

SYMPTOMS TO DIAGNOSIS

GREGORY W. RUTECKI, MD, Section Editor

Binoy Yohannan, MD

Division of Hematology/Oncology,
McGovern Medical School,
The University of Texas Health Science Center,
Houston, TX

Allen Omo-Ogboi, MD

Department of Pathology and Laboratory
Medicine, McGovern Medical School,
The University of Texas Health Science Center,
Houston, TX

Johncy John Kachira, MBBS

Department of Health Services Research,
The University of Texas MD Anderson Cancer
Center, Houston, TX

Harinder Juneja, MD

Division of Hematology/Oncology,
McGovern Medical School,
The University of Texas Health Science Center,
Houston, TX

Hematologic complications after kidney and pancreas transplant in a patient with chronic myeloid leukemia

A 35-YEAR-OLD WOMAN with a history of type 1 diabetes mellitus, diabetic retinopathy, and end-stage renal disease secondary to diabetic nephropathy underwent simultaneous pancreas and kidney transplant. She received induction therapy with thymoglobulin 100 mg and methylprednisolone 500 mg prior to her transplant. Maintenance immunosuppression consisted of tacrolimus, prednisone, and mycophenolate mofetil. One week after her transplant, she was noted to have hyperleukocytosis, with a white blood cell count of $80 \times 10^9/L$ (reference range 4–10). Her hemoglobin was 9.5 g/dL (12–16), and her platelet count was $440 \times 10^9/L$ (150–400).

1 Which of the following diagnostic tests would you order?

- ☐ Repeat complete blood cell count with differential count and peripheral blood smear
- ☐ Computed tomography of the chest, abdomen, and pelvis
- ☐ Bone marrow biopsy
- ☐ Skeletal survey

■ DIFFERENTIAL DIAGNOSIS

Leukemoid response secondary to infection, inflammation, asplenia, and certain medications should be considered in the differential diagnosis of a patient with hyperleukocytosis. Glucocorticoids and infections are common causes of leukocytosis in patients who have undergone organ transplant. A preliminary

evaluation should include a repeat complete blood cell count with differential count and peripheral blood smear. The differential count can provide helpful clues to the underlying etiology. If prior records are available, a review of previous complete blood cell counts is necessary to determine whether the hyperleukocytosis is new or a chronic process.

■ CASE CONTINUED

The differential count showed neutrophilia of $29 \times 10^9/L$ (1.5–8), eosinophilia of $0.8 \times 10^9/L$ (0–0.5), and basophilia of $0.8 \times 10^9/L$ (0–0.5). In addition, increases in promyelocytes at 2% (0%), myelocytes at 1% (0%), and metamyelocytes at 11% (0%–1%) were noted. The peripheral blood smear showed normocytic, normochromic red cells with polychromasia; marked neutrophilic leukocytosis with left shift; and normal platelet morphology. On review of the laboratory tests done 1 month prior to the transplant, the patient was noted to have had mild leukocytosis (white blood cell count $20 \times 10^9/L$), hemoglobin of 10.6 g/dL, and a platelet count of $281 \times 10^9/L$.

2 What is the most likely etiology of hyperleukocytosis?

- ☐ Parasitic infection
- ☐ Allergies
- ☐ Hypereosinophilia
- ☐ Chronic myeloid leukemia (CML)

In addition to neutrophilia, patients with eosinophilia and basophilia may have allergies, parasitic infection,

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or myeloproliferative neoplasm. Hypereosinophilia, defined as an absolute eosinophil count greater than $1.5 \times 10^9/L$, was not present in our patient. All cells of the neutrophilic series are usually present in CML. One of the classic findings of CML is a higher percentage of myelocytes than of metamyelocytes. More than 90% of patients with CML have absolute basophilia.¹ After excluding a leukemoid response and given the high clinical suspicion for a malignant process, we ordered specialized testing including flow cytometry, molecular testing, and bone marrow biopsy.

Fluorescence in situ hybridization testing on a peripheral blood sample showed p210 BCR-ABL1 fusion transcript. Results from a bone marrow biopsy showed hypercellular bone marrow for the patient's age (90%), with trilineage hematopoiesis. A polymerase chain reaction test done on a bone marrow sample showed a ratio of BCR-ABL1 to ABL1 of 100% using the National Institutes of Health international scale (IS) for measuring BCR-ABL1 transcripts, confirming a diagnosis of CML.² Cytogenetic analysis showed an abnormal female karyotype, with all cells (20/20 cells) exhibiting the translocation of chromosomes 9 and 22 that leads to fusion of the ABL1 and BCR genes. Our patient had only 1% blasts in the bone marrow. Based on the blood cell counts (basophils 0.8%), she was diagnosed with chronic-phase CML.

■ ASSOCIATION BETWEEN AUTOIMMUNITY, ORGAN TRANSPLANT, AND CML

CML is a clonal myeloproliferative disorder characterized by the BCR-ABL1 fusion gene that drives leukemogenesis.³ The CML phenotype may vary depending on the type of BCR-ABL1 fusion. The 3 common variants include p210 BCR-ABL1, p190 BCR-ABL1, and p230 BCR-ABL1. The most common variant is p210 BCR-ABL1, which results from a breakpoint in the major BCR region at exon e13 or e14 and fusion with ABL1 exon a2 to produce an e13a2 (b2a2) or e14a2 (b3a2) transcript of BCR-ABL1.³

Autoimmunity can increase the risk of myeloproliferative neoplasm. A population registry-based study from Sweden reported a higher prevalence of autoimmune diseases prior to the diagnosis of CML.⁴ Given her history of type 1 diabetes, our patient had evidence of organ-specific autoimmunity, and this could have played a role in the pathogenesis of CML. In addition, persons who receive a solid-organ transplant have a significantly higher risk of developing myeloid neoplasms, presumably from immune dysfunction.^{5,6}

Wu et al⁷ reported that the median interval from organ transplant to diagnosis of a myeloid neoplasm is around 56 months. Our patient was diagnosed with CML 3 weeks after renal transplant. However, based on the complete blood cell count and differential count done before transplant, there was a clear signal for an underlying CML. A more detailed and meticulous workup that included a peripheral blood smear should have been performed for unexplained leukocytosis. In the era of highly effective tyrosine kinase inhibitor therapy, patients with CML who achieve a molecular response have a normal life span. Further, a CML diagnosis should not exclude patients from receiving a lifesaving solid-organ transplant.

■ CASE CONTINUED

Six weeks after the diagnosis of CML, the patient was started on dasatinib 70 mg per day, and 6 months later she achieved a molecular response (BCR-ABL1/ABL1 ratio 0.06% IS). First-generation tyrosine kinase inhibitors such as imatinib and second-generation tyrosine kinase inhibitors such as dasatinib are appropriate first-line treatment options, but the second-generation inhibitors can achieve a faster and deeper molecular remission. The approved dasatinib dose in chronic-phase CML is 100 mg daily, although data show that even 50 mg daily is very effective and has a better safety profile.⁸ The 70-mg daily dosing in our patient was based on the treating physician's discretion and clinical judgment considering the patient's medical comorbidities.

Six years after the CML diagnosis, the patient presented with easy bruising and vaginal bleeding. On physical examination, her vital signs were stable. There was no evidence of bleeding from the oropharynx or nasopharynx. The cardiovascular and respiratory system examinations were normal. The abdominal examination revealed a well-healed surgical scar from her prior transplant. No hepatosplenomegaly was detected. The pelvic examination showed around 5 mL of blood in the vaginal vault without active bleeding from the cervix. The cervix appeared normal without any lesions, and there was no adnexal tenderness. The skin examination showed petechiae and ecchymosis over the abdominal wall and both arms and legs.

Routine laboratory tests showed a white blood cell count of $14 \times 10^9/L$, hemoglobin 11 g/dL, and platelet count $24 \times 10^9/L$. The patient denied any recent change in her medications or use of herbal supplements, over-the-counter medications, or Chinese medications. She had no history of chronic liver disease. She was advised

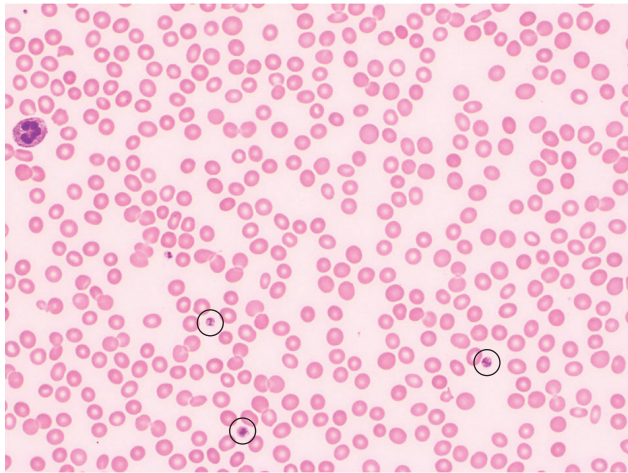


Figure 1. The peripheral blood smear shows giant platelets highlighted in black circles (hematoxylin and eosin, magnification x 400).

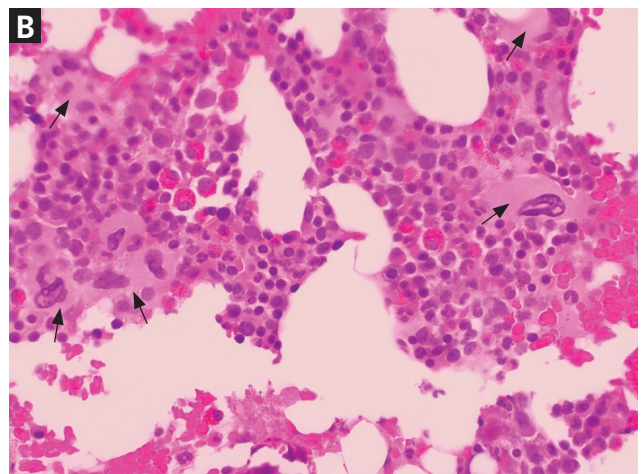
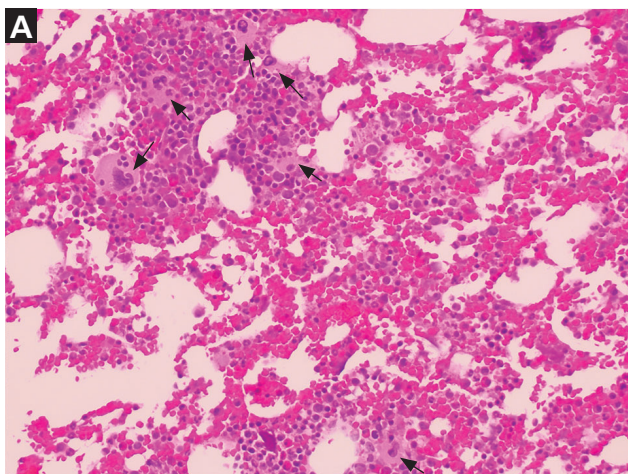
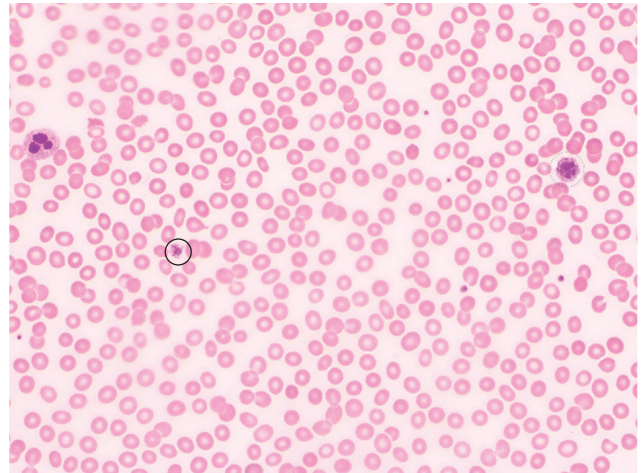


Figure 2. Bone marrow biopsy shows increased megakaryopoiesis indicated by black arrows at magnification x 200 (panel A) and at magnification x 400 (panel B).

to stop dasatinib because of her unexplained thrombocytopenia. A repeat complete blood cell count done 1 week later showed a platelet count of $6 \times 10^9/L$, hemoglobin 11 g/dL, and white blood cell count $6 \times 10^9/L$. Her coagulation profile (prothrombin time, international normalized ratio, partial thromboplastin time, fibrinogen, and dimerized plasmin fragment D) was normal. A peripheral blood smear showed normochromic normocytic anemia with slight polychromasia, no increase in schistocytes, and marked thrombocytopenia with giant platelets (**Figure 1**).

She was hospitalized for further evaluation and received 3 units of platelets, but her platelet count

did not improve. Human immunodeficiency virus and hepatitis B and C serologies were negative. Computed tomography of the abdomen showed multiple splenules. Vitamin B₁₂ and folate levels were within normal limits. Tests for heparin-induced thrombocytopenia antibodies were negative. We did not check for antinuclear antibody as the patient did not have any clinical features of connective tissue disease. The direct antiglobulin test was negative. Bone marrow biopsy showed normal cellularity for the patient's age (60%) with increased megakaryopoiesis (**Figure 2A and B**). The *BCR-ABL1/ABL1* ratio was 0.061% IS.

3 What is the most likely etiology of thrombocytopenia?

- ☐ Drug-induced thrombocytopenia
- ☐ Immune thrombocytopenia (ITP)
- ☐ Drug-induced thrombotic microangiopathy
- ☐ CML blast crisis

Evaluation of a patient with isolated thrombocytopenia should include a repeat complete blood cell count, reticulocyte count, and peripheral blood smear. The peripheral blood smear is important to rule out pseudothrombocytopenia from platelet clumping and microangiopathic hemolytic anemia. The patient's coagulation profile was normal, ruling out disseminated intravascular coagulation. Important differential diagnoses to consider in a patient with isolated thrombocytopenia include ITP and drug-induced thrombocytopenia.

ITP is a diagnosis of exclusion, so ruling out alternate etiologies of thrombocytopenia is crucial. ITP is an acquired thrombocytopenia caused by autoantibodies targeting glycoprotein IIb/IIIa complex and glycoprotein Ib/IX complex on the surface of platelets, leading to accelerated platelet destruction.⁹ In addition, these autoantibodies inhibit megakaryocyte proliferation in the bone marrow, leading to impaired platelet production.^{10,11} ITP can be primary or secondary to an underlying systemic illness. Secondary ITP is often seen in the setting of autoimmune diseases, infection, immunodeficiency syndromes, and lymphoproliferative disorders.^{12,13} Our patient had type 1 diabetes, and these patients have a significantly higher risk of developing other rheumatologic diseases and other autoimmune endocrinopathies. In patients with type 1 diabetes, autoimmune hematologic abnormalities, including ITP, are rare.¹⁴

ITP is often difficult to distinguish from drug-induced thrombocytopenia except for the fact that thrombocytopenia in drug-induced thrombocytopenia is triggered by the drug, and the platelet count usually improves once the offending agent is discontinued. Our patient was taking dasatinib for CML, which rarely can cause drug-induced thrombocytopenia due to inhibition of megakaryocyte colony formations.¹⁵ In addition, tacrolimus can cause drug-induced thrombocytopenia or refractory ITP in solid-organ transplant recipients.¹⁶ BCR-ABL tyrosine kinase inhibitors have complex immunoregulatory properties, and their use has been associated with multiple autoimmune disorders.¹⁷ Hence, it is plausible that tyrosine kinase inhibitors can drive immune-mediated platelet destruction as well.

In addition, tyrosine kinase inhibitors can cause platelet dysfunction. This likely explained the patient's bleeding manifestation that seemed to be out of proportion to her degree of thrombocytopenia.¹⁸ Our patient had been taking dasatinib and tacrolimus for almost 6 years, and there was no recent change in the dosing. Hence, we thought that dasatinib and tacrolimus were unlikely culprits. Drug-induced thrombotic microangiopathy is an important consideration. Both dasatinib and tacrolimus can cause this condition, which is potentially fatal if left untreated.¹⁹ The peripheral blood smear did not show any schistocytes, and there was no evidence of hemolysis or organ dysfunction. Hence, drug-induced thrombotic microangiopathy was excluded.

When evaluating a patient with CML and thrombocytopenia, it is important to differentiate between inadequate platelet production due to bone marrow infiltration by aberrant myeloid cells and immune-mediated peripheral destruction of platelets. Thrombocytopenia is usually not seen in the chronic phase of CML and instead is often seen during the accelerated phase or blast crisis. Other differentials to consider in a patient with CML who presents with thrombocytopenia include transformation into myelofibrosis or acute leukemia.

Bone marrow biopsy is usually not required in a patient with ITP. However, unexplained isolated thrombocytopenia in a patient with CML warrants bone marrow biopsy. The biopsy results showed that our patient was in major molecular remission and had no evidence of disease transformation. A few helpful clues supporting the theory of immune-mediated peripheral destruction of platelets in our patient included a favorable response to glucocorticoids, a discordancy between severe thrombocytopenia and increased megakaryocyte count in the bone marrow, evidence of other autoimmune disease, and a poor response to platelet transfusions. The increased megakaryopoiesis noted in our patient's bone marrow could have been secondary to her CML and not necessarily a response to destructive thrombocytopenia.

Although ITP can occur secondary to lymphoproliferative disorders, it is quite rare and less studied in patients with myeloid neoplasms. There have been case reports of ITP in patients with polycythemia vera and essential thrombocythosis.^{20,21} Also, there are several reports of primary ITP later transforming to CML.^{22,23} However, the diagnosis of ITP occurring several years later in a patient with established CML is extremely rare. Our patient was diagnosed with ITP 6 years after being diagnosed with CML, and she

TABLE 1

Laboratory values for a 35-year-old woman who underwent simultaneous pancreas and kidney transplant and developed chronic myeloid leukemia

Laboratory parameters (reference range)	Pretransplant	1 week after transplant	Thrombocytopenia admission (about 6.5 years after transplant)	Bicytopenic cycle (2 weeks after the thrombocytopenia admission)
White blood cell count ($4\text{--}10 \times 10^9/\text{L}$)	20	80	6	7
Hemoglobin (12–16 g/dL)	10.6	9.5	11	7.8
Platelet count ($150\text{--}400 \times 10^9/\text{L}$)	281	440	6	20
Reticulocyte count (0.5%–1.5%)	NA	NA	2.1%	16.3%
Neutrophils ($1.5\text{--}8 \times 10^9/\text{L}$)	15	29	4.4	5.3
Lymphocytes ($1\text{--}5 \times 10^9/\text{L}$)	3.5	3	1.3	1.5
Eosinophils ($0\text{--}0.5 \times 10^9/\text{L}$)	0.4	0.8	0.2	0.2
Basophils ($0\text{--}0.2 \times 10^9/\text{L}$)	0.2	0.8	0.1	0.1
Metamyelocytes (0%–1%)	2%	11%	NA	NA
Myelocytes (0%)	2%	1%	NA	NA
Promyelocytes (0%)	2%	NA	NA	NA
Peripheral blood smear	NA	Normocytic hypochromic anemia with anisopoikilocytosis, slight polychromasia, a few burr cells, leukocytosis with reactive polymorphonuclear leukocytes and left shift No blasts were seen	Normochromic normocytic anemia with slight polychromasia No increase in schistocytes Marked thrombocytopenia with a few large forms	Normocytic anemia with increased polychromasia, increased microspherocytes No significant schistocytes or blasts Platelets showed normal morphology without clumping
Prothrombin time (10–13 seconds)	13	17.3	13	12.3
International normalized ratio (0.8–1.1)	1.05	1.3	1	0.9
Partial thromboplastin time (25–35 seconds)	34	45	27	23
Fibrinogen (200–400 mg/dL)	NA	NA	367	NA

NA = not available

was in major molecular remission at the time of the ITP diagnosis. Rarely, renal transplant recipients may develop ITP, presumably from immune dysfunction.

Laub et al²⁴ reported a case of new-onset ITP that started 2 days after renal transplant and was successfully managed with romiplostim. Our patient

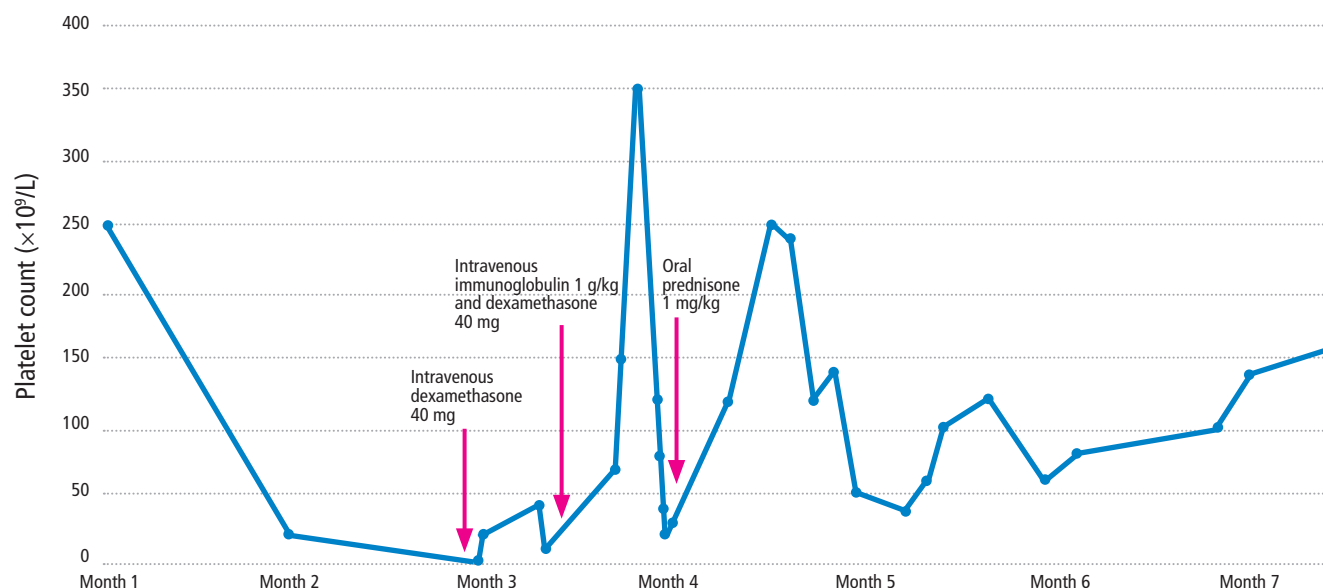


Figure 3. Trend in platelet counts and treatment interventions implemented to manage thrombocytopenia over a period of 7 months.

developed ITP 7 years after renal transplant, and the underlying trigger is still unknown. Although the mainstay of treatment for ITP is immunosuppression, it is quite intriguing that renal transplant recipients on immunosuppression therapy still develop ITP.

Approximately 10% to 20% of patients with other myeloid neoplasms such as myelodysplastic syndrome or chronic myelomonocytic leukemia may have ITP. Bourgeois et al²⁵ reported on a study of 61 patients with low-risk myelodysplastic syndrome and observed that 15% had ITP. Komrokji et al²⁶ reported that the prevalence of ITP in 1,408 patients with myelodysplastic syndrome was 12%. Patients with secondary ITP from myelodysplastic syndrome/chronic myelomonocytic leukemia tend to have a higher risk of bleeding but a lower risk of blast transformation than patients who have primary ITP.²⁷ ITP may precede the diagnosis of myelodysplastic syndrome/chronic myelomonocytic leukemia by several months to years.²⁷

A causal relationship between ITP and myeloid neoplasms is plausible, although we seldom see myeloid malignancies being listed as a cause of secondary ITP. Immune dysregulation could be a common pathogenic link between ITP and clonal myeloid neoplasms. This hypothesis is reinforced by reports of ITP being observed in other diseases with immune dysregulation such as indolent lymphomas, chronic lymphocytic leukemia, common variable immunodeficiency, and monoclonal gammopathy of undetermined significance.^{28–30}

In addition to ITP, there is a higher prevalence of other autoimmune disorders in patients with clonal myeloid disorders.²⁶ It remains unclear whether the primary immune dysregulation drives the lymphoid or myeloid clonal disorder or vice versa. Given the complex interplay between the immune system, genetics, the hematopoietic system, and environmental factors, it will be extremely challenging to solve this enigma. ITP may precede or present simultaneously or may manifest after the diagnosis of myeloid neoplasms. Hence, it is appropriate to use the term “secondary ITP” in the latter 2 instances.

CASE CONTINUED

Given the working diagnosis of ITP, our patient received intravenous dexamethasone 40 mg per day for 4 days, and her platelet count transiently improved to the mid- $40 \times 10^9/L$ range. One week later, the repeat platelet count results had dropped to $8 \times 10^9/L$. In patients with ITP, if the platelet counts fall after steroids are discontinued, it is reasonable to consider alternate therapies such as intravenous immunoglobulin (IG), or a second course of steroids can be attempted given the favorable response with the first course. The patient was hospitalized again and received 2 doses of intravenous IG 1 g/kg and a second course of pulse dexamethasone 40 mg for 4 days. Three days later, her platelet counts had normalized.

A repeat complete blood cell count 1 week later showed bicytopenia with a decrease in hemoglobin to 7.8 g/dL from 11 g/dL and platelet counts of $20 \times 10^9/L$. The reticulocyte count was 16.3%, haptoglobin was less than 8 mg/dL, total bilirubin was 1.6 mg/dL, and lactate dehydrogenase was 319 units/L. A peripheral blood smear showed normocytic anemia with increased polychromasia, rare nucleated red blood cells, and increased microspherocytes. No significant schistocytes or blasts were seen. Platelets showed unremarkable morphology. A direct antiglobulin test was positive, with IgG detected on circulating red blood cells, and no complement fixation was noted.

4 What is the most likely etiology of this clinical presentation?

- ☐ Cold agglutinin disease
- ☐ Delayed hemolytic transfusion reaction
- ☐ Evans syndrome
- ☐ Paroxysmal cold hemoglobinuria

The laboratory studies and peripheral blood smear were highly suggestive of hemolytic anemia. The Coombs test is helpful to differentiate immune from nonimmune causes. Although a direct antiglobulin test was positive with IgG during the current admission, the direct antiglobulin test done prior to the platelet transfusion was negative. A delayed hemolytic transfusion reaction from her previous platelet transfusion is an important consideration, given that platelet products may contain small quantities of red blood cells and cause alloimmunization. However, it does not explain the thrombocytopenia. The direct antiglobulin test pattern in cold agglutinin disease and paroxysmal cold hemoglobinuria are similar, with a positive direct antiglobulin test using anti-C3 and negative using IgG.

Warm autoimmune hemolytic anemia should be considered in the differential diagnosis of a patient with hemolytic anemia and a positive direct antiglobulin test for IgG or c3d, and after excluding alternate causes of hemolysis. ITP can rarely co-occur with warm autoimmune hemolytic anemia, often referred to as Evans syndrome, and this is the most likely etiology in our patient. Evans syndrome is known to complicate

solid-organ transplant.³¹ The trend in complete blood cell counts with differential count, coagulation profile, and peripheral blood smear during our patient's entire clinical course is provided in **Table 1**.

CASE CONCLUSION

Given evidence of brisk hemolysis and a drop in hemoglobin, we decided to treat the patient with prednisone 1 mg/kg, which was gradually tapered over a period of 2 months with normalization of bicytopenia. The platelet trend in our patient is shown in **Figure 3**. She continues to be in remission, with normal blood cell counts at the end of 1 year of follow-up.

Evans syndrome is usually resistant to standard immunosuppressive therapies and has a higher relapse rate. Although short-term responses tend to be high (80%), only one-third of patients achieve a durable remission while off immunosuppression.³² Given that our patient is on immunosuppressive drugs for her organ transplant, she could potentially stay in remission, although longer follow-up is required.

TAKE-HOME POINTS

- This case highlights the complex interplay linking autoimmunity, solid-organ transplant, myeloid neoplasm, and Evans syndrome.
- A broad differential diagnosis and detailed evaluation including a differential count and peripheral blood smear are important in a patient with unexplained leukocytosis.
- Although rare, autoimmune cytopenias can arise secondary to CML.
- Evans syndrome can arise in the setting of solid-organ transplant and is characterized by concurrent or sequential presentation of immune hemolytic anemia and ITP.

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The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Address: Binoy Yohannan, MD, Division of Hematology/Oncology, McGovern Medical School, The University of Texas Health Science Center, 6410 Fannin Street, Houston, TX 77030; binoyyohannan87@gmail.com