Systemic Lupus Erythematosus, Immune Thrombocytopenic Purpura, and Autoimmune Hemolytic Anemia

Natacha Esber, M.D.[1], Katherine Howle, M.D.[1], Sylvia Orozco-Do, M.D.[1], Phu Truong, M.D.[1,2], Michael E. Grant, M.D. [1,3], Timothy Shaver, M.D.[1,4]
[1]University of Kansas School of Medicine-Wichita Department of Internal Medicine
[2]Cancer Center of Kansas, Wichita, KS
[3]Wichita Nephrology Group, Wichita, KS
[4]Arthritis Rheumatology Clinics of Kansas, Wichita, KS

Introduction

Thrombocytopenia in patients with acute systemic lupus erythematosus (SLE) frequently presents to the clinician with considerable diagnostic and therapeutic difficulties. SLE patients with thrombocytopenia are more likely to have significant organ damage such as in the heart, kidneys, or the central nervous system.[1]

Case Report

A 62-year-old Vietnamese woman was admitted to the hospital with a one-month history of high-grade fever (up to 104°F), decreased appetite, nausea, postprandial vomiting, and worsening abdominal pain. She previously had two days of mucus-like diarrhea. Her past medical history included primary hypothyroidism.

This patient visited Vietnam on a number of occasions, most recently returning two months prior to admission after a six-month stay. While in Vietnam, she developed fatigue. Upon her return to the US, she was progressively more tired and weak with diminished appetite. She reported progressive shortness of air beginning about four to five weeks prior to her hospital admission with associated chills, fever, severe diaphoresis, and a dry cough. She was given a week of antibiotic therapy at that time without relief.

Ten days prior to admission, she was admitted to another hospital, where an esophagogastroduodenoscopy and a *Camplyobacter*-like organism (CLO) test for *Helicobacter pylori* were negative. An echocardiogram revealed moderate mitral and mild tricuspid insufficiency and a normal ejection fraction of 51%. A CT scan of the abdomen and pelvis was negative. CT angiography of the chest revealed bibasilar scarring, pleural thickening, and atelectasis. She had scattered axillary lymph nodes at the upper limits of normal size (right greater than left), breast nodules, and a positive Antinuclear Antibody test (ANA). She was dismissed on acetaminophen, sucralfate, and a proton pump inhibitor with recommendations for outpatient colonoscopy and follow-up with her primary care physician. Her symptoms persisted and increased over a one-week period. Thus, she presented at our hospital.

At the time of admission, she was pyrexial (100.6°F) and tachycardic (105 beats per minute). Her respiratory rate was 18, her oxygen saturation was 94% on room air, and her blood pressure was 153/93 mmHg. She had very dry mucous membranes with poor dentition. She had mild rhonchi on her right lower lobe with no wheezes or crackles. She had normal S1 and

S2 heart sounds with no murmur. Her abdomen was soft with positive bowel sounds. She had positive peripheral pulses without lower leg edema. She had a few small petechiae on her lower extremities.

The initial investigation revealed a normocytic anemia with a platelet count of 133,000. Over a few days, the platelets decreased to 21,000. She had a high erythrocyte sedimentation rate (ESR of 90), hematuria, proteinuria, a positive ANA (anti-histone, anti-Sm, and anti-Sjögren's syndrome A and B were high) along with a low C3 and C4, positive platelet antibodies, a positive direct Coomb's test, positive IgM and IgG for *Helicobacter pylori*, and a small pericardial effusion on the 2D echocardiogram.

During her hospitalization, she received the following medications:

- two pulse therapy IV methyl-prednisolone, 125mg every six hours for two days and 1g daily for three days,
- oral prednisone, 60mg daily,
- mycophenolate mofetil, 500mg twice daily,
- hydroxychloroquine, 200mg twice daily,
- intravenous immunoglobulin (IVIG), 400mg/kg for five days,
- rituximab, three doses,
- triple therapy for *H. pylori* (clarithromycin, amoxicillin, and a proton pump inhibitor),
- iron IV, 4 doses,
- erythropoietin, 10,000 IU subcutaneous three times per week,
- sulfamethoxazole and trimethoprim, double strength three times per week, for pneumocystis carinii prophylaxis (started after thrombocytopenia).
- tube feeding.

After administration of steroids, the fever resolved. Her hospital stay was marked by one episode of volume overload, following the transfusion of two packed red bloods cells, which resolved with diuretics.

The patient's course was complicated by hemoptysis, attributed both to underlying thrombocytopenia and lupus-related alveolar hemorrhage. A bronchoscopy revealed a diffuse alveolar hemorrhage. The bronchial washing was negative for *Pneumocystis carinii* pneumonia; a fungal culture revealed a small amount of candida. She received platelet transfusions and a Bilateral Positive Airway Pressure device. The urine culture grew *Escherichia coli* and she was treated with ciprofloxacin.

Twenty-five days after admission, the patient was discharged home in stable condition with no hemoptysis and decreased of shortness of air. Thrombocytopenia had stabilized. The diffuse alveolar hemorrhage on chest x-ray and perimyocarditis on 2D echo were stable and unchanged. She was discharged on 60mg/day of prednisone, 500mg of mycophenolate mofetil daily with a plan to increase the dose to twice daily, hydroxychloroquine sulfate 200mg twice daily, a fourth dose of rituximab, erythopoetin 10,000 IU subcutaneous three times per week, and pioglitazone hydrochloride 15mg daily with diabetic education for steroid-induced hyperglycemia. One month after receiving her fourth dose of rituximab and while taking prednisone 40mg/day, her platelet count had risen to 150,000.

Discussion

Diagnostic issues. Our patient satisfied 5 of 11 American College of Rheumatology criteria for systemic lupus erythematosus (4 or more being required for a diagnosis).[2] Conventional laboratory markers (a raised ESR and C-reactive protein hypocomplementemia, high-titer ANA, and multi-organ damage) indicated that her lupus was active at the time of presentation with her acute illness.[3-5]

A severe immune thrombocytopenic purpura (ITP) was associated with her lupus. She had no history of drug-induced

thrombocytopenia, and a negative blood smear and bone marrow biopsy. Other causes of thrombocytopenia (HIV, HCV) also were negative. She also had positive antiplatelet antibodies.[6,7]

Several potential causes of thrombocytopenia in patients with SLE are noted. The major mechanism is immunoglobulin binding to platelets followed by phagocytosis in the spleen, as in ITP.[8] Membrane glycoproteins (GP) are most often the target of such antibodies (e.g., GP IIb/IIIa), but anti-HLA specificity also occurs.[9] Antigen-dependent B cell development in lymphoid tissues is influenced by binding of CD40 on B cells to CD40-ligand on activated T cells. The finding of autoantibodies to CD40-ligand in patients with SLE, ITP, and Antiphospholipid Antibody Syndrome, but not in the serum of healthy blood donors suggests that interference with T cell and B cell interaction may play a role in the development of thrombocytopenia.[10] SLE patients with thrombocytopenia are more likely to have associated significant organ damage to the heart, kidneys, and the central nervous system.[1]

An autoimmune hemolytic anemia (AIHA) can be associated with SLE and ITP.[11] Our patient had a high LDH and a positive direct Coomb's test, but she did not have low haptoglobin and her peripheral blood smear did not show spherocytosis.[12] The possibility of Evans syndrome also was suggested with both autoimmune thrombocytopenia and autoimmune hemolytic anemia, which may precede the onset of SLE[5], but our patient presented simultaneously with SLE, ITP, and possible AIHA.

Implications for treatment. Among patients with co-existent SLE and ITP reported in the literature, the most commonly employed treatment was prednisone (1 mg/kg per day in divided doses).[13,14] Most patients responded within one to eight weeks.[15] High-dose dexamethasone and high-dose methylprednisolone also are being investigated.[16-19] If there is no significant increase in the platelet count within one to three weeks or side effects are intolerable, the following options may be considered. The order in which they are used depends in part upon the severity of the thrombocytopenia and the presence or absence of other manifestations of SLE.

1. Azathioprine (0.5 to 2 mg/kg per day).[15]
2. Cyclophosphamide, given as daily oral or intravenous pulse therapy. Intravenous pulse cyclophosphamide is preferred in patients who also have severe active lupus nephritis. In one report of six such patients, all had normal platelet counts within 2 to 18 weeks after the onset of pulse cyclophosphamide.[20]
3. Intravenous immunoglobulin. This treatment is effective and may be preferred to azathioprine or cyclophosphamide when a rapid rise in platelet count is necessary (as in the patient who is actively bleeding or requires emergent surgery).[21]
4. Mycophenolate mofetil. This treatment may be useful in the patient refractory to other medical therapy.[22] Due to the fact that our patient had proteinuria and an active urine sediment, but was not a candidate for renal biopsy due to thrombocytopenia, mycophenolate mofetil was chosen due to the published literature demonstrating efficacy in treating lupus nephritis.[19]
5. Rituximab 375 mg/m^2 IV approximately once weekly for four consecutive weeks.[23] Rituximab has been used to treat ITP in patients without SLE who were refractory to other treatments and this B lymphocyte depleting approach

may be beneficial for other manifestations of lupus.[24]

6. Splenectomy. Splenectomy can raise the platelet count, but it does not produce a durable remission of thrombocytopenia reliably. Relapse following splenectomy may occur and has been noted at varying times up to 54 months after surgery.[25] Patients with persistent thrombocytopenia after splenectomy subsequently may respond to azathioprine, cyclophosphamide, rituximab, IVIG, danazol[26,27], or vincristine[28].

Conclusion

In summary, our patient had active SLE with hypocomplementemia, ITP, and possible AIHA. Therapy with high-dose corticosteroids, mycophenolate mofetil, hydroxychloroquine, IVIG, and four doses of rituximab were effective in stabilizing her nephritis, perimyocarditis, transaminitis, and thrombocytopenia.

References

[1] Wheeler CA, Calhoun L, Blackall DP. Warm reactive autoantibodies: Clinical and serologic correlations. Am J Clin Pathol 2004; 122:680-685.

[2] Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25:1271-1277.

[3] Liang MH, Socher SA, Larson MG, Schur PH. Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum 1989; 32:1107-1118.

[4] Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002; 29:288-291.

[5] 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.

[6] Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). Blood 2005; 106:2244-2251.

[7] Pujol M, Ribera A, Vilardell M, Ordi J, Feliu E. High prevalence of platelet autoantibodies in patients with systemic lupus erythematosus. Br J Haematol 1995; 89:137-141.

[8] Michel M, Lee K, Piette JC, et al. Platelet autoantibodies and lupus-associated thrombocytopenia. Br J Haematol 2002; 119:354-358.

[9] Nakamura M, Tanaka Y, Satoh T, et al. Autoantibody to CD40 ligand in systemic lupus erythematosus: Association with thrombocytopenia but not thromboembolism. Rheumatology (Oxford) 2006; 45:150-156.

[10] Ziakas PD, Giannouli S, Zintzaras E, Tzioufas AG, Voulgarelis M. Lupus thrombocytopenia: Clinical implications and prognostic significance. Ann Rheum Dis 2005; 64:1366-1369.

[11] Marchand A, Galen RS, Van Lente F. The predictive value of serum haptoglobin in hemolytic disease. JAMA 1980; 243:1909-1911.

[12] Schur P, Berliner N. Hematologic manifestations of systemic lupus erythematosus in adults. http://www.uptodate.com/online/content/topic.do?topicKey=lupus/4726&selectedTitle=8~150&source=search_result. Accessed: January 12, 2009.

[13] Blanchette V, Freedman J, Garvey B. Management of chronic immune thrombocytopenic purpura in children and adults. Semin Hematol 1998; 35(1 Suppl 1):36-51.

[14] Goebel, KM, Gassel, WD, Goebel, FD. Evaluation of azathioprine in autoimmune thrombocytopenia and lupus erythematosus. Scand J Haematol 1973; 10:28-34.

[15] Boumpas DT, Barez S, Klippel JH, Balow JE. Intermittent cyclophosphamide for the treatment of autoimmune thrombocytopenia in systemic lupus erythematosus. Ann Intern Med 1990; 112:674-677.

[16] Borst F, Keuning JJ, van Hulsteijn H, Sinnige H, Vreugdenhil G. High-dose dexamethasone as a first- and second-line treatment of idiopathic thrombocytopenic purpura in adults. Ann Hematol 2004; 83:764-768.

[17] Mazzucconi MG, Fazi P, Bernasconi S, et al. Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura: A GIMEMA experience. Blood 2007; 109:1401-1407.

[18] Alpdogan O, Budak-Alpdogan T, Ratip S, et al. Efficacy of high-dose methylprednisolone as a first-line therapy in adult patients with idiopathic thrombocytopenic purpura. Br J Haematol 1998; 103:1061-1063.

[19] Kapitsinou P, Boletis J, Skopouli F, Boki KA, Moutsopoulos HM. Lupus nephritis: Treatment with mycophenolate mofetil. Rheumatology (Oxford) 2004; 43;377-380.

[20] Maier WP, Gordon DS, Howard RF, et al. Intravenous immunoglobulin therapy in systemic lupus erythematosus-associated thrombocytopenia. Arthritis Rheum 1990; 33:1233-1239.

[21] Vasoo S, Thumboo J, Fong KY. Refractory immune thrombocytopenia in systemic lupus erythematosus: Response to mycophenolate mofetil. Lupus 2003; 12:630-632.

[22] Looney RJ. B cell-targeted therapy in diseases other than rheumatoid arthritis. J Rheumatol Suppl 2005; 73:25-28.

[23] Braendstrup P, Bjerrum OW, Nielsen OJ, et al. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adult refractory idiopathic thrombocytopenic purpura. Am J Hematol 2005; 78:275-280.

[24] Hall S, McCormick JL Jr, Greipp PR, Michet CJ Jr, McKenna CH. Splenectomy does not cure the thrombocytopenia of systemic lupus erythematosus. Ann Intern Med 1985; 102:325-328.

[25] You YN, Tefferi A, Nagorney DM. Outcome of splenectomy for thrombocytopenia associated with systemic lupus erythematosus. Ann Surg 2004; 240:286-292.

[26] Vesely SK, Perdue JJ, Rizvi MA, Terrell DR, George JN. Management of adult patients with persistent idiopathic thrombocytopenic purpura following splenectomy: A systematic review. Ann Intern Med 2004; 140:112-120.

[27] Ahn YS, Harrington WJ, Seeman RC, Eytel CS. Vincristine therapy of idiopathic and secondary thrombocytopenias. N Engl J Med 1974; 291:376-380.

[28] Cheng Y, Wong RS, Soo YO, et al. Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. N Engl J Med 2003; 349:831-836.

Keywords: systemic lupus erythematosus, autoimmune thrombocytopenic purpura, autoimmune hemolytic anemia