

CLINICAL VIGNETTE

Management of Portal Vein Thrombosis in Cirrhosis

Alyssa Y. Choi, MD

Abstract

There is debate regarding the utility of anticoagulation for portal vein thrombosis (PVT) or superior mesenteric vein (SMV) thrombosis. The primary aim of this case presentation is to discuss and provide a framework for determining the appropriate setting in which to anticoagulate cirrhotic patients who are detected to have PVT incidentally on imaging. PVT or SMV thrombosis in itself cannot be an absolute and only indication for anticoagulation therapy. Therefore, the management should be personalized until further randomized control trials are available.

Introduction

Hypercoagulability prevails over hypocoagulability in cirrhosis as the hemostatic balance is broken. Cirrhotics are subject to a prothrombotic state by increasing procoagulant factor VIII and von Willebrand plasma levels while concurrently decreasing factors II, V, VII, IX, X, XI, anticoagulant proteins C, S, Z and antithrombin, antiplasmin, thrombin-activatable fibrinolysis inhibitor, histidine-rich glycoprotein, heparin cofactor II, plasminogen plasma levels.^{1,2} The International normalized ratio (INR) does not take these factor deficiencies into consideration and overestimates the bleeding risk in a cirrhotic. A retrospective study by Dabbagh et al confirmed that an elevated INR >2.2 does not protect patients with chronic liver disease against the risk of venous thromboembolism (VTE).³ For that reason, we administer VTE prophylaxis in cirrhotics despite a high INR. Calculating MELD-XI, factor V (which is not affected by vitamin K antagonists), thrombin generation test, thromboelastography (TEG) may be appropriate alternatives.^{4,5} We should also keep note that the Model for End-Stage Liver Disease (MELD) score was designed as a measure of liver transplant wait-list mortality and is not as a measure of synthetic liver dysfunction. Not only does cirrhosis increase one's risk of VTE, it is the most common cause of PVT due to hypercoagulability, endothelial damage, and clinically significant influences on portal hemodynamics with decreased portal vein flow velocity/stasis due to increased intrahepatic vascular resistance.^{6,7}

PVT increases with the severity of the cirrhosis i.e. small liver weights at liver transplantation, more severe ascites, refractory variceal bleeding, encephalopathy, and high Child-Pugh/MELD scores.¹ PVT is a negative prognostic factor for mortal-

ity and early rebleeding,^{8,9} while others disagree.⁶ Although complete PVT is not an absolute contraindication for liver transplantation, PVT is associated with increased post-transplant mortality and morbidity, especially if the thrombus is complete and extensive⁴ but does not affect waiting list mortality¹⁰ therefore MELD exception points in this patient population are not warranted. Despite the likely association, the causality- meaning whether or not PVT actually causes an aggravation in liver disease or whether it is merely a reflection of the severity of the underlying liver disease- remains unclear. The incidence of PVT ranges from 7-18% per year and prevalence varies from 5-25% among patients with cirrhosis and portal hypertension.^{1,11} Of those, occlusive thrombus are found in one fourth to one third of PVT patients and the rest have non occlusive thrombi.¹

Case Presentation

A 29-year-old male with Caroli's syndrome with associated congenital hepatic fibrosis (evidenced by portal hypertension/splenomegaly, peri-splenic collateralization) and esophageal varices s/p multiple band ligations, ascites, hepatic encephalopathy, and recurrent cholangitis. He presents with several days of RUQ abdominal pain, nausea, vomiting, intermittent nonbloody diarrhea. He denies fevers, chills, diarrhea, hematochezia, chest pain, shortness of breath. His vitals are normal and exam largely benign. Labs are notable for Hgb 12.4, Plt 97, normal lactate. Abdominal ultrasound with dopplers shows a "likely nonocclusive thrombus within the portal vein at the portosplenic confluence." CTA of the abdomen pelvis with and without contrast shows a "SMV thrombus extending to the portal confluence." There is no evidence to suggest small bowel ischemia. Interventional Radiology, consulted from the ED for possible catheter-directed thrombolysis, recommended heparin gtt. The GI consultants recommended stopping anticoagulation.

Discussion

There are no consensus guidelines regarding the management of PVT in cirrhosis. The American College of Chest Physicians (ACCP) and American Association for the Study of Liver Disease (AASLD) have discrepant clinical recommendations for treatment of PVT; the former discourages anticoagulation

for asymptomatic, incidentally diagnosed PVT whereas the latter suggests anticoagulation for all acute PVT regardless of symptomatology.¹² Four small studies have addressed anticoagulation in cirrhosis. Francoz et al reports 42.1% complete recanalization rates, Senzolo et al reported 36% and Amitrano et al reported 33.3% and 75% after 6 and 11 months of anticoagulation therapy, respectively.^{4,13,14} Delgado reported that anticoagulation safely led to partial or complete recanalization of the PVT in 60% of patients with cirrhosis.¹⁵ Compare this to spontaneous resolution of PVTs, without anticoagulation, in 16.7% of cases.¹¹

Besides the obvious role of anticoagulation to prevent clotting, it can potentially decrease fibrinogenesis and even reduce bacterial translocation and the incidence of further decompensation in patients listed for liver transplantation.¹⁶ However, it is unclear if recanalization of a PVT improves survival. In pre liver transplantation patients with PVT, anticoagulation or TIPS are two options to recanalize or at least prevent the extension of the thrombus so that a splanchnic vein can be used as the inflow vessel to restore physiological blood flow to the allograft.^{4,13}

Overall, initiation of anticoagulation as early as possible is recommended because early initiation of anticoagulation (<14 days after the diagnosis of PVT) is the only factor significantly associated with repermeation.^{15,17} Therapy with low molecular weight heparin and vitamin K antagonists has been shown to achieve complete and partial recanalization in 33-45% and 15-35% of cases, respectively.⁵

Other studies have explored the use of tPA in acute PVT defined as within 60 or 90 days before the possible therapeutic approach and found it to significantly reduce the pressure in esophageal varices with potential implications on reduction of extrahepatic consequences of portal hypertension without clinically significant side effects.¹⁸ There is growing literature demonstrating that direct-acting oral anticoagulants (DOACs) such as rivaroxaban and apixaban displayed similar efficacy and safety characteristics when compared to traditional anticoagulation in patients with^{19,20} and without cirrhosis.²¹ Therefore, DOACs may be attractive agents for anticoagulation therapy as we get more reversal agents.^{22,23}

Conclusion

Given that this cirrhotic patient had a partial, non-obstructive, likely chronic PVT with no mesenteric or splenic vein involvement causing severe venous congestion in the bowel, not on the transplant list, and symptoms likely unrelated to this incidental finding, observation with no anticoagulation was chosen. The risks and benefits of anticoagulation must be weighed on a case by case basis such as evaluating the extent of portal hypertension, the presence of varices, and inquiring about history of gastrointestinal bleeding. Helpful categorizations to consider include cirrhotic versus non-cirrhotic, partial versus complete, non-obstructive versus obstructive, acute versus chronic, symptomatic versus asymptomatic, and anticipated transplant versus no transplant.

REFERENCES

1. **Valla D.** Management of Portal Vein Thrombosis in Cirrhosis. <https://liverlearning.aasld.org/aasld/2013/stc.aasld.easl/31942/dominiquecharles.valla.management.of.portal.vein.thrombosis.in.cirrhosis.html?f=m3e633>. Accessed November 29, 2017.
2. **Cheong JY.** [Anticoagulation in Patients with Liver Cirrhosis]. *Korean J Gastroenterol.* 2017 Nov 25;70(5):218-222. doi: 10.4166/kjg.2017.70.5.218. Review. Korean. PubMed PMID: 29161790.
3. **Dabbagh O, Oza A, Prakash S, Sunna R, Saeetele TM.** Coagulopathy does not protect against venous thromboembolism in hospitalized patients with chronic liver disease. *Chest.* 2010 May;137(5):1145-9. doi: 10.1378/chest.09-2177. Epub 2009 Dec 29. PubMed PMID: 20040609.
4. **Francoz C, Valla D, Durand F.** Portal vein thrombosis, cirrhosis, and liver transplantation. *J Hepatol.* 2012 Jul;57(1):203-12. doi: 10.1016/j.jhep.2011.12.034. Epub 2012 Mar 21. PubMed PMID: 22446690.
5. **Raja K, Jacob M, Asthana S.** Portal vein thrombosis in cirrhosis. *J Clin Exp Hepatol.* 2014 Dec;4(4):320-31. doi: 10.1016/j.jceh.2013.12.003. Epub 2013 Dec 31. Review. PubMed PMID: 25755579; PubMed Central PMCID: PMC4298635.
6. **Maruyama H, Okugawa H, Takahashi M, Yokosuka O.** De novo portal vein thrombosis in virus-related cirrhosis: predictive factors and long-term outcomes. *Am J Gastroenterol.* 2013 Apr;108(4):568-74. doi: 10.1038/ajg.2012.452. Epub 2013 Feb 5. PubMed PMID: 23381015.
7. **Primignani M, Tosetti G, La Mura V.** Therapeutic and clinical aspects of portal vein thrombosis in patients with cirrhosis. *World J Hepatol.* 2015 Dec 18;7(29):2906-12. doi: 10.4254/wjh.v7.i29.2906. Review. PubMed PMID: 26689354; PubMed Central PMCID: PMC4678377.
8. **D'Amico G, De Franchis R; Cooperative Study Group.** Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology.* 2003 Sep;38(3):599-612. PubMed PMID: 12939586.
9. **Englesbe MJ, Kubus J, Muhammad W, Sonnenday CJ, Welling T, Punch JD, Lynch RJ, Marrero JA, Pelletier SJ.** Portal vein thrombosis and survival in patients with cirrhosis. *Liver Transpl.* 2010 Jan;16(1):83-90. doi: 10.1002/lt.21941. PubMed PMID: 20035521.
10. **Englesbe MJ, Schaubel DE, Cai S, Guidinger MK, Merion RM.** Portal vein thrombosis and liver transplant survival benefit. *Liver Transpl.* 2010 Aug;16(8):999-1005. doi: 10.1002/lt.22105. PubMed PMID: 20677291; PubMed Central PMCID: PMC2915450.
11. **Borja A, Xing W, Lyman E, Azucena B, Sule AA.** Thrombus Resolution in Two Patients with Portal Vein Thrombosis without Anticoagulation: Do We Need to Anticoagulate Patients with Portal Vein Thrombosis? *Int J Angiol.* 2016 Dec;25(5):e93-e96. doi: 10.1055/s-0034-1395980. Epub 2015 Jan 14. PubMed PMID:28031666; PubMed Central PMCID: PMC5186214.

12. **Sharma AM, Zhu D, Henry Z.** Portal vein thrombosis: When to treat and how? *Vasc Med.* 2016 Feb;21(1):61-9. doi: 10.1177/1358863X15611224. Epub 2015 Nov 19. Review. PubMed PMID: 26584887.
13. **Senzolo M, M Sartori T, Rossetto V, Burra P, Cillo U, Boccagni P, Gasparini D, Miotto D, Simioni P, Tsochatzis E, A Burroughs K.** Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. *Liver Int.* 2012 Jul;32(6):919-27. doi: 10.1111/j.1478-3231.2012.02785.x. Epub 2012 Mar 21. PubMed PMID: 22435854.
14. **Amitrano L, Guardascione MA, Menchise A, Martino R, Scaglione M, Giovine S, Romano L, Balzano A.** Safety and efficacy of anticoagulation therapy with low molecular weight heparin for portal vein thrombosis in patients with liver cirrhosis. *J Clin Gastroenterol.* 2010 Jul;44(6):448-51. doi:10.1097/MCG.0b013e3181b3ab44. PubMed PMID: 19730112.
15. **Delgado MG, Seijo S, Yepes I, Achécar L, Catalina MV, García-Criado A, Abrales JG, de la Peña J, Bañares R, Albillos A, Bosch J, García-Pagán JC.** Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. *Clin Gastroenterol Hepatol.* 2012 Jul;10(7):776-83. doi:10.1016/j.cgh.2012.01.012. Epub 2012 Jan 28. PubMed PMID: 22289875.
16. **Villa E, Cammà C, Marietta M, Luongo M, Critelli R, Colopi S, Tata C, Zecchini R, Gitto S, Petta S, Lei B, Bernabucci V, Vukotic R, De Maria N, Schepis F, Karampatou A, Caporali C, Simoni L, Del Buono M, Zambotto B, Turolo E, Fornaciari G, Schianchi S, Ferrari A, Valla D.** Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. *Gastroenterology.* 2012 Nov;143 (5): 1253-60.e1-4. doi:10.1053/j.gastro.2012.07.018. Epub 2012 Jul 20. PubMed PMID: 22819864.
17. **Leonardi F, Maria N, Villa E.** Anticoagulation in cirrhosis: a new paradigm? *Clin Mol Hepatol.* 2017 Mar;23(1):13-21. doi: 10.3350/cmh.2016.0110. Epub 2017 Mar 14. Review. PubMed PMID: 28288507; PubMed Central PMCID: PMC5381832.
18. **De Santis A, Moscatelli R, Catalano C, Iannetti A, Gigliotti F, Cristofari F, Trapani S, Attili AF.** Systemic thrombolysis of portal vein thrombosis in cirrhotic patients: a pilot study. *Dig Liver Dis.* 2010 Jun;42(6):451-5. doi: 10.1016/j.dld.2009.08.009. Epub 2009 Oct 12. PubMed PMID: 19819770.
19. **Intagliata NM, Henry ZH, Maitland H, Shah NL, Argo CK, Northup PG, Caldwell SH.** Direct Oral Anticoagulants in Cirrhosis Patients Pose Similar Risks of Bleeding When Compared to Traditional Anticoagulation. *Dig Dis Sci.* 2016 Jun;61(6):1721-7. doi: 10.1007/s10620-015-4012-2. Epub 2016 Jan 2. PubMed PMID:26725062.
20. **Yang H, Kim SR, Song MJ.** Recurrent acute portal vein thrombosis in liver cirrhosis treated by rivaroxaban. *Clin Mol Hepatol.* 2016 Dec;22(4):499-502. doi: 10.3350/cmh.2016.0016. Epub 2016 Nov 25. PubMed PMID: 27880998; PubMed Central PMCID: PMC5266341.
21. **Nery F, Valadares D, Morais S, Gomes MT, De Gottardi A.** Efficacy and Safety of Direct-Acting Oral Anticoagulants Use in Acute Portal Vein Thrombosis Unrelated to Cirrhosis. *Gastroenterology Res.* 2017 Apr;10(2):141-143. doi:10.14740/gr806w. Epub 2017 Apr 19. PubMed PMID: 28496539; PubMed Central PMCID: PMC5412551.
22. **Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kam CW, Kamphuisen PW, Kreuzer J, Levy JH, Royle G, Sellke FW, Stangier J, Steiner T, Verhamme P, Wang B, Young L, Weitz JI.** Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. *N Engl J Med.* 2017 Aug 3;377(5):431-441. doi: 10.1056/NEJMoa1707278. Epub 2017 Jul 11. PubMed PMID: 28693366.
23. **Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, Mathur VS, Castillo J, Bronson MD, Leeds JM, Mar FA, Gold A, Crowther MA.** Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *N Engl J Med.* 2015 Dec 17;373(25):2413-24. doi: 10.1056/NEJMoa1510991. Epub 2015 Nov 11. PubMed PMID: 26559317.

Submitted May 22, 2018