Management of Portal/Mesenteric Vein Occlusion

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Question 1: Splanchnic vein thrombosis (SVT) may affect the portal vein (portal vein thrombosis (PVT)), the splenic vein (splenic vein thrombosis (SpVT)), and/or the intestinal veins (mesenteric vein thrombosis (MVT)) either isolated or in different combinations. How do you assess the dimension of SVT, and which symptoms/signs induce the diagnostic steps?

Valla: Computed tomography (CT) scan is the most accurate means to assess the extension of the thrombus within the portal venous system. For the detection of PVT, however, Doppler ultrasound, which is more available than CT scan, is extremely accurate, provided the operator is experienced and aware of the diagnostic suspicion.

Any kind of severe or prolonged abdominal pain as well as any suspicion of portal hypertension must lead to a comprehensive examination of the portal venous system.

Rössle: If SVT is suggested, CT scan or duplex sonography are the tests of choice to confirm or exclude SVT. In patients with cirrhosis with a very low flow velocity in the portal vein or even with stagnant flow, both tests are of limited accuracy and may lead to a false-positive result.

Any new and obscure abdominal pain should give rise to a duplex sonography with special attention to vascular abnormalities. If the duplex cannot be performed with sufficient accuracy, a CT scan should be made.

In cirrhotic patients, abdominal pain is often subtle or lacking. Therefore, routine duplex examination of the portal vein system should be performed every 6 months.

Hopt/Neeff: Since SVT does often present with acute abdominal pain, emergency CT diagnostics with intravenous

contrast and a ‘late phase’ is probably the most widely used routine to assess the dimensions of SVT. From our point of view, in the subacute setting, SVT is often detected during routine imaging for various symptoms. In this case, Doppler or duplex ultrasound is also capable of making precise assessments of the dimensions of SVT.

Question 2: Predisposing conditions may be local (liver cirrhosis, abdominal infections, trauma, malignoma), systemic (derangement of coagulation), or combined. When do you perform an extensive investigation for prothrombotic disorders?

Valla: Patients without cirrhosis must be discussed differently from those with cirrhosis. In patients without cirrhosis, a general risk factor for venous thrombosis (a prothrombotic condition) is present in one third of the patients in whom a local factor is shown. Therefore, finding a disorder in the abdomen or pelvis should not preclude a comprehensive investigation for underlying general risk factors. Indeed, some of these risk factors can be corrected, though specific treatment means are required.

In patients with cirrhosis, the investigation should be discussed according to the extension of the thrombus and the severity of liver disease. A partial portal vein thrombus in a patient with an advanced liver disease is likely to be explained merely by liver disease, so that a comprehensive work-up would not be cost-effective. In contrast, patients with extensive superior mesenteric vein involvement should be investigated for underlying prothrombotic conditions. Similarly, patients with compensated cirrhosis should be investigated for prothrombotic conditions when they develop PVT, regardless of the extent of the latter. Indeed, finding strong prothrom-

botic conditions in such cases will be of great help in making a decision for prolonged anticoagulation therapy.

Pötzsch: The development of spontaneous thrombosis and thrombosis at an untypical site are two main clinical criteria characterizing thrombophilic patients. These patients are at high risk for the development of recurrent thromboembolic events and will therefore benefit from long-term anticoagulant treatment. Thus, all patients who develop a spontaneous SVT should be considered for long-term anticoagulant treatment. A thrombophilia work-up is helpful to support this decision and to balance the risk of bleeding against the potential benefit of long-term anticoagulation. Thrombophilia testing should include testing for antithrombin, protein C, protein S, activated protein C (APC) resistance, antiphospholipid antibodies, paroxysmal nocturnal hemoglobinuria (PNH), and JAK2 V617F mutation.

Rössle: An extensive investigation for prothrombotic disorders should be performed in any patient with an SVT because in both groups, i.e. non-cirrhotic as well as cirrhotic patients, a thrombophilic disorder has an impact on the treatment. In the case of a positive test result, long-term anticoagulation is required while in patients without such a disease transient anticoagulation for 6 or 12 months may suffice.

Hopt/Neeff: Since the combination of factors can occur in up to 50% of the cases, we would strongly advise to include an extensive investigation for prothrombotic disorders in all cases. One has to bear in mind that the acute need for systemic anticoagulation (e.g. after surgical treatment of bowel infarction) may delay the work-up of those disorders.

Question 3: If you have excluded a prothrombotic disease, do you initiate anticoagulation? If this is the case, when, which anticoagulant, and for how long?

Valla: In patients with recent (so-called acute) thrombosis in the portal venous system, we recommend anticoagulation therapy for at least 6 months and even 1 year when complete recanalization has not occurred within 6 months. In patients with long-standing PVT (usually a cavernoma), we recommend permanent anticoagulation therapy for strongly prothrombotic conditions such as myeloproliferative neoplasm, antiphospholipid syndrome, or homozygous factor V Leiden or homozygous G20210A mutation I factor II gene. For the other patients we do not have clear recommendations to give and are waiting for data from randomized controlled trials.

At present, in patients with cirrhosis, only those with a strong underlying prothrombotic condition, or patients who are actual or potential transplant candidates, are proposed for anticoagulation at our center. We are eagerly awaiting a con-

firmation of the results showing an improved outcome in patients with cirrhosis of intermediate severity who are given prophylactic anticoagulation.

Pötzsch: The primary management of patients with SVT is anticoagulation. The goal of this treatment is to prevent thrombus growth and to support endogenous recanalization. Limited data suggest that even patients with SVT in the setting of cirrhosis benefit from anticoagulation. Therefore, I recommend anticoagulant treatment in all patients presenting with acute SVT. Patients should be started on low-molecular-weight heparin (weight-adjusted) or fondaparinux followed by a switch to oral anticoagulant treatment once no or no more invasive procedures are planned. In patients showing a high risk of bleeding, I prefer aPTT-adjusted unfractionated heparin (1.5- to 2.0-fold increase) as initial anticoagulant because of its shorter half-life and the availability of an antidote. Anticoagulant treatment is recommended for 6 months. In patients with unprovoked SVT, long-term anticoagulant treatment should be considered.

Rössle: All patients with SVT, including those without prothrombotic disease, should receive anticoagulation as soon as possible. Anticoagulation should start with therapeutic low-molecular-weight heparin and change to vitamin K antagonists (VKA) within the first month. Alternatively, oral anticoagulation with rivaroxaban or dabigatran may be given from the beginning. However, respective studies are missing.

Hopt/Neeff: In the absence of contraindications, anticoagulation should in our view be used even if there is no proven prothrombotic disorder for 3–6 months. In our setting, therapy is started with low-molecular-weight heparin (or unfractionated heparin during the first 72 h after emergency surgery) and will be replaced by VKA for long-term treatment.

Question 4: In the case that you find JAK2 mutation in an otherwise unremarkable patient with a platelet count of less than $400 \times 10^9/l$, do you perform a bone marrow biopsy? Why yes, why not?

Valla: We have little personal experience with these patients as we refer them to highly specialized hematologists. Bone marrow biopsy is rarely performed, if ever, for diagnostic purposes but for prognostic purposes instead. Indeed, in the context of SVT, the positive predictive value of a V617F JAK2 mutation is 100%.

Pötzsch: The presence of this mutation characterizes the thrombotic event as a thrombosis associated with a myeloproliferative disorder. However, the JAK2 mutation does not allow differentiation between essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis

(PMF). If the patient shows a hemoglobin > 18.5 g/dl in men or 16.5 g/dl in women or other evidence of increased red cell volume, the diagnosis of PV can be established and a bone marrow examination is not required. If not, I would recommend a bone marrow aspiration and biopsy including bone marrow genetic testing to discriminate between PMF and ET.

Rössle: Bone marrow biopsy is not very sensitive in detecting early myeloproliferative disease. It may be justified in patients with suspected PV. If a JAK2-positive patient has a normal platelet count and PV is not suspected, I do not see a need for bone marrow biopsy. The patient should be followed and, in case of rising platelets, treated with ASS.

Question 5: In the case of finding hypercoagulability, which anticoagulant treatment do you use and how long for which disease? Do you have rules for stopping treatment and do you consider new oral anticoagulants (factor Xa inhibitors or direct thrombin inhibitors)?

Valla: For recent (acute) PVT, we administer low-molecular-weight heparin for 3–5 days while initiating VKA administration. Our decision to stop or maintain anticoagulation is not based on the actual course (recanalization or persistent obstruction) but on the risk for recurrence or extension. The latter is related to the number and nature of the underlying prothrombotic conditions and to the past history of deep vein thrombosis. The decision to stop or to continue is made at about 6 months when thrombosis is limited to the portal vein and its branches, and at about 1 year when thrombosis also involves the superior mesenteric vein or splenic vein.

In patients with long-standing PVT (cavernoma), we give long-term VKA without preceding heparin.

At present, we do not use new oral anticoagulant agents.

Pötzsch: Patients presenting with unprovoked SVT and/or thrombophilic risk factors are at a high risk for recurrent thrombotic events including fatal events. This justifies long-term oral anticoagulant treatment. VKA (international normalized ratio (INR) 2–3) and the direct-acting factor Xa/thrombin inhibitors seem to be equally effective. In patients with cirrhosis showing impaired plasma levels of vitamin K-dependent clotting factors, I prefer direct-acting oral anticoagulants because the INR may not adequately reflect the patient's level of anticoagulation. Anticoagulation should be stopped when the risk of bleeding exceeds the risk of thrombosis. In patients showing a first episode of hemoglobin-relevant bleeding while on oral anticoagulant treatment, I recommend to continue oral anticoagulant treatment at a lower intensity. Anticoagulation should be stopped after a second episode of bleeding.

Rössle: The present recommendation for long-term anticoagulation of patients with SVT (with or without prothrombotic disease) is VKA. Other oral anticoagulation may also be given when the patient is well informed about the pros and cons of non-vitamin K anticoagulants. If VKA are not tolerated or accurate adjustment of the INR is not possible, other oral anticoagulation should be given. Treatment should be lifelong in patients with a coagulation disorder unless side effects or contraindications warrant a withdrawal. The most common reasons for withdrawal are esophageal varices with a danger of bleeding and low platelet count (<40,000–80,000/μl). Thrombopenia may develop with time due to increasing spleen size, and therefore, tests should be performed regularly.

Hopt/Neeff: After the initial phase we commonly use VKA for a duration period of 6 months. The use of factor Xa inhibitors for this indication is currently 'off-label', and evidence is purely anecdotal. For short-term treatment in the initial phase, 'off-label' use might be indicated in heparin-induced thrombocytopenia, for example.

Question 6: If you are sure that the patient has acute PVT/MVT thrombosis, do you perform any kind of interventional therapy (transjugular intrahepatic portosystemic shunt (TIPS) or thrombectomy) and/or thrombolysis (e.g. systemic or local application of urokinase) in certain conditions or do you always adhere to low-molecular-weight heparin (with switch to an oral anticoagulant?) without further measures?

Valla: We do not use interventional procedures or pharmacologic thrombolysis. The risk benefit ratio does not seem to be favorable with the means currently available.

Pötzsch: Successful lysis of acute PVT using streptokinase or tissue-type plasminogen activator has been reported. However, this approach bears the risk of serious complications, including significant and life-threatening bleeding. The risk of bleeding seems to be lower if the fibrinolytic agent is administered locally by a catheter. As a consultant specialized in thrombosis and hemostasis I usually do not recommend lysis of acute PVT.

Rössle: If a non-cirrhotic patient has a condition where anticoagulation will most likely be inefficient (e.g. complete thrombosis of the intra- and extrahepatic portal system and/or more than one thrombophilic factor), a transjugular approach to the portal system with local mechanical and thrombolytic treatment is offered in our hospital. It may resolve most of the thrombus within a short time, thus increasing the chance of sufficient/complete recanalization under subsequent anticoagulation.

In patients with cirrhosis and asymptomatic portal hypertension, a transjugular approach is safe and should be performed in combination with a small-diameter TIPS (5–6 mm). As demonstrated recently, the TIPS alone leads to a high success rate (80%) without additional anticoagulation and protects from rethrombosis. Transient anticoagulation for 1 or 2 months may accelerate the response to TIPS.

In patients with cirrhosis and symptomatic portal hypertension, the TIPS is the treatment of choice. It treats the respective symptom and does not negatively affect liver function.

Cirrhotic patients who deteriorate during the development of the SVT (liver function, hepatic encephalopathy) should be treated with anticoagulation and not with a TIPS. In these patients, the reconstitution of the portal blood flow has priority.

Hopt/Neeff: It strongly depends on the clinical signs and symptoms. Since bowel ischemia sometimes cannot be ruled out by imaging alone, laparoscopy and laparotomy should be performed if only the slightest doubt about bowel integrity is present or if the patient shows signs of peritonitis. If MVT is detected during surgery, every attempt has to be made to perform open catheter thrombectomy. Segments of the bowel that do not recover after thrombectomy have to be surgically removed either during the same operation or a ‘second-look’ operation. Local lysis can be additionally performed; however, after successful thrombectomy unfractionated heparin is commonly used for the first 72 h, followed by low-molecular-weight heparin and VKA.

Question 7: There is increasing evidence that laparoscopic surgery (especially bariatric surgery) may predispose to SVT. Do you think there is a need for preoperative examinations to define patients at risk, and do you think that certain perioperative measures are mandatory to achieve timely diagnosis or to prevent postoperative SVT?

Valla: Some data suggest that underlying prothrombotic conditions are frequent in patients affected by PVT. However, the incidence of PVT appears to be low according to the limited data available. It is therefore difficult to answer this question. We first need to identify the risk factors by means of large cohort studies.

In patients with a past history of venous thromboembolic disease, preoperative assessment for underlying prothrombotic conditions is sensible. Indeed, finding such a condition could lead to prophylactic anticoagulation. However, there is currently no solid evidence to confirm such a view.

Pötzsch: A variety of data demonstrate that bariatric surgery patients are at moderate to high risk for venous thromboembolic complications. Risk adjustment of these patients should include history of prior thrombosis, age, gender, immo-

bility, use of hormone therapy, obesity hypoventilation therapy, pulmonary hypertension, and operative time. All bariatric patients should receive risk-adjusted thromboprophylaxis using low-molecular-weight heparin or fondaparinux.

Rössle: I would not recommend preoperative diagnostic tests in a patient without previous thrombosis. The patient should have a regular postoperative anticoagulation. In the case of development of abdominal pain, an immediate CT scan should be performed. Duplex sonography may not be accurate enough in these obese patients.

Hopt/Neeff: Obese patients are believed to be at a higher risk for thrombotic events especially after surgery. However, we do not routinely perform special examinations for hypercoagulability states in these patients in the absence of a medical history for those diseases. We did not experience specifically increased rates of SVT after bariatric laparoscopic surgery, despite a rather large bariatric program at our institution. An increased dose of prophylactic low-molecular-weight heparin administered perioperatively (‘half the therapeutic dose’), starting the night before surgery, probably seems justified predominantly in order to prevent deep vein thrombosis and pulmonary embolism.

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