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REVIEW ARTICLE

Management of Acute Post-operative Portal Venous Thrombosis

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Abstract
Background Portal vein thrombosis can be a devastating, but often overlooked, complication of hepatobiliary procedures. Symptoms of acute portal vein thrombosis range from nondescript abdominal pain to septic shock secondary to mesenteric ischemia.
Discussion The surgeon must be cognizant of these symptoms and the potential for portal vein thrombosis after any hepatobiliary procedures as an expedient diagnosis and treatment is necessary in order to prevent thrombus propagation, bowel ischemia, and death. This report outlines the symptoms, diagnosis, and a review of the literature on the treatment of acute portal vein thrombosis after hepatobiliary surgery with a special note made regarding a case of portal vein thrombosis after pancreatectomy and autologous islet cell transplantation.

Keywords Portal vein thrombosis · Islet cell transplantation · Chronic pancreatitis · Portal vein thrombectomy

Introduction

Portal vein thrombosis refers to any thrombosis developing in the portal vein, its branches, or with extension into the splenic, superior mesenteric, or inferior mesenteric veins. As with any venous thrombotic condition, the etiology of acute portal vein thrombosis (PVT) can be categorized based on Virchow's triad of venous stasis, hypercoaguable state, and endothelial injury. These etiologies are not independent of each other and often times several factors may coexist.[1] Venous stasis may occur with conditions in which intrahepatic blood flow is impeded, such as with the Budd–Chiari syndrome or portal hypertension associated with cirrhosis.[2,3] Hypercoaguable states may be divided into inherited and acquired disorders with inherited disorders encompassing such disease states as antithrombin III deficiency, protein C/S deficiency, and factor V Leiden mutation. Acquired states of hypercoaguability include malignancy, myeloproliferative disorders, oral contraceptive medications, and pregnancy. Finally, states of endothelial injury include intra-abdominal infections/inflammatory processes such as pancreatitis, cholecystitis, or diverticulitis/colitis and also involve direct injury or manipulation of the portal vein which may occur with splenectomy, surgical shunts, liver transplantation, or abdominal surgeries.[2,4] It is this last group of etiologies, specifically acute PVT after hepatobiliary surgery, which is the focus of this review.

Most literature regarding PVT after hepatobiliary surgery refers to liver transplantation with a reported incidence of 2–6%.[5,6] Smoot et al. reported a 5% acute (less than 30 days post-operative) PVT rate in patients who underwent portal vein reconstruction during pancreaticoduodenectomy (PD).[7] Although there was a difference in rates based on reconstruction with polytetrafluoroethylene interposition graft versus lateral venorrhaphy and primary end-to-end reconstruction, the difference was not significant (33%

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versus 12%, respectively, $p=0.16$). The low incidence of acute PVT may be secondary to a lack of detection until chronic changes have occurred. These chronic manifestations of PVT most often present with esophageal varices and subsequent rupture as Witte et al. demonstrated 60% of their cohort with chronic PVT presented with hematemesis.[8,9] In addition, splenomegaly is a common finding secondary to increased resistance to splenic outflow and is reportedly found in 75–100% of patients.[4,8,10] Histologically, increased reticulin deposition has been demonstrated around the hepatic portal triads reminiscent of non-cirrhotic portal fibrosis.[4] The utility of liver biopsy in the setting of PVT is limited, but this finding does demonstrate that hepatic architectural changes do take place and perhaps potentiate portal hypertension. Although the formation of varices, variceal hemorrhage, and portal hypertension is not seen in acute PVT, as it is in chronic PVT, the most feared complication is propagation of the thrombus into the superior mesenteric vein resulting in bowel ischemia, sepsis, and death. Certainly, mortality rates are higher in cases with associated mesenteric ischemia. The ability to diagnose and, therefore, treat PVT is of paramount importance in order to prevent the catastrophic case of mesenteric ischemia resulting from this complication.

Signs and Symptoms

The symptoms of acute PVT are usually non-specific but may involve vague abdominal pain, nausea, and potentially fevers. Klempnauer et al. reported that 71% of the patients in their series had a presenting symptom of acute abdominal pain, 13% presented with abdominal colic, and 6.5% of patients in their series presented with bloody stool.[11] Ascites is usually a rare presenting sign, but if present, is usually transient because collateral circulation has not yet developed. Otherwise, the presence of ascites denotes chronic liver dysfunction.[8] Laboratory values are usually nondescript as liver function tests are usually normal, although mild elevations in transaminases, alkaline phosphatase, and bilirubin can be seen.[4,8] Sharp increases in liver function tests should raise the suspicion of the clinician of the potential for PVT, especially when taken in the context of other signs and symptoms. Decreased white blood cell and platelet counts may also be present when associated with hypersplenism, but an increased white blood cell count in the presence of metabolic acidosis, increased abdominal pain, and hemodynamic instability should warrant further diagnostic imaging as the potential for bowel ischemia is great.[4,8] Hemodynamic instability outside of that associated with septic shock does not typically occur with acute PVT. It has been suggested that with portal vein occlusion, hepatic arterial flow increases but a hyperkinetic state soon develops. A significant decrease in systemic vascular resistance with a concomitant increase in cardiac output has been noted.[10] A high index of suspicion must, therefore, be present in patients with the above signs and symptoms when they are out of the ordinary for what should be expected after typical hepatobiliary procedures.

Diagnosis

Acute PVT after hepatobiliary surgery may not be suspected because of a lack of symptoms and relative paucity of cases reported. However, several modalities exist in order to secure the diagnosis of portal vein thrombosis. The choice of imaging in order to visualize the location and extent of portal thrombus depends on each individual institution's ability to mobilize the proper resources in order to provide an expeditious diagnosis and ultimately, treatment (Table 1). Color Doppler has been used to visualize portal thrombus but is extremely user-dependent, may be limited secondary to body habitus or overlying bowel gas, often cannot visualize acute thrombus secondary to its non-echogenic nature, and often cannot be acquired late at night. However, the fact that it is non-invasive and inexpensive makes it a valuable screening tool. The sensitivity and specificity for color Doppler to detect portal thrombosis vary and range from 89% to 93% and 92% to 99%, respectively.[12,13] Compared to color Doppler evaluation, computed tomography (CT) of the abdomen, especially when coupled with thin cuts through the porta hepatis, yields results similar to that seen with Doppler. The advantages of abdominal CT include a high sensitivity (90%) and specificity (99%) to diagnose PVT as well as more accurate delineation of the portal vein anatomy that contains thrombus.[13] However, cost may preclude its use in some instances. Magnetic resonance angiography (MRA), although costly and time-consuming, can provide exquisite detail of the portal anatomy including flow direction and disturbances. In regards to acute PVT, MRA usually is not required but is instead more useful in the chronic state of thrombosis seen in patients with liver failure who may be considered for liver transplantation. Historically, the gold standard for the diagnosis of PVT is portal venography. Not only does this allow diagnosis but also treatment of the thrombosed vessels, although it is more invasive with associated complications. In one small series, portal venography was correlated with the surgical presence of PVT and had a sensitivity of 100% and specificity of 90%.[12] The surgeon, therefore, can utilize a multimodality approach as it relates to the workup of this potentially lethal complication.

Treatment Options

Anticoagulation

Treatment of portal vein thrombosis is dictated by the acuity of the thrombus and associated complications. Serial abdominal exams as well as serial lactic acid levels, liver function tests, and factor V levels should be measured to assess for the progression of potential bowel ischemia and liver dysfunction. After securing the diagnosis of PVT, therapeutic anticoagulation with heparin should be instituted as soon as possible in order to prevent propagation of thrombus with its associated repercussions. It has been demonstrated that expeditious anticoagulation results in a greater likelihood of portal vein recanalization. Turnes et al. retrospectively evaluated 38 patients who had the diagnosis of acute portal vein thrombosis either alone or in combination with other associated veins (splenic, mesenteric). Anticoagulation was instituted in 27 patients within 30 days of the onset of their symptoms. Twelve patients demonstrated recanalization with 50% demonstrating complete recanalization of the thrombosed portal vein versus the 11 patients who did not receive anticoagulation in which no evidence of recanalization was demonstrated. Of interest is the fact that in this group of 12 patients who demonstrated recanalization, 83% (ten of 12) were started on anticoagulation within 1 week of symptom onset versus the remaining two patients who were started on anticoagulation greater than 1 week after diagnosis.[14] This study was confirmed in a prospective analysis of patients with acute PVT in which 38% of patients with associated ascites had recanalization versus 65% of patients without ascites at 1 year. The presence of ascites was an independent predictor of failure of anticoagulation to produce recanalization of the portal vein.[15] This is likely secondary to the fact that ascites dictates a more chronic process and this further supports the necessity of the expeditious institution of anticoagulation in patients with acute PVT. Thrombus burden also has an effect on response to anticoagulation therapy and should be taken into account when selecting patients for anticoagulation alone in the treatment of acute PVT. In a retrospective study performed by Condat et al., patients presenting between 1983 and 1999 with acute portal vein thrombosis, as defined by (a) the onset of recent

Table 1 Comparison of Portal and Mesenteric Vein Thrombosis Etiology and Diagnosis in Selected Series

Author	*N*	Etiology (%)					Diagnosis (%)			Location (%)		
		Hypercoag	Malignancy	Infxn/Infl	Operative	Idiopathic	U/S	CT	MRA	PV	SMV	Comb
Janssen[1]	172	27	24	17	23	16	–	–	–	89	0	11
Demertzis[42]	1	0	0	0	0	100	–	100	–	100	0	0
Klempnauer[11]	31	6.5	29	0	32.3	0	39	16	0	26	61	13
Zyromski[26]	1	0	0	0	100	0	100	–	–	0	0	100
Dutta[43]	20	25	5	0	10	50	–	–	–	20	5	75
Amitrano[44]	121	69.4	–	10	19.2	0	–	–	–	33.9	17.3	48.8
Condat[16]	33	54.5	3	36.3	3	24.2	84.8	66.6	0	–	–	–
Henao[45]	1	0	0	0	100	0	0	100	0	0	0	100
Malkowski[21]	33	66.7	0	0	0	33.3	–	–	–	75.8	0	24.2
Ozkan[46]	1	0	0	0	100	0	100	100	0	0	0	100
Stambo[34]	1	0	0	0	100	0	0	100	0	100	0	0
Kaplan[47]	1	0	0	100	0	0	100	0	0	0	0	100
Turnes[14]	38	57.9	0	18.4[a]	18.4[a]	21.1	81.6	84.2	23.7	26	0	43
Hollingshead[24]	20	–	–	–	–	–	30	60	10	15	10	75
Thomas[b]	1	0	0	0	100	0	100	100	0	100	0	0

In some instances multiple etiologies were identified for a single patient and are reported together. In addition, more than one diagnostic imaging may have been used for a single patient and are likewise reported together. Etiologies include hypercoaguable state which includes acquired/hereditary, oral contraceptives, or myeloproliferative disorder (*hypercoag*), malignancy, infectious/inflammatory (*infxn/infl*), operative, or idiopathic. Diagnostic imaging involved the use of Doppler ultrasonography (*U/S*), computed tomography (*CT*), or magnetic resonance angiography (*MRA*). Location of thrombus was identified as either portal vein (*PV*), superior mesenteric vein (*SMV*), or a combination of portal vein and superior mesenteric vein involvement (*Comb*)

[a] Infectious, inflammatory, and operative etiologies were not discriminated in this study and are thus listed together

[b] The current series of PVT after AICT is listed

abdominal pain, (b) no evidence of chronic portal hypertension, and (c) the absence of porto-portal collaterals on imaging studies, were evaluated for recanalization of the portal vein after anticoagulation but without operative thrombectomy or lytic therapy. A total of 27 patients with acute thrombus who were anticoagulated had follow-up imaging either by color Doppler ultrasound or CT scan at a mean of 4.9 months from their initial imaging which demonstrated an acute PVT. The group demonstrated that complete recanalization was achieved more frequently in cases where thrombosis involved only the portal vein or superior mesenteric vein (eight of 11, 73%) versus more extensive involvement of the portal venous system (two of 16, 13%). Of note, two patients did not receive any anticoagulation treatment, and there was no recanalization noted in either of these cases on follow-up imaging.[16] Finally, Sheen et al. reported their series of nine patients diagnosed with acute PVT of which five (55.5%) resolved with anticoagulation alone at a median of 197 days after diagnosis.[17] Immediate anticoagulation is, therefore, a viable option for patients with acute PVT in order to restore portal vein flow, albeit a slower option. Systemic anticoagulation, however, may be contraindicated in the immediate post-operative period, necessitating invasive modalities in order to restore portal flow.

Thrombolytic Therapy

Evidence exists that only approximately 50% of patients will have complete recanalization of the portal vein with anticoagulation as the sole modality of treatment.[16–20] Condat et al. reported only 37% of patients in their study having complete recanalization with 55.5% and 7.4% of patients demonstrating incomplete or no recanalization with only anticoagulation as treatment, respectively.[16] In cases where anticoagulation may be contraindicated, site-directed thrombolytic therapy may be an appropriate alternative. Techniques of thrombolytic therapy differ in that thrombolytics can be infused via a catheter positioned in the superior mesenteric artery (SMA) to achieve indirect lysis of PV thrombus or in the portal vein itself. Like the use of anticoagulation, expedient institution of venous thrombolytic therapy demonstrated a higher rate of thrombus resolution compared to delayed treatment. Malkowski et al. showed that 36% of patients had "excellent" recanalization results when symptoms did not exceed 14 days compared to 0% recanalization in those who had symptoms that persisted greater than 30 days.[21] Numerous series have demonstrated the excellent response rate of site-directed venous thrombolysis with rates ranging from 75% to 100% partial or complete recanalization (Table 2). An alternative

Table 2 Comparison of Portal and Mesenteric Vein Thrombosis Treatment Patterns and Response Rates in Selected Series

Author	*N*	Treatment (%)			Treatment response (%)			Median time to Tx (days)
		Surg	Lytics	Anti-Coag	Surg	Lytics	Anti-Coag	
Janssen[1]	172	0.6	0	27	NR	–	NR	28
Demertzis[42]	1	100	100	0	100	100	–	0
Klempnauer[11]	31	35.5	16	13	91	100	0	7
Zyromski[26]	1	100	0	0	100	–	–	0
Amitrano[44]	121	0	3.3	33.9	–	100	24.4	–
Condat[16]	33	0	0	94	–	–	80.6	14
Henao[45]	1	0	100	0	–	100	–	–
Malkowski[21]	33	0	85	0	–	82	–	–
Ozkan[46]	1	0	100	0	–	100	–	21
Stambo[34]	1	100	100	0	100	100	–	5
Kaplan[47]	1	0	100	0	–	100	–	5
Turnes[14]	38	0	0	71	–	–	44.4	6
Hollingshead[24]	20	10	100	0	100	75	–	12.5
Thomas[a]	1	100	100	0	100	100	–	1

Treatment (percent) refers to the percentage of patients who underwent the specified modality of treatment for acute PVT. Many series involved the use of anticoagulation early in the treatment algorithm but this was not the primary mode of treatment for the PVT. Where indicated, anticoagulation is designated as the sole method of treatment of the PVT with corresponding treatment response rates. Some patients received more than one treatment, such as combined thrombolytic and mechanical thrombectomy

Surg surgical thrombectomy, *Lytics* pharmacologic thrombolytic therapy, *Anti-coag* anti-coagulation therapy, *NR* not reported

[a] The current series of PVT after AICT is listed

strategy of thrombolytic delivery is via the superior mesenteric artery. Proponents of SMA-directed thrombolytics argue that arterial infusion allows resolution of small venous thrombi that cannot be treated with PV thrombolytic infusion.[22,23] Hollingshead et al. utilized either the PV or SMA route for thrombolysis of PV or mesenteric venous thrombosis. A comparison of the PV versus SMA routes demonstrates a similar time from symptom presentation to thrombolysis (11.3 versus 15 days, respectively), but increased duration of thrombolysis (29.4 versus 42.3 h, respectively) and better recanalization with the PV route compared to the SMA route (83% partial recanalization versus 50%, respectively). Arterial infusion has, therefore, been shown to result in longer infusion times, delayed time to resolution of thrombus, and inefficient thrombus resolution when compared to portal venous thrombolysis.[24] With either modality, there is a reduction in thrombus burden with restoration of portal flow that is more expeditious than anticoagulation therapy alone and helps to avoid the complications of inadequate recanalization seen with anticoagulation alone (Table 2).

Operative and Mechanical Thrombectomy

Operative thrombectomy for SMV thrombosis was first reported by Mergenthaler and Harris in 1968 after a PD for duodenal neoplasm.[25] Since then, many advances have been made in the diagnosis and treatment of PV/SMV thrombosis after hepatobiliary surgery. Patients who, after hepatobiliary surgery, develop signs of ischemic bowel secondary to porto-mesenteric vein thrombosis should be anticoagulated and proceed directly to laparotomy for bowel resection. It is at that time that some authors argue that portal vein thrombectomy should be carried out in order to immediately reduce thrombus burden. This is especially true in the case where venous reconstructions

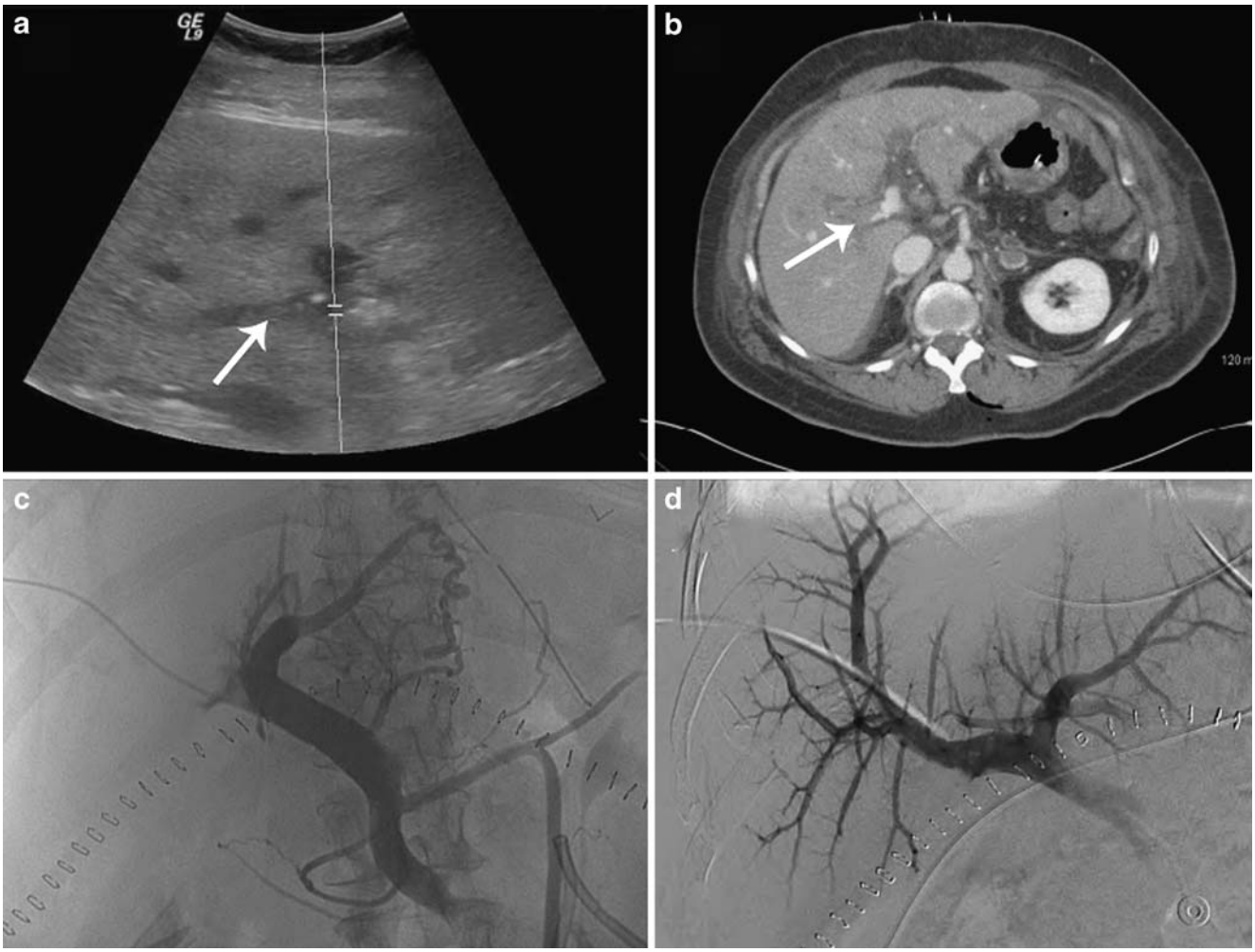

Figure 1 Diagnostic imaging of acute portal vein thrombosis pre- and post-thrombolytic treatment. **a** Color duplex ultrasonography demonstrates PVT in the right branch of the portal vein and was confirmed by CT (**b**). **c** Initial portal venography confirms the findings of ultrasonography and CT and confirms a patent superior mesenteric vein. **d** After mechanical thrombolysis and 33.5 h of r-TPA therapy, there was almost complete resolution of the PVT. *Arrows* indicate large thrombus burden in the right portal vein.

have been performed involving the portal vein, which may be the case during PD secondary to tumor involvement of the PV/SMV confluence or during liver transplantation.

In these situations, operative thrombectomy affords the surgeon the opportunity to inspect any vascular anastomosis and revise if needed.[26] This is especially important in cases of liver transplantation when graft survival is dependent on hepatopetal flow. At one time, portal vein thrombosis was considered a contraindication to liver transplantation, but even complete PVT is no longer considered a contraindication to surgery.[27] An evaluation of the efficacy of operative portal vein thrombectomy is best accomplished through an analysis of the liver transplantation literature. Although cases of portal vein thrombectomy at the time of liver transplantation relate to episodes of chronic PVT, this management gives insight into re-thrombosis rates that may be applicable to thrombectomy for acute PVT. Portal vein thrombectomy alone at the time of transplantation has been demonstrated to have a re-thrombosis rate of 4.2–38.5%.[28–31] In many of the cases of re-thrombosis, patients had to undergo repeat liver transplantation or underwent observation. In one series, surgical thrombectomy was carried out in six patients with acute PVT after liver transplantation, with a success rate of 83%, demonstrating its efficacy.[32] Additionally, Klempnauer et al. reported one case of re-thrombosis (n=11, 9%) after initial thrombectomy for porto-mesenteric thrombosis or various etiologies.[11] In their series, five patients received thrombolytic therapy via a mesenteric vein and none of these patients developed re-thrombosis. The trend with operative thrombectomy is thus to infuse thrombolytics concurrently as complete thrombectomy is extremely difficult as small adherent thrombi often are still attached to the vessel wall serving as a nidus for thrombus propagation. The use of thrombolytics, therefore, treats these undetected foci of thrombus. Adani et al. demonstrated this in their series of three patients who developed PVT after a liver transplantation, liver resection, and a splenectomy. Systemic heparinization at the time of diagnosis followed by mechanical thrombectomy and lytic treatment resulted in a 0% re-thrombosis rate in these patients.[33] In addition, the use of newer mechanical thrombectomy devices such as the AngioJet reholytic mechanical thrombectomy system (Possis Medical) has demonstrated promising results with a complete resolution of a PVT that occurred as a result of a pancreatic biopsy in one report.[34] Operative thrombectomy is, therefore, an alternative treatment of acute PVT but proper patient selection must be implemented. When performed by itself, high rates of re-thrombosis have been reported so follow-up imaging and a high index of suspicion must be present in order to detect potential re-accumulation of thrombus. Operative/mechanical thrombectomy performed concomitantly with thrombolytics has been demonstrated to provide at least equivalent results to site-directed thrombolytics but with a more expedient resolution of the thrombus and should be the procedure of choice except when absolute contraindications to thrombolytic therapy are present.

Special Circumstances

The process of portal vein thrombosis usually occurs in the presence of endothelial injury, hypercoaguable state, malignancy, sepsis, or portal hypertension. Although rare, portal vein thrombosis can occur in conjunction with autologous islet cell transplantation (AICT) and can be a devastating complication. In our experience at the University of Cincinnati, having performed 107 AICT cases to date, we have encountered one case of PVT after purified AICT. The case involved a 61-year-old female with a history of recurrent acute on chronic pancreatitis who underwent AICT and was diagnosed with PVT by color

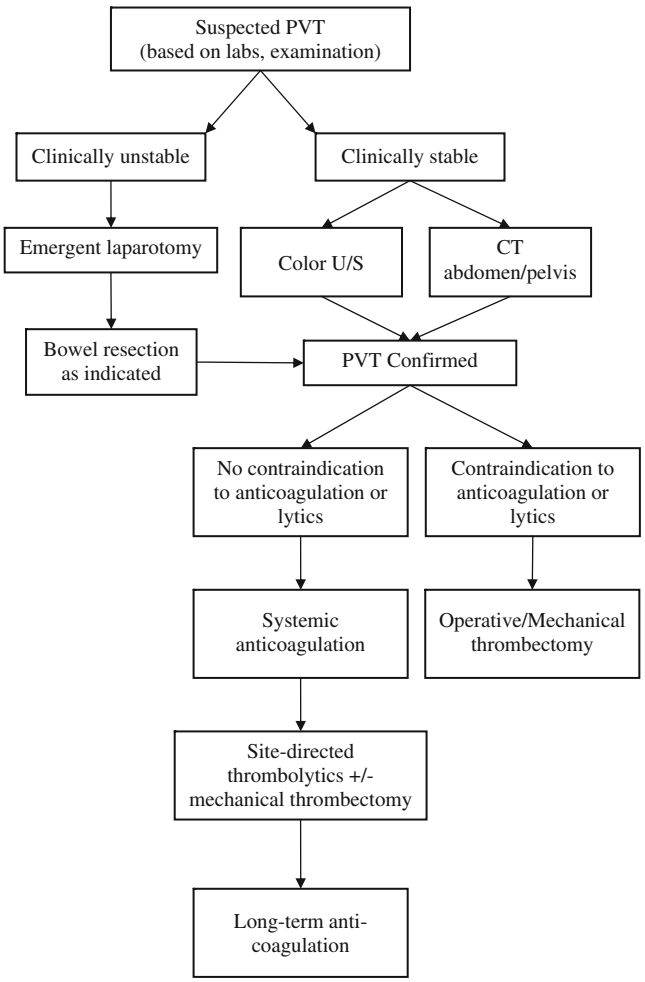

Figure 2 Diagnostic and treatment algorithm for acute portal vein thrombosis after hepatobiliary surgery.

Doppler and CT angiogram when her post-operative liver function tests became elevated (Fig. 1a, b). The patient was immediately anticoagulated with heparin and taken to the interventional radiology suite where portal venography was performed demonstrating right PV occlusion, thrombosis of multiple left portal veins, but a widely patent main PV (Fig. 1c). Utilizing a combination of mechanical thrombectomy and thrombolytics, patency of the portal vein was restored by post-operative day 3 after less than 35 h of thrombolytics (Fig. 1d). Institutions that perform autologous islet transplantation appear to have a lesser risk of portal/mesenteric venous thrombosis compared to cadaveric islet transplantation. Wahoff et al. presented 48 cases of AICT without an incidence of portal vein thrombosis.[35] In 2001, the Leicester group reported their experience over 54 months of 24 patients who underwent AICT. In this series, one patient (4.2%) developed a partial portal vein thrombosis who was treated with anticoagulation for 6 months.[36] Finally, Argo et al. from Alabama reported in June 2008 of 26 patients who underwent AICT in which none of them developed PVT.[37] Prior to new techniques of islet preparation and purification, portal vein thrombosis after AICT had a higher incidence likely due to the larger volume of islets required for transplantation as well as an increased thrombogenicity of the crude preparation thought to be due to elevated thromboplastin activity.[38] The preparation of islet cells has been modified throughout the years since first being described by Mirkovitch and Campiche and modified by Horaguchi and Merrell.[39,40] The most common methods are variations of the method described by Ricordi et al. which is currently employed at our institution.[41] With the advent of this preparation method, the incidence of PVT after AICT has significantly decreased such that it is a rare complication of autologous islet cell transplantation.

Conclusion

Portal vein thrombosis after hepatobiliary surgery is a rare yet important complication. Diagnosis can be made by the cost-effective color Doppler ultrasound or the higher resolution CT scan to delineate portal vein obstruction. Sensitivity and specificity for these two tests are similar, but each has its own distinct set of positive and negative attributes. Once portal vein thrombosis is diagnosed, treatment is determined by the clinical situation. In most cases, PVT is treated with immediate anticoagulation in order to limit the propagation of thrombus. As indicated previously, only 50% of patients will have complete resolution of their PVT and may need further intervention in order to prevent the complications of chronic PVT thrombosis such as portal hypertension. With the advent of more sophisticated devices and improved interventional techniques, we recommend site-directed thrombolytics to the area of thrombus as this results in excellent recanalization in a relatively short period of time with low re-thrombosis rates (Fig. 2). At the same time, this algorithm avoids laparotomy in the face of recent hepatobiliary procedures which could prove difficult or be fraught with iatrogenic injuries. That being said, in patients with evidence of bowel ischemia secondary to thrombus propagation, laparotomy must be employed in order to eradicate the source of septic shock in a patient. In these situations, site-directed thrombolytics should still be employed either alone or coupled with operative/mechanical thrombectomy in experienced hands. With this management algorithm and a high index of suspicion, the complications of acute portal vein thrombosis, whether associated with hepatobiliary procedures or not, can be limited, and restoration of normal portal venous flow can be attained.

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