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CLINICAL VIGNETTE

Presentation of Aplastic Anemia after Years of Presumed Idiopathic Thrombocytopenic Purpura

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Our patient was found to have thrombocytopenia at age 16. He received high dose steroids for a presumed diagnosis of idiopathic thrombocytopenia purpura with a subsequent improvement in his platelet count to 70,000/mcL. However, each time the steroids were tapered or stopped his platelet count dropped to the 10,000/mcL range. He received a dose of rituximab, but he had a severe infusion reaction. No further rituximab treatments were given. He was then maintained on steroids for two years. After two years, a bone marrow aspiration and biopsy were performed. The bone marrow examination showed 30 to 40% cellularity without evidence of dysplasia, excess blasts or reticulin fibrosis. Megakaryocytes were nearly absent. At the time of the bone marrow biopsy, his white blood cell count was 4800/mcL with an ANC of 2400/mcL, hemoglobin of 13.6 gm/dL, and platelet count of 38,000/mcL.

After review of the bone marrow biopsy, he was given a diagnosis of presumed congenital amegakaryocytic thrombocytopenia without *MPL* testing sent. He was started on eltrombopag at 75mg daily, which maintained his platelet count above 20,000/mcL. This therapy continued for three years until his hemoglobin and platelet counts decreased. At that time his white blood cell count was 4700 per mcl, hemoglobin was 8.1 gm/dL, and platelet count was 10,000 per mcl. The differential was 45% neutrophils, 48% lymphocytes, and 6% monocyte. As a result of these changes, he was referred to our transplant center and underwent a second bone marrow biopsy that was completely devoid of granulocytic precursors or erythroid precursors. There were no aggregates of blasts, plasma cells, lymphocytes, or atypical infiltrate. There were no megakaryocytes identified. Molecular testing for myelodysplastic syndrome and acute myeloid leukemia showed no mutations. These results were consistent with aplastic anemia. He was found to have a matched sibling donor, and he underwent an allogeneic stem cell transplant with conditioning with cyclophosphamide, ATG, and a single 200cGy dose of total body irradiation. He is over one year from transplant with excellent graft function and no graft versus host disease.

Discussion

This case highlights the diagnostic challenges related to thrombocytopenia and bone marrow failure syndromes. Congenital amegakaryocytic thrombocytopenia (CAMT) is a very rare disorder caused by mutations in the *MPL* gene.[1] In contrast to many of the congenital thrombocytopenia syndromes, such as Fanconi Anemia and Thrombocytopenia Absent Radii, it is not characterized by birth defects. Although testing for *MPL* mutations are available, it remains a diagnosis of exclusion and other etiologies of congenital thrombocytopenia should be ruled out as not all patients will have a detectable *MPL* mutation.[2] Patients generally present with severe thrombocytopenia soon after birth and progress to bone marrow failure. In a series of 20 patients, the median age at onset of pancytopenia was 38 months with a range of 6-84 months.[3] The etiology of bone marrow failure in this disorder is at least partially due to the involvement of the thrombopoietin receptor in hematopoietic stem and progenitor cells (HSPCs).[2] Hematopoietic stem cell transplant is the only potential therapy for patients with CMAT. Patients can be supported with transfusions, but there are no other effective or curative therapies. Attempts at using steroids and cytokines have not been successful.

This patient has several features that are not consistent with CAMT. The first aspect that argues against CAMT is his age at diagnosis of thrombocytopenia. The majority of patients develop severe pancytopenia early in life with an extremely limited number of reported cases discovered after ten years of age.[4,5] Further, he responded to steroids and a thrombopoietin stimulating agent, which would also be inconsistent with CAMT. Steroids, immunoglobulins, splenectomy, and cytokines have not shown efficacy in CAMT.

Given the course, it appears more likely that the patient developed aplastic anemia, which responded to immunosuppression with steroids as well as demonstrated hematologic improvement with the eltromobopag. In the trial of eltrombopag in refractory aplastic anemia patients, there were improvements seen in the hemoglobin and neutrophil counts as well as the platelet counts. The maximum dose given to him was 75m due to his ethnic background. As these therapies alone would not be sufficient to treat severe aplastic anemia, his disease eventually progressed to aplastic anemia as was shown on his second bone marrow biopsy and laboratory evaluation; the therapies were no longer sufficient.

The advent of molecular testing has allowed for improved diagnostic ability for these disorders. The available genetic testing panels can help distinguish among the congenital bone

marrow failure syndromes as well as the acquired bone marrow failure states. In the acquired states, the distinction among myelofibrosis, aplastic anemia, and hypoplastic myelodysplastic syndrome can be very difficult and is aided by molecular testing. Although in this case, both diagnoses require a stem cell transplant, delays in therapy, or additional therapies bring along potential for toxicity and complication.

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