TIPS is usually not suggested in patients with unfavorable anatomy (portal venous cavernous transformation and marked liver atrophy) or with high risk for bleeding.\textsuperscript{40,62,64} When performed in a controlled fashion and without disrupting the liver capsule, it could offer many advantages over transhepatic and transsplenic interventions, because it not only allows restoration of hepatopedal flow, but it also facilitates use of a larger platform for mechanical thrombectomy and stent deployment.\textsuperscript{65,69} In a recent report, 70 consecutive cirrhotic patients with nontumoral, noncavernous SVT were treated with TIPS. In 57\% of patients, thrombus was completely recanalized, and in 30\%, a marked decrease in thrombus was observed over the course of a few months to over 12 months without the need for anticoagulant or thrombolytic therapy. Predictors of recanalization were extent of thrombus, de novo diagnosis, and absence of gastroesophageal varices. In this cohort, encephalopathy at 12 and 24 months was 27\% and 32\%, and survival at 1, 12, and 24 months was 99\%, 89\%, and 81\%, respectively.\textsuperscript{21}

CONCLUSION

The incidence of SVT is likely to increase with the rise in incidence of obesity in the era of laparoscopic bariatric surgery. There are limited surgical, several systemic, and many percutaneous tools and techniques available for treating SVT. In the absence of comprehensive or universally accepted guidelines, management decisions for these patients are largely made on a case-by-case basis, given the available tools and expertise. Interventionists are in a unique position to play a leading role in the management of patients with both acute and chronic SVT as a part of a multidisciplinary team consisting of surgeons, hepatologists, and hematologists.

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