Acquired Amegakaryocytic Thrombocytopenia Misdiagnosed as Immune Thrombocytopenia in a Patient with Seronegative Arthritis: A Case Report

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ABSTRACT

Acquired amegakaryocytic thrombocytopenia (AATP) is an uncommon cause of severe thrombocytopenia with preserved cells of other lineages, which can present with severe bleeding episodes. We report a case of a 45-year-old male with seronegative arthritis who was diagnosed with idiopathic thrombocytopenic purpura (ITP) and was being treated with steroids for ITP. Despite aggressive treatment, the patient had persistently low levels of platelets. In view of persistent thrombocytopenia, bone marrow biopsy was done and was diagnosed as Acquired Amegakaryocytic Thrombocytopenia (AATP). Patient was successfully treated with cyclosporine. Correct identification of AATP is essential because it can lead to life threatening bleeding manifestations and advance into Aplastic anemia or MDS.

INTRODUCTION

Acquired amegakaryocytic thrombocytopenia (AATP) is an uncommon cause of severe thrombocytopenia, which occurs due to the marked reduction or absence of thrombocyte precursors in the bone marrow while preserving the hematopoiesis of other cell lineages.1 While the precise prevalence of AATP is not known,2 it could be higher than reported as many of the cases are being wrongly identified as idiopathic thrombocytopenic purpura (ITP). The mainstay of treatment for ITP are steroids and intravenous immunoglobulin (IVIg), whereas AATP poorly responds to these. Hence, it becomes very pertinent to differentiate between ITP and AATP.3

The deregulated immune response is considered to be the major mechanism behind AATP. Currently, there are no standard treatment guidelines for the treatment of AATP. The treatment currently is dependent on the various case reports illustrating successful management of AATP. We present a patient who was treated for ITP for a couple of years, despite which his platelet counts worsened. Later, the patient was identified to have AATP, which was successfully managed with cyclosporine.

CASE DESCRIPTION

A 45-year-old male with a previous diagnosis of seronegative arthritis presented to the emergency room complaining of bleeding from gums to easy fatigability for 2 months. The patient reported that he was detected with ITP in May 2022, and a complete blood count was done, which showed a platelet count of 20,000 cells/mm³. He received a 15-day course of oral prednisolone daily; after this, his platelets improved to 30,000 cells/mm³. Following this, his platelets remained stable between 30,000 and 40,000 cells/mm³. He denied any history of hematoma formation or major bleeding. He had no personal or family history of bleeding diathesis, autoimmune diseases like lupus erythematosus, rheumatoid arthritis, or malignancy.

An initial clinical examination of the patient revealed stable vitals. Head-to-toe examination showed swollen neck deformity of both hands (Fig.1). Initial tests on arrival at our center revealed anemia with hemoglobin of 11.5 gm/dL, thrombocytopenia with a platelet count of 19,000 cells/mm³ and white blood cell within normal limits. A peripheral smear done had unremarkable findings except for thrombocytopenia with no giant platelet. The reticulocyte count was 1.4%. Tests, including renal function tests, liver function tests, human immunodeficiency virus and hepatitis C virus, antinuclear antibody profile, coagulation panel, anticyclo citrullinated peptide, rheumatoid factor, and both direct and indirect Coomb tests, yielded unremarkable or negative levels. Folic acids and vitamin B12 levels were within normal limits. Dengue immunoglobulin M (IgM), IgG, and nonstructural protein 1 were negative. As the patient had severe thrombocytopenia with bleeding manifestation, the patient received platelet transfusions. Abdominal imaging did not show any organomegaly or malignancy.

The patient received a short course of oral steroids for 4 days, but despite the steroid supplement, his platelets remained at about 20,000 cells/mm³. A biopsy of the bone marrow was done, which showed megakaryocytic hypoplasia with few hypolobulated forms. Otherwise, the bone marrow was normocellular, without dysplasia or other cytogenetic abnormalities. The myeloid to erythroid ratio

Fig. 1: Image showing swan neck deformity in the patient

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Acquired Amegakaryocytic Thrombocytopenia was 0.83:1 (Fig. 2). There was no morphologic evidence of myelodysplastic syndrome (MDS). These features are more suggestive of amegakaryocytic thrombocytopenia instead of chronic ITP because, in ITP, there is a compensatory increase in thrombocyte precursors in the marrow. Agglutinins directed against thrombopoietin were not detectable, nor were any antibodies against platelets detected. The patient was initiated on cyclosporine 200 mg daily in two divided doses. After the initiation and continuation of the treatment for a couple of months, the patient experienced an increase in the platelet count above 50,000 cells/mm³.

**DISCUSSION**

The etiology for acquired thrombocytopenia is quite vast and includes defective thrombocyte production with sufficient marrow cellularity, flaved thrombopoietin action with adequate marrow cellularity, acquired marrow hypocellularity, and increased platelet extermination.

Our patient was previously diagnosed with chronic immune thrombocytopenic purpura and received oral prednisone with minimal furtherance in his platelet count. Nonetheless, the gradual depletion of his thrombocyte levels over time and lamentable response to high-dose oral glucocorticoids raised the possibility of an alternative cause for thrombocytopenia. Moreover, the absence of thrombocyte precursors in the biopsy of bone marrow in patients with inscrutable, isolated thrombocytopenia or in patients with the diagnosis of idiopathic thrombocytopenic purpura not responding to glucocorticoids or intravenous Ig (IVig).

Amegakaryocytic thrombocytopenia (AMT) is a frightful cause of thrombocytopenia with lowered or no platelet precursor in the bone marrow. AMT can be acquired or congenital. Eventually, there is a concatenation to involve and hamper all of the three cell lines.¹

**Acquired amegakaryocytic thrombocytopenia (AATP)** can be a primary disorder or idiopathic, or it may be seen in consort with immune-mediated diseases such as systemic lupus erythematosus, rheumatoid arthritis, viral infections such as Epstein–Barr virus, hepatitis C or parvovirus B19, vitamin B₁₂ deficiency, subjection to environmental toxins such as benzene and lymphoproliferative disorders. It might eventually lead to aplastic anemia, MDS, or acute leukemia.⁴⁵

The exact mechanism of AATP is not known; however, it is resolutely reckoned to be an immune-mediated process. Thrombocyte production is primarily regulated by thrombopoietin, the majority being produced by the hepatocytes. It acts on every single stage of megakaryocyte production, including the production, differentiation, and maturation of megakaryocytes into platelets. Impaired antibody-mediated immunity is described as one of the mechanisms for AATP.⁵⁶ This has been put across as there is the presence of the anti-thrombopoietin IgG agglutinins and agglutinins against the cellular-myeloproliferative leukemia receptor in patients with AAMT, hampering the role of thrombopoietin. T-lymphocytes obtained from a patient with AATP selectively inhibited thrombocyte lineage in vivo, indicating the role of T-cell-mediated immunity. Improvement after immunosuppressant administration further subsists the immune-mediated pathogenesis of AATP.

Currently, there are no established management guidelines for AATP.⁷ Contrary to immune thrombocytopenic purpura, treatment with prednisolone and IVIg has been found to be predominantly unproductive. Even though there is no expert consensus, many case reports have shown cyclosporine to be effective, including our patient. Cyclosporine has to be taken for many days to weeks for remission. The strength of the dose can be tapered gradually after the platelets have normalized. In patients with severe bleeding due to low thrombocyte counts or refractory to cyclosporine alone, treating patients with cyclosporine in conjunction with ATG has been found to be effective. Other treatment modalities that are used with varying success include rituximab,⁸ mycophenolate mofetil,⁹ danazol, and azathioprine. In patients refractory to the above treatment or disease progressing to MDS or aplastic anemia, an allogeneic bone transplant must be strongly considered. Roy et al. showed alemtuzumab, a T-cell depleting agent, to be quite effective in patients with refractory AATP. Even thrombopoietin receptor agonist agonists like romiplostim and eltrombopag have also been shown to summon an admissible response in people with refractory acquired autoimmune thrombocytopenia.¹⁰

The clinical trial and prognosis of acquired autoimmune thrombocytopenia are quite variable, with few having a durable response, although the rest have relapsing–remitting disease courses. In addition, there are those who advance rapidly to MDS,¹¹ aplastic anemia,¹² or even leukemia in spite of bellicose immunosuppressive treatment, which makes well-ordered follow-up a necessity.

**CONCLUSION**

Amegakaryocytic thrombocytopenia (AATP) is an uncommon cause of thrombocytopenia, which requires a high degree of clinical intuition for identification before consequential complications like lethal hemorrhage occur. Successful identification of the patient requires an integrative approach between physicians and pathologists.

Enlistment of patients in international and national trials is necessary as the disease is rare, and currently, there are no established treatment guidelines; hence, the treatment is dependent on case reports describing success with various therapies for congenital AATP and AATP.

**REFERENCES**