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Case Report

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Anti-CD20 Antibody is Effective in the Patient with Refractory Amegakaryocytic Thrombocytopenia, 25 Months Follow up

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ABSTRACT
Amegakaryocytic thrombocytopenia (AMT) is a rare cause of acquired thrombocytopenia. The pathogenesis and treatment of AMT is not clearly known. Here we demonstrate a 50-year-old man presented with the clinical manifestations of severe thrombocytopenia (7000 platelets/µl) with a marked decrease to absent of megakaryocytes in the bone marrow. The patient did not respond to intravenous immunoglobulin, cyclosporine or high dose prednisone. After the treatment with anti-CD20 antibody (Rituximab), the patient's clinical symptoms and platelet counts improved.

KEY WORDS: Amegakaryocytic thrombocytopenia; Anti-CD20 antibody; Platelet

BACKGROUND

Acquired amegakaryocytic thrombocytopenia (AMT) is a rare hematologic disorder characterized by thrombocytopenia and is association with a markedly diminished number of bone marrow megakaryocytes.[1] This condition has been observed in patients with lupus erythematosus, T-cell large granular lymphocyte leukemia and eosinophilic fasciitis.[2,3] AMT is associated with a marked increase of T-activated suppressor cells (CD8+ /DR+) and a high level of autoantibodies against the thrombopoietin receptor (c-Mpl).[4,5] No cytogenetic abnormality has been shown to be consistently present in AMT.[6] In most patients, an etiology cannot be determined, and empirical therapy is necessary.[7] Here we describe a rare case of AMT syndrome which did not respond to any of the previous therapies except rituximab (Ant-CD20 antibody).

PRESENTATION OF CASE

In September 2008; a 50-year-old man with petechial rash, large ecchymosed, gross hematuria and severe shoulder and periumbilical pain was admitted to our center.

In the past medical history: he had symptoms of bleeding for 15 months ago and laboratory studies revealed a severe thrombocytopenia with platelet count of 12000/µl, a leukocytosis with white blood cell (WBC) count of 25000/µl and hemoglobin (Hb) of 15 gr/dl. There was an increased level of myeloid/erythroid series and a severe decrease of megakaryocytes series, in the bone marrow examinations. Patient was treated with intravenous

immunoglobulin (IVIG) and transient clinical response was taken.

After six months, he was referred to our center for the complaint of severe bleeding. He had a WBC count of 12100/µl, Hgb of 13 gm/dl, hematocrit (HCT) of 31.3%, a mean corpuscular volume (MCV) of 93ƒL, and a platelet count of 7000/µl. The patient undergone bone marrow examination again, cellularity was 75%, myeloid and erythroid series were mildly increased and megakaryocytes severely decreased to absented. Additional studies including antinuclear antibodies (ANA), rheumatoid factor (RF), and IgM/IgG antiplatelet antibody tests were normal. The Patient with diagnosis of amegakaryocytic thrombocytopenia was treated with IVIG again, but clinical and laboratory response were not taken. We then treated the patient with oral cyclosporine plus prednisone for one month. There was not any improvement in patient's signs and symptoms (Figure 1). Platelet count was lower than 10000/µl and he was experiencing diffuse petechial rash, easy bruising, gingival bleeding and hematuria. Bleeding symptoms were controlled by platelets transfusions, however it did not cause into a dramatic increase in the platelets count. We explained the treatment options, including Anti-thymocyte globulin (ATG) and rituximab to the patient. He did not accept the treatment with ATG; due to its side effects. Anti-CD20 antibody (rituximab) therapy is one of the choices in this refractory AMT case. Hence Rituximab (Anti-CD20 antibody) with dose of 375 mg/m2, with three weeks interval, for three consequent doses was started. The platelet count rose dramatically to 20000/µl on the 6th day, to 30000/µl on the 29th day and to 200 000/µl on the 42th day. In 25 months follow up; the patient had normal blood counts without any medications, except that WBC was mildly increased (Figure 1).

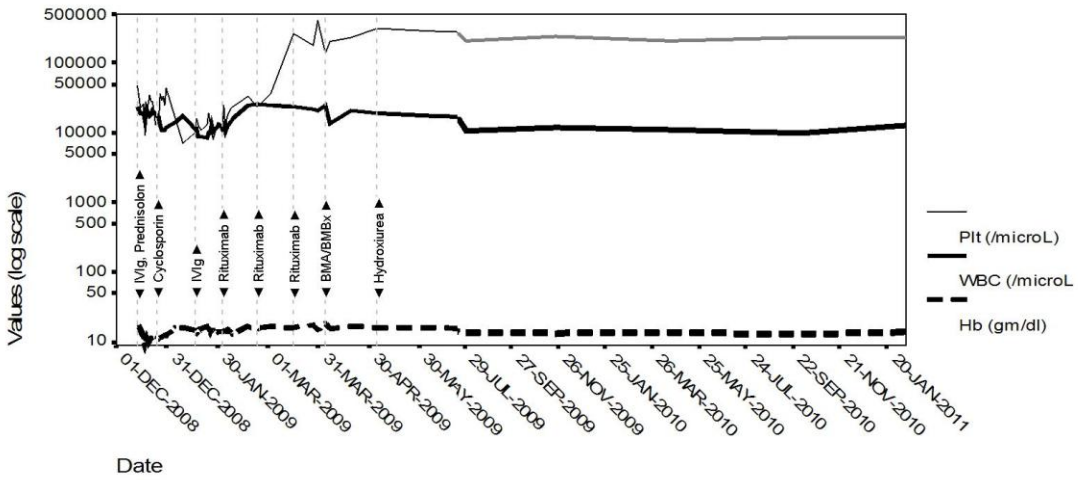

Figure 1: Laboratory Course of Patient.

IVIG: Intravenous Immunoglobulin. BMA/BMBx: Bone Marrow Aspiration/ Bone Marrow Biopsy. Plt: Platelet. WBC: With Blood Cell Count. Hb: Hemoglobin

The patient had a hypercellular marrow with adequate to increased megakaryocyte in the 63th day after treatment. We diagnosed myeloproliferative disease according to the morphological changes observed in the bone marrow examinations. The search for BCR/ABL, Philadelphia chromosome, and Janus kinase2 (JAK2) V617F by PCR test was also negative, and the diagnosis of myeloproliferative disease was not approved in our patient. Anti-platelet antibody was not also detected.

DISCUSSION

Here we presented a case of refractory AMT which responded to anti CD-20 antibody therapy. The differential diagnosis of patients suspected to have AMT are idiopatic (immune) thrombocytopenic purpura, with misinterpretation

of morphologic findings, hereditary and acquired aplastic anemia, preleukemia and systemic lupus erythematosis.[8,9]

The clinical course of the disease is variable, and suggested treatment have shown variable efficacy in the management of disease.[10,11] Immunosuppressive therapies including administration of steroids, cyclophosphamide, cyclosporine, androgens, ATG have been used with varying degrees of success.[12]

IVIG, prednisone, cyclophosphamide, and vincristine have not been efficacious in AMT, unlike the response to these agents in immune-mediated thrombocytopenia, although there are isolated reports of prednisone, IVIG,[13] and cyclophosphamide[14] being transiently effective in occasional patients with AMT. Danazol has also been reported to be effective in two cases of AMT.[15,16] Myeloablative chemotherapy (busulfan and cyclophosphamide) followed by allogeneic bone marrow transplant from a fully HLA-matched sibling has been reported to be effective.[17] ATG has been reported to induce complete remission in a case of longstanding AMT.[18] ATG was also reportedly effective in a case of AMT associated with a marked increase of T-activated suppressor cells (CD8+/DR+).[5] Cyclosporine alone[19] or in combination with ATG has been shown to be very effective in treatment of AMT.[12,20] In one of the reports of cyclosporine use, longitudinal follow-up revealed a relapsing and remitting disease course of AMT, which correlated with the dosing of cyclosporine.[21] Recombinant IL-11 is a thrombopoietic growth factor. It has been shown to be effective in patients with bone marrow failure due to myelodysplastic syndromes (MDS), graft failure, chemotherapy, or aplastic anemia. Its role in cases of AMT is uncertain.[22] There are a limited number of studies reporting hematopoietic cell transplantation in patient with the acquired AMT.17

In 2008, Fukushima et al., firstly reported a case of amegakaryocytic thrombocytopenia due to systemic lupus erythematosis.[23] She was successfully treated with anti-CD20 antibody. another report shows the successful treatment of AMT with rituximab.[24] Rituximab is a chimeric monoclonal antibody against the protein CD20, which is primarily found on the surface of B cells.[25] CD20 is expressed on most stages of B cells, such as immature B cells, naive B cells, memory B cells, and germinal center B cells, but not early pro-B cells or plasma cells. It has been described that rituximab may suppress pathogenic B-cell clones which produce anti-TPO(thrombopoietin) receptor antibodies that are resistant to conventional immunosuppressive therapy, including cyclosporine and prednisone.[26]

Our patient did not respond to any of the traditional treatments previously described.[1,13,14] We hence used anti CD20 antibodies for the management of his condition. Anti-CD20 antibody acting against CD20 receptors over membrane of B-cell type lymphocytes, and suppressed the humoral immunity. Anti-CD20 antibody was taken and this refractory AMT patient that was depended to platelet transfusions, responded to this drug, and after first dose, the dependency of patient to platelet transfusions does not continued, and at the beginning of 3th dose, the platelet count became normal. Rituximab was effective in this refractory case of AMT, the platelet count is normal after 25 months of last dose without any medication, but mild leukocytosis (WBC 11000 to 25200/µl) remained sustained. Moreover we did not have any documentation for diagnosis of chronic myeloproliferative disease except morphology of bone marrow examination.

Conflict of interest

The authors declare no conflict of interest.

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