Acquired Amegakaryocytic Thrombocytopenia Misdiagnosed as Immune Thrombocytopenia: A Case Report

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INTRODUCTION

Acquired amegakaryocytic thrombocytopenia (AATP) is a rare bleeding disorder that causes severe thrombocytopenia with preserved hematopoiesis of other cell lineages. Many cases are misdiagnosed and treated as immune thrombocytopenia.

Case Presentation: We report a case of AATP, in a 50-year-old man, that was treated as immune thrombocytopenia for years with no clinical response. The disorder later was diagnosed as AATP after bone marrow biopsy and was successfully treated with cyclosporine.

Discussion: The exact mechanism of AATP remains unclear; it is suspected to be an immune-mediated process. Patients with AATP present with severe bleeding and thrombocytopenia, which is usually unresponsive to high-dose corticosteroids. There are no standard treatment guidelines for AATP. Cyclosporine and antithymocyte globulin are found to be effective in some cases. The prompt diagnosis of AATP is vital because it carries high mortality because of excessive bleeding, and it can progress into aplastic anemia or myelodysplastic syndrome.

CASE PRESENTATION

Presenting Concerns

A 50-year-old man with a previous diagnosis of ITP (chronic idiopathic thrombocytopenic purpura) reestablished care in our clinic because of a recent drop in his platelet count. He reported that ITP was diagnosed 6 years earlier, in 2012, and his platelet count was 50 × 10^3/μL at the time of initial diagnosis. He received a 15-day course of prednisone, 1 mg/kg daily, at that time, with some improvement in his platelet count. His platelet count remained stable at around 100 × 10^3/μL to 150 × 10^3/μL for 5 years after the diagnosis of ITP and then gradually started to trend down. His platelet count on presentation to our clinic in August 2018 was 19 × 10^3/μL. He denied a history of major bleeding or hematoma but reported having easy bruising and prolonged bleeding after trivial trauma for years. He had no personal or family history of bleeding disorders, autoimmune disorders such as rheumatoid arthritis or lupus, or malignancy.

Results of his laboratory workup on presentation to our clinic showed anemia with a hemoglobin level of 11.5 g/dL, thrombocytopenia with a platelet count of 19 × 10^3/μL, and normal white blood cell count. Results of the physical examination were unremarkable. Workup including HIV, hepatitis C virus, Helicobacter pylori, and liver function tests as well as a coagulation panel, antinuclear antibody panel, and rheumatoid factor yielded negative or normal results. Vitamin B12 and folate levels were normal. A peripheral blood film (“peripheral smear”) had unremarkable findings except for a decreased number of platelets. Abdominal images showed no splenomegaly or malignancy.

Therapeutic Intervention and Treatment

The patient received a 4-day course of oral dexamethasone, 40 mg daily, without experiencing any improvement in platelet count. A bone marrow biopsy specimen showed
varying cellularity with an average cellularity of approximately 20%. The biopsy specimen also showed normal erythropoiesis and myelopoiesis, but a markedly decreased number of megakaryocytes with no morphologic evidence of myelodysplastic syndrome (MDS). There was less than 1 megakaryocyte per high-power field (Figures 1 and 2). Flow cytometry results of bone marrow demonstrated no monoclonality or malignancy. This picture was consistent with amegakaryocytic thrombocytopenia rather than ITP because there is usually a compensatory increase in megakaryocytes in the bone marrow in ITP. This emphasizes the importance of performing a bone marrow biopsy in patients with unexplained, isolated thrombocytopenia or in patients with an ITP diagnosis if they are not adequately responding to corticosteroids or IVIG.

AATP can be idiopathic and occur as a primary disorder or be seen in association with lymphoproliferative disorders;
autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, or Still disease; viral infections such as cytomegalovirus, Epstein–Barr virus, parvovirus B19, or hepatitis C; exposure to environmental toxins such as benzene; and vitamin B12 deficiency. It could also be a precursor for aplastic anemia, MDS, or acute leukemia. In our patient, we could not find any cause for AATP, and hence it is likely idiopathic.

Although the exact mechanism of AATP remains unclear, it is strongly suspected to be an immune-mediated process. The primary regulator of platelet production is TPO, which is mainly produced by the hepatocytes. It binds to the TPO cellular–myeloproliferative leukemia receptor on megakaryocytes and hematopoietic stem cells, affecting nearly all stages of platelet production including proliferation, differentiation, and maturation of megakaryocyte into platelets. Dysregulated humoral immunity as one of the mechanisms for AATP has been proposed because of the presence of anti-TPO immunoglobulin G antibodies and autoantibodies against the cellular–myeloproliferative leukemia receptor, blocking the function of TPO. Cell-mediated immunity appears to play a more important role because T lymphocytes obtained from a patient with AATP were found to selectively inhibit megakaryocyte lineage in vitro. The response of AATP to immunosuppressants further supports the immune-mediated pathogenesis of AATP.

There are no standard treatment guidelines for AATP. Unlike in ITP, prednisone and IVIG have been found to be largely inefficacious or transiently effective in patients with AATP. Although there is no expert consensus, cyclosporine monotherapy has been found to be quite effective in several reported cases, including our patient. Cyclosporine with a target serum level between 150 and 350 ng/mL has been found to be most effective. Cyclosporine needs to be continued for several weeks to months for complete remission. In patients with severe bleeding from thrombocytopenia or who are refractory to treatment with cyclosporine alone, administration of antithymocyte globulin along with cyclosporine has been found to be effective.

Other therapies such as rituximab, mycophenolate mofetil, danazol, and azathioprine have also been used to treat AATP with varying success. In patients refractory to cyclosporine or antithymocyte globulin and in patients with relapsed disease or disease progression into aplastic anemia or MDS, allogeneic bone marrow transplant should be strongly considered, especially in relatively young patients with matched siblings. Some case reports showed that alemtuzumab, a T cell-depleting agent, and TPO receptor agonists such as eltrombopag and romiplostim have also been found to evoke a satisfactory response in patients with refractory AATP.
### Table 1. Timeline of the case

<table>
<thead>
<tr>
<th>Date</th>
<th>Summaries from initial and follow-up visits</th>
<th>Diagnostic testing</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/7/2018</td>
<td>On initial presentation to our clinic, patient reported easy bruising and prolonged bleeding on trivial trauma</td>
<td>Laboratory tests on presentation included: Hemoglobin: 11.5 g/dL, WBC: 3.8 x 10^3/μL, Platelet count: 19x 10^3/μL, HIV, HCV, Helicobacter pylori, liver function test, coagulation panel, antinuclear antibody, rheumatoid factor, vitamin B12, folate, Normal results, CT scan of abdomen and pelvis: Normal results, Peripheral smear: Decreased number of platelets</td>
<td>Dexamethasone, 40 mg daily, for 4 d without improvement in platelet count</td>
</tr>
<tr>
<td>9/4/2018</td>
<td>On follow-up visit, no new symptoms</td>
<td>Platelet count: 17 x 10^3/μL</td>
<td>Bone marrow biopsy: Varying cellularity from 40% to 0% with normal erythropoiesis and myelopoiesis but absent megakaryocytes, no morphologic evidence of MDS. Fluorescence in situ hybridization and cytogenetics were negative for MDS. Flow cytometry of bone marrow was negative for monoclonality or malignancy.</td>
</tr>
<tr>
<td>9/18/2018</td>
<td>Diagnosis of AATP made from bone marrow biopsy. Reported new spontaneous bruises on inner left thigh</td>
<td>Platelet count: 18 x 10^3/μL, Antibodies against thrombopoietin: Negative, Antiplatelet antibody panel: Negative</td>
<td>Started on regimen of cyclosporine, 2.5 mg/kg/d (150 mg twice daily)</td>
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<tr>
<td>9/25/2018</td>
<td>Patient tolerated cyclosporine, denied adverse effects</td>
<td>Platelet count: 22 x 10^3/μL, Cyclosporine level: 116.1 ng/mL</td>
<td>Cyclosporine dose increased to 175 mg twice daily</td>
</tr>
<tr>
<td>10/9/2018</td>
<td>Patient tolerated cyclosporine, denied adverse effects</td>
<td>Platelet count: 33 x 10^3/μL, Cyclosporine level: 142.3 ng/mL</td>
<td>Cyclosporine dose increased to 200 mg twice daily</td>
</tr>
<tr>
<td>12/11/2018</td>
<td>Patient tolerated cyclosporine</td>
<td>Platelet count: 56 x 10^3/μL, Cyclosporine level: 213.9 ng/mL</td>
<td>Continued cyclosporine, 200 mg twice daily</td>
</tr>
<tr>
<td>4/16/2019</td>
<td>No new bleeding; patient tolerated cyclosporine</td>
<td>Platelet count: 62 x 10^3/μL, Cyclosporine level: 202.4 ng/mL</td>
<td>Cyclosporine dose reduced to 175 mg twice daily</td>
</tr>
<tr>
<td>11/12/2019</td>
<td>No new symptoms; patient denied bleeding</td>
<td>Platelet count: 67 x 10^3/μL, Cyclosporine level: 183.0 ng/mL</td>
<td>Received cyclosporine, 175 mg twice daily</td>
</tr>
<tr>
<td>02/04/2020</td>
<td>On most recent clinic visit, no rash or bleeding</td>
<td>Platelet count: 68 x 10^3/μL, Cyclosporine level: 146.8 ng/mL</td>
<td>Continued Cyclosporine 175 mg twice daily</td>
</tr>
</tbody>
</table>

AATP = acquired amegakaryocytic thrombocytopenia; CT = computed tomography; HCV = hepatitis C virus; MDS = myelodysplastic syndrome; WBC = white blood cells.
The prognosis and clinical course of AATP is variable, with some patients achieving remission and having a durable response, whereas others have a long relapsing–remitting disease course. Furthermore, there are a few patients who progress rapidly to aplastic anemia,11 MDS,12 or even leukemia6 despite aggressive immunosuppressive treatment, which makes regular long-term follow-up necessary.

CONCLUSION

AATP is a rare disease that can easily be confused with other causes of thrombocytopenia, especially ITP. This case report highlights the importance of performing a bone marrow biopsy in cases of unexplained thrombocytopenia and in patients who have a diagnosis of ITP but do not adequately respond to corticosteroids or IVIG, to rule out amegakaryocytic thrombocytopenia. This form of thrombocytopenia requires prompt treatment and close follow-up. Additionally, our observations also confirm successful treatment of this rare entity with cyclosporine.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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References