

CLINICAL VIGNETTE

Recurrent Thromboses in Polycythemia Vera

Susan D. Leonard, MD

Case Report

A 75-year-old female with history of hypertension and polycythemia vera was evaluated for recurrent right leg pain and swelling. She was found to have right leg deep vein thrombosis (DVT). The patient had history of prior right leg DVT several years ago, thought to be provoked by immobilization after surgery. She was adequately treated for 6 months with resolution of the clot on repeat ultrasound. The patient did not smoke, take hormone therapy or have any known history of malignancies. This time, there were no provoking factors, such as prolonged immobility or recent surgery. Hypercoagulable workup and age-appropriate cancer screening remained negative. Her polycythemia vera had been managed closely by her hematologist, with monthly blood count monitoring and phlebotomy as needed to keep her hematocrit less than 45. Further questioning revealed that although she was supposed to take hydroxyurea regularly, she had not been compliant for the last few months due to difficulty getting this medication filled. She was anticoagulated appropriately for her DVT and was advised to continue long-term anticoagulation given her recurrent history and risk. She also continued phlebotomy therapy and was advised to remain compliant with hydroxyurea. Since then, she has not had further recurrence of any thrombotic events.

This case illustrates an example of polycythemia increasing the risk for thrombosis. The background, risks, prevention and management will be reviewed and discussed to evaluate the recommended treatment options for this category of conditions.

Discussion

Essential thrombocythemia and polycythemia vera are chronic myeloproliferative disorders characterized by proliferation of blood precursors, causing increased production of erythrocytes, leukocytes and platelets.¹ This can increase viscosity and microcirculatory disturbances, leading to increased risk for arterial and venous thromboembolism.² An estimated 30-50% of patients with polycythemia vera have some form of thrombotic complications, which correlates with higher vascular mortality.³

The presence of the Janus Kinase 2 (JAK2) gene mutation can increase thrombotic phenomenon and complications. Patients with the mutation generally present with higher erythrocytes and leukocytes and bone marrow hypercellularity.⁴ Also, those with the mutation have higher expression of surface tissue

factor and fibrinogen with a tendency to form higher leukocyte-platelet aggregates. Myelosuppressive drugs such as hydroxyurea, are advised to help to reduce thrombotic events.⁵ Additionally, certain hematologic variables and lifestyle habits can increase thrombotic risk with risk significantly increased by smoking and with leukocytosis over 15.⁶

A retrospective multicenter cohort study looked at patients with polycythemia and prior arterial or venous thrombosis.⁷ Thrombosis occurred from cerebrovascular disease, acute coronary syndrome, peripheral arterial thrombosis and venous thromboembolism. The study concluded that cytoreductive agents protected against recurrent thrombosis, especially in those after acute coronary syndrome. Oral anticoagulants were advised after venous thromboembolism and antiplatelet agents after cerebrovascular disease for further protective effects.⁷

Another multicenter prospective study evaluated over 1600 patients from 12 countries, looking at various outcomes: survival, rate of cardiovascular death and thrombosis, and rate of leukemia and myelodysplasia. Age older than 65 years and a prior history of thrombosis were positive predictors for cardiovascular events. Antiplatelet and cytoreductive agents reduced the risk. Older age correlated with higher risk for leukemia and longer duration of the disease was associated with higher risk for myelodysplasia.³

Regarding treatment, therapeutic and preventive strategies have improved outcomes and survival. Treatment modalities are aimed at reducing the risk of thrombotic events as well as treating existing complications. For venous thrombosis in polycythemia, treatment is similar to other cases of thrombosis, but with careful attention to primary and secondary prevention. Therapy agents may include aspirin, phlebotomy, and cytoreductive medications such as hydroxyurea, as well oral anticoagulation for cases of known thrombosis.

A primary goal of therapy in polycythemia is to prevent thrombotic events while avoiding hemorrhagic complications. Patients should be risk stratified based on their risk for thrombosis.⁸ Low risk patients include those less than 60 years old who have had no thrombosis, no cardiovascular risk factors, and whose platelets are $< 1,500 \times 10^9/L$. These individuals can be continued on phlebotomy alone or phlebotomy with low dose aspirin, unless contraindicated by bleeding or gastric side effects. One study showed that low aspirin dose helped to

reduce risk of fatal thrombotic events and mortality, although the reduction was not statistically significant. The study also did not find any increased risk in major bleeding with low dose aspirin therapy.⁹ Intermediate risk patients are those less than 60 years old, with no prior thrombosis history, but have platelet counts $>1,500 \times 10^9/L$, or with cardiovascular risk factors. Treatment includes addressing the cardiovascular risk factors, along with phlebotomy or with IFN-alpha. High risk patients include those who are over 60 years old with a prior history of thrombosis. Treatment should include phlebotomy to keep hematocrit $<45\%$, and cytoreductive therapy with hydroxyurea. If patients are intolerant or refractory to hydroxyurea, IFN-alpha can be used as the second-line drug. In addition, oral anticoagulation should be initiated if there is current or recurrent thrombosis. It is important to balance the thrombotic risk with the hemorrhagic risk with certain treatments. Moreover, due to the common link between JAK mutations and myeloproliferative disorders, recent advancements in treatment include JAK inhibitors. The JAK2 inhibitor ruxolitinib has been approved for those who have failed treatment with hydroxyurea.¹⁰

Conclusion

Polycythemia vera and essential thrombocythemia are myeloproliferative neoplasms that generally follow an indolent course. However, thromboses are complications of polycythemia and constitute the major cause of morbidity and mortality. Prior thrombosis is a well-known risk factor for re-thrombosis. Advanced age and history of thrombosis are significant risk factors for vascular complications and thrombotic manifestations.⁷ Furthermore, the JAK mutation and other biomarkers may have a strong association with the development of thrombosis. After an event, the incidence of recurrence in MPN remains elevated, which requires primary and secondary prophylaxis. Therapy options include aspirin, phlebotomy, hydroxyurea and other cytoreductive agents, as well as oral anticoagulants for current thrombosis. Treatment is based on risk stratification and balancing the thrombotic versus hemorrhagic events. There are also newer therapeutic agents including JAK2 inhibitors in different stages of clinical testing and development.

This case is an example of a patient with recurrent thromboses with need for ongoing prophylactic management based on risk stratification. She met criteria for high risk based on older age and prior thrombosis and required both phlebotomy and cytoreductive therapy with hydroxyurea. However, due to noncompliance with hydroxyurea, she remained at increased risk for recurrent thrombotic events. Since resuming hydroxyurea consistently, continuing phlebotomy to maintain hematocrit <45 , as well as appropriately treating her clot burden with oral anticoagulation, she has not had a recurrence or thrombotic complications. Further investigation on treatment recommendations is needed to understand the risks and benefits of various therapeutic modalities in the management of recurrent thromboses and myeloproliferative disorders.

REFERENCES

1. **Tefferi A.** Pathogenetic mechanisms in chronic myeloproliferative disorders: polycythemia vera, essential thrombocythemia, agnogenic myeloid metaplasia, and chronic myelogenous leukemia. *Semin Hematol.* 1999 Jan;36(1 Suppl 2):3-8. Review. PubMed PMID: 9930550.
2. **Landolfi R, Marchioli R, Patrono C.** Mechanisms of bleeding and thrombosis in myeloproliferative disorders. *Thromb Haemost.* 1997 Jul;78(1):617-21. Review. PubMed PMID: 9198226.
3. **Marchioli R, Finazzi G, Landolfi R, Kutti J, Gisslinger H, Patrono C, Marilus R, Villegas A, Tognoni G, Barbui T.** Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. *J Clin Oncol.* 2005 Apr 1;23(10):2224-32. Epub 2005 Feb 14. PubMed PMID: 15710945.
4. **Campbell PJ, Scott LM, Buck G, Wheatley K, East CL, Marsden JT, Duffy A, Boyd EM, Bench AJ, Scott MA, Vassiliou GS, Milligan DW, Smith SR, Erber WN, Bareford D, Wilkins BS, Reilly JT, Harrison CN, Green AR; United Kingdom Myeloproliferative Disorders Study Group; Medical Research Council Adult Leukaemia Working Party; Australasian Leukaemia and Lymphoma Group.** Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. *Lancet.* 2005 Dec 3;366(9501):1945-53. PubMed PMID: 16325696.
5. **Finazzi G, Rambaldi A, Guerini V, Carobbo A, Barbui T.** Risk of thrombosis in patients with essential thrombocythemia and polycythemia vera according to JAK2 V617F mutation status. *Haematologica.* 2007 Jan;92(1):135-6. PubMed PMID: 17229651.
6. **Landolfi R, Di Gennaro L, Barbui T, De Stefano V, Finazzi G, Marfisi R, Tognoni G, Marchioli R; European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP).** Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. *Blood.* 2007 Mar 15;109(6):2446-52. Epub 2006 Nov 14. PubMed PMID: 17105814.
7. **De Stefano V, Za T, Rossi E, Vannucchi AM, Ruggeri M, Elli E, Micò C, Tieghi A, Cacciola RR, Santoro C, Gerli G, Vianelli N, Guglielmelli P, Pieri L, Scognamiglio F, Rodeghiero F, Pogliani EM, Finazzi G, Gugliotta L, Marchioli R, Leone G, Barbui T; GIMEMA CMD-Working Party.** Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. *Haematologica.* 2008 Mar;93(3):372-80. doi: 10.3324/haematol.12053. Epub 2008 Feb 11. PubMed PMID: 18268279.
8. **Tefferi A, Barbui T.** Polycythemia vera and essential thrombocythemia: 2017 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2017 Jan;92(1):94-108. doi: 10.1002/ajh.24607. PubMed PMID: 27991718.

9. **Squizzato A, Romualdi E, Passamonti F, Middeldorp S.** Antiplatelet drugs for polycythaemia vera and essential thrombocythaemia. *Cochrane Database Syst Rev.* 2013 Apr 30;(4):CD006503. doi: 10.1002/14651858.CD006503.pub3. Review. PubMed PMID: 23633335.
10. **McMullin MF, Wilkins BS, Harrison CN.** Management of polycythaemia vera: a critical review of current data. *Br J Haematol.* 2016 Feb;172(3):337-49. doi: 10.1111/bjh.13812. Epub 2015 Oct 22. Review. PubMed PMID: 26492433.