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CASE STUDY

Complicated Lower Extremity Wound Caused by Immune Thrombocytopenic Purpura Leading to Hypercoagulable State: A Team Approach for Limb Salvage

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Abstract This article describes a complicated lower extremity wound due to hypercoagulable state caused by immune thrombocytopenic purpura. A team approach was important to limb salvage. A literature review is included.

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Introduction

Immune-mediated thrombophilias, the most common being secondary to antiphospholipid syndrome, can present clinically in various forms. One clinical presentation may be venous thromboembolism. Patients found to be hypercoagulable are at risk for developing recurrent thromboses, thrombocytopenia, and lower extremity wounds requiring a comprehensive approach by various specialties.

The degree of wounds may range from purpura to complicated necrotic wounds. Chronic immune thrombocytopenic purpura (ITP) alone represents a particular

challenge in the setting of wound care. The immune-mediated platelet destruction seen in ITP is a complex disease process involving all areas of the immune response.

Coordination of treatment between hematology, oncology, and the wound care specialist is required for comprehensive patient care. The following case discusses a patient with antiphospholipid syndrome and chronic ITP, presenting with recurrent deep venous thrombosis (DVT) and pulmonary embolisms and significant limb-threatening lower extremity necrosis.

Case Report

The patient is a 57-year-old man with a past medical history of recurrent thromboses. He was initially diagnosed with a pulmonary embolism in 1991. The patient

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subsequently experienced another pulmonary embolism in 1995, with inferior vena cava filter placement in 1997. Hypercoagulable workup at that time revealed positive lupus anticoagulant. The patient presented to the hematologist in 2007 for consultation regarding his hypercoagulable state. At the time of presentation, patient was therapeutic on warfarin treatment. Other diagnoses for the patient at the time of consultation included known peripheral vascular disease, as well as Addison's disease. Family medical history includes 2 sisters and 1 brother having splenectomies for unknown reason.

After initial consult with the hematologist, the patient experienced recurrent thrombosis of the left leg despite international normalized ratio (INR) being therapeutic at 2.2. The patient underwent a thrombectomy twice by the vascular surgeon for the treatment of his DVTs, followed by venous bypass surgery due to recurrent thromboses.

The initial hematological workup included the following laboratory results: white blood cell, $7.6 \times 10^3/\mu\text{L}$; hemoglobin, 13.4 g/dL; mean corpuscular volume, 91.3 fL; platelet count, $101 \times 10^3/\mu\text{L}$; prothrombin time, 46.4 seconds; with INR 3.5 (on warfarin) and PTTa, 47.6 seconds. Serum protein electrophoresis was within normal limits.

Serum urea nitrogen was 36 seconds, and creatinine was 1.4 seconds. Patient was found to be negative for prothrombin and Leiden gene mutation. Antithrombin III was not low; homocysteine level was high at $12.7 \mu\text{mol/L}$, but methylenetetrahydrofolate reductase DNA analysis was negative (normal). Phospholipid antibodies were as follows: cardiolipin immunoglobulin G antibodies (IgG AB), 73.6; cardiolipin IgM AB, 6.6; cardiolipin IgA AB, 26.4; phosphatidylserine IgG, 258.7; phosphatidylserine IgM, 8.6; phosphatidylserine IgA, 21.5; beta-2 glycoprotein IgG, 165.5; beta-2 glycoprotein IgM, 13.2; beta-2 glycoprotein IgA 283.3; antiprothrombin AB IgG, 1.9; and IgM, 11.0 (recommend listing normal parameters for each of these tests). Protein C, S, and lupus anticoagulant could not be evaluated because the patient was on a therapeutic level of warfarin.

After a complete workup, the patient was placed on fondaparinux at 7.5 mg subcutaneous daily, and warfarin was discontinued. While on fondaparinux, the patient did not experience any further thromboses. However, the patient did experience thrombocytopenia. Initial platelet count was $101 \times 10^3/\mu\text{L}$ prior to starting therapy. After initiation of new anticoagulant, the clinical course was complicated by thrombocytopenia that was variable in nature. Ultimately, the platelet count decreased to $40 \times 10^3/\mu\text{L}$. Further testing showed the patient to be AB IgG positive. ITP was the presumed diagnosis. At this time, the patient was concurrently being treated for leg soft tissue necrosis under the care of plastic surgery (Figure 1). After clear demarcation of his leg tissue necrosis, the patient was taken to the operating room for surgical debridement of his necrotic leg wound and the application of allografts to provide biological dressing and allow stabilization of his condition.

Figure 1 Immune Thrombocytopenic Purpura Leading to Left Calf Necrosis at Presentation.

Tissue necrosis involved subcutaneous tissue and muscles, mainly the gastrocnemius muscle. Because of his low platelet count, platelets were transfused preoperatively to prevent massive bleeding. Six weeks later and once stable, he returned to the operating room for further debridement of previously applied allografts, and autologous split skin grafts were applied for permanent coverage. A small area of skin graft loss was noticed postoperatively and was treated conservatively with daily dressing changes using collagenase ointment and a protective dressing wrap (Figure 2). During his recovery time, the patient underwent 20 treatments of hyperbaric oxygen therapy to support his potentially compromised tissue and maximize viability of the skin graft and the underlying wound bed. Stress-dose steroids were initiated because of the underlying Addison's disease.

Postoperatively, he was treated with rituximab at 500 mg/kg twice, resulting in negative indirect platelet AB (IgG). However, the measured platelet count was only $58 \times 10^3/\mu\text{L}$. The patient was then given intravenous immunoglobulin (IVIG) for the treatment of ITP refractory to rituximab.

Figure 2 Healing Left Leg Wound After Skin Grafting, With a Small Area of Graft Loss.

Figure 3 Healed Right Leg and Limb Salvage.

With treatment, the platelet count increased to $177 \times 10^3/\mu\text{L}$ for a short time, then decreased to $56 \times 10^3/\mu\text{L}$ months later. After a second IVIG treatment, the platelet count increased to $119 \times 10^3/\mu\text{L}$ but then decreased again, to $63 \times 10^3/\mu\text{L}$, just 4 weeks later. After the third dosing of IVIG, platelet counts increased to $123 \times 10^3/\mu\text{L}$ and have continued to be variable throughout his course, but generally above $85 \times 10^3/\mu\text{L}$. Currently, the patient has remained stable off warfarin and on fondaparinux. As the patient was now off warfarin, we tested him for lupus anticoagulant and found him to have a positive test for it. His wounds finally healed, with salvage of threatened limb, after 2 years of an aggressive multidisciplinary approach (Figure 3).

Discussion

ITP is an disorder whose etiology is still unclear. Currently, it is thought that ITP is a combination of acquired and genetic factors.^{1,2} It appears that some cases of ITP are seen following viral infections including acute as well as chronic infections.³ Other chronic diseases that cause abnormalities of the immune system, such as antiphospholipid syndrome, Evans syndrome, and lymphocytic leukemia, among others, are associated with ITP and may be a predisposing factor.

The pathophysiology of ITP involves increased platelet destruction and inhibiting megakaryocyte platelet production. IgG autoantibodies are produced by the patient's B cells. These autoantibodies are often directed against membrane glycoproteins of the platelet. The platelets with their associated autoantibody are then phagocytosed by macrophages in the spleen.

ITP is a diagnosis of exclusion based on the presence of isolated thrombocytopenia and the absence of other associated causes. The diagnosis is made with a complete history and physical exam, complete blood count, and peripheral

blood smear review. Testing for human immunodeficiency virus and hepatitis C are further diagnostic testing that may be necessary for those patients at risk. Thyroid function tests should be performed before splenectomy in order to rule out thyroid abnormalities. In patients older than 60 years and who have poorly responded to initial treatment, a bone marrow aspirate should be performed to rule out myelodysplastic syndrome. Once ITP is suspected, hematologic consultation should be requested, especially if there is evidence of bleeding.^{4,5}

This article has described a case in which a patient experienced a chronic hypercoagulable state with antiphospholipid syndrome⁶ and recurrent thrombosis while therapeutic on warfarin. His clinical course was complicated by the development of lower extremity necrotic wounds involving skin, subcutaneous tissue, and calf muscles. This was because of myocutaneous bleeding associated with mild to severe thrombocytopenia and normal bone marrow aspirate. The patient was diagnosed with ITP.

Differential diagnosis includes those disorders that also develop isolated thrombocytopenia. Disseminated intravascular coagulation or thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome can be mistaken for ITP. However, these are often associated with other cell line abnormalities, including schistocytes and coagulation abnormalities not present in ITP.⁷ Gestational thrombocytopenia is considered with the onset of thrombocytopenia (less than 70,000) during late gestation, in patients without history of thrombocytopenia, absence of fetal thrombocytopenia, and with resolution after delivery without treatment.² Gestational thrombocytopenia and ITP are typically indistinguishable till after delivery. Drug-induced thrombocytopenia is also difficult to distinguish initially from ITP. Many drugs, including alemtuzumab and purine analogs, have been linked to ITP. Resolution of thrombocytopenia is noted on drug cessation.⁸ Infections including viral as well as bacterial infections can cause thrombocytopenia, and therefore acute and chronic infections should be ruled out before the diagnosis of ITP is presumed.⁹ Hypersplenism secondary to portal hypertension and liver disease can be a cause of thrombocytopenia from pooling of the platelets in the splenic sinusoids.¹⁰ However, other signs of portal hypertension are present, along with a palpable spleen, which is not present with ITP. Myelodysplastic syndrome may initially present with thrombocytopenia in the elderly and may warrant a bone marrow aspirate.¹¹ In those patients who show no signs of improvement with treatment, causes of congenital, familial thrombocytopenia should be considered, including, but not limited to, von Willebrand disease type 2B, Wiskott-Aldrich syndrome, Alport syndrome, and Bernard-Soulier syndrome.^{12,13,14} Acquired pure megakaryocytic aplasia is rare and is clinically indistinguishable from ITP. Bone marrow examination shows the absence of megakaryocytes and is necessary for the diagnosis.

Chronic ITP is seen most often in adulthood, and it must persist for at least 6 months with the exclusion of other

causes of thrombocytopenia. The annual incidence is estimated to be from 1 in 1,000 to 1 in 10,000, with a female-to-male ratio of approximately 2 or 3 to 1.¹⁵ The disease process involving chronic ITP includes both the cellular and humoral immune response.¹⁶ Autoimmune mechanisms include secretion of antiplatelet antibodies, autoreactive T cells, cytotoxicity mediated by T cells, and activation of natural killer cells.¹⁶ Impaired production of platelets is also involved in ITP.¹⁶ Megakaryopoiesis and thrombopoiesis are impaired by autoantibodies as well as dysregulation of thrombopoietin.

Currently, the treatments for chronic ITP include corticosteroids, rituximab, cytotoxic chemotherapy, and immune globulin medications. It is recommended that therapy should begin with corticosteroids as the first line. In those with refractory disease, intravenous methylprednisolone, IVIG, or anti-D immunoglobulin are other available options.¹⁵ Splenectomy is recommended for patients with chronic ITP who do not respond to these treatments.¹⁵ According to initial studies, additional therapies for refractory ITP in the future may include etanercept, anti-CD40 ligand, mycophenolate mofetil, recombinant human thyroid peroxidase (TPO) preparations, and TPO receptor agonists.¹⁷

In the patient described, the initial treatment included rituximab. However, the therapy was changed to IVIG because the patient did not respond to rituximab. In our case, fondaparinux was very effective in preventing further thrombosis. Thrombocytopenia is a rare side effect of fondaparinux. The patient had thrombocytopenia prior to treatment initiation with fondaparinux, so there is less likelihood for this patient to have thrombocytopenia secondary to fondaparinux. The patient also received stress-dose steroids because of underlying Addison's disease.

Studies show that patients with venous disease of the lower limb have an increased prevalence of thrombophilia compared with patients of similar age and sex.¹⁶ The development of venous disease, including chronic venous insufficiency, venous ulceration, or even varicose veins, ultimately results from venous hypertension. Patients with the diagnosis of DVT, as in this patient, are particularly prone to venous insufficiency and ulceration secondary to postthrombotic syndrome involving venous reflux and obstruction.¹⁶ Macrovascular and microvascular thrombosis play an important role in the development of chronic venous insufficiency. Patients with thrombophilia alone are predisposed to developing extensive and recurrent DVTs.¹⁶

Clinically, it is important to recognize those patients with thrombophilia because it has been shown to be an important risk factor in the development of chronic venous insufficiency leading to chronic ulceration.

A team approach to this complicated condition is important for treatment and positive outcome. In this case

hematology, vascular surgery, plastic surgery, wound care, and hyperbaric oxygen therapy were all instrumental in the patient's limb salvage. Preventing a recurrent acute episode of ITP was managed by hematology. Keeping his veins patent with the input of vascular surgery or intervention radiology was also important. Removing his necrotic tissue and grafting his wounds to achieve healing and prevent infection and further necrosis were achieved with the input of plastic surgery, wound care, and hyperbaric oxygen therapy specialists. This case emphasizes the importance of a team approach in the treatment of complex wounds that are life and limb threatening.

References

1. Cooper N, Bussel J: The pathogenesis of immune thrombocytopenic purpura. *Br J Haematol.* 2006;133:364–374.
2. George JN, Woolf SH, Raskob GE, et al: Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood.* 1996;88:3–40.
3. Cines DB, Bussel JB, Liebman HA: Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. *Blood.* 2009;113:6511–6521.
4. Cines DB, Blanchette VS: Immune thrombocytopenic purpura. *N Engl J Med.* 2002;346:995–1008.
5. Nugent D, McMillan R, Nichol JL, Slichter SJ: Pathogenesis of chronic immune thrombocytopenia: increased platelet destruction and/or decreased platelet production. *Br J Haematol.* 2009;146:585–596.
6. Robertson B, Greaves M: Antiphospholipid syndrome: an evolving story. *Blood Rev.* 2006;20:201–212.
7. George JN: Clinical practice: thrombotic thrombocytopenic purpura. *N Engl J Med.* 2006;354:1927–1935.
8. George JN, Raskob GE, Shah SR, et al: Drug induced thrombocytopenia: a systemic review of published case reports. *Ann Intern Med.* 1998;129:886–890.
9. Stasi R, Willis F, Shannon MS, Gordon-Smith EC: Infectious causes of chronic immune thrombocytopenia. *Hematol Oncol Clin North Am.* 2009;23:1275–1297.
10. Aster RH: Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombocytopenia. *J Clin Invest.* 1966;45:645–657.
11. Najean Y, Lecompte T: Chronic pure thrombocytopenia in elderly patients: an aspect of the myelodysplastic syndrome. *Cancer.* 1989;64:2506–2510.
12. Drachman JG: Inherited thrombocytopenia: when a low platelet count does not mean ITP. *Blood.* 2004;103:390–398.
13. Mhawech P, Saleem A: Inherited giant platelet disorders: classification and literature review. *Am J Clin Pathol.* 2000;113:176–190.
14. Najean Y, Lecompte T: Genetic thrombocytopenia with autosomal dominant transmission: a review of 54 cases. *Br J Haematol.* 1990;74:203–208.
15. Pruemer J: Epidemiology, pathology and initial management of chronic immune thrombocytopenic purpura. *Am J Health Syst Pharm.* 2009;66(suppl 2):4–10.
16. Darvall KA, Sam RC, Adam DJ, Silverman SH, Fegan CD, Bradbury AW: Higher prevalence of thrombophilia in patients with varicose veins and venous ulcers than controls. *Journal of Vasc Surg.* 2009;45(5):1235–1241.
17. Gernsheimer T: Chronic idiopathic thrombocytopenic purpura: mechanisms of pathogenesis. *Oncologist.* 2009;14:12–21.