

# Unresponsive Severe Aplastic Anemia in a Young Patient: Case Report and Short Review of the Literature

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## ABSTRACT

Aplastic anemia or medullary aplasia is a medical condition characterized by pancytopenia and is associated with a high prevalence of morbidity and mortality. In patients in whom bone marrow transplantation cannot be attempted, an immunosuppressive regimen is considered to be the first-line therapy. Also, the addition of eltrombopag from the first day of immunosuppressive treatment seems to significantly increase response rate. Unfortunately, there are a small number of patients who remain unresponsive to all these therapies. Here we present the case of a young woman who was referred by the family doctor complaining of marked physical asthenia, new onset dyspnea, and dizziness. Apart from a severe pancytopenia, no further changes have been brought to light by paraclinical investigations. After multiple secondary causes were excluded, the patient was diagnosed with idiopathic aplastic anemia. Even if bone marrow transplant was the first-line therapy in this case, because of the severe leukopenia, it was not possible to determine the HLA type. Therefore, the patient was prescribed immunosuppressive treatment. Despite the three drug-associated therapy (horse anti-thymocyte globulin, cyclosporin A, and eltrombopag), the response was unsatisfactory, with the persistence of severe pancytopenia.

**Keywords:** aplastic anemia, bone marrow, eltrombopag, horse anti-thymocyte globulin, medullary aplasia

## INTRODUCTION

Aplastic anemia or medullary aplasia, a life-threatening disease in its severe form, is characterized by pancytopenia in the peripheral blood (leukopenia, anemia, and thrombocytopenia) associated with hypocellular hematopoietic bone marrow, affecting all three cell lines.<sup>1</sup> The disease can be idiopathic, in which case the cause remains unknown, or it can be secondary to viral infections (human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, parvovirus B19, hepatitis B or C virus), to physical, chemical, pharmacologi-

cal (chloramphenicol, sulphonamides, penicillamine, carbamazepine) agents, or to ionizing radiation (the effect is dependent on the radiation dose). It can also be associated with pregnancy, or certain congenital anomalies such as Fanconi anemia. In order to establish a diagnosis, bone marrow biopsy and exclusion of malignant or fibrotic infiltration is required.<sup>1-4</sup> Because severe pancytopenia can lead to life-threatening complications, early diagnosis and initiation of treatment are mandatory. Definitive treatment is represented by allogeneic transplant from a matched sibling donor, or immunosuppressive therapy for those without a matched sibling donor or over the age of 40 years.<sup>5-7</sup>

## CASE REPORT

We present the case of a 23-year-old woman, referred by the family doctor, complaining of marked physical asthenia, new-onset dyspnea, and dizziness. Her symptoms had gradually installed over a period of one month. The patient had no significant family history and a personal history of polycystic ovary syndrome and a non-functioning pituitary adenoma. In order to find out the cause of her symptoms, the family doctor started laboratory investigations with some initial common blood tests including blood count. After a severe anemic syndrome along with severe thrombocytopenia have been detected, the patient was admitted to the hematology department for further investigations and therapeutic management.

On admission, the patient was afebrile, her general condition was slightly influenced, and her skin and conjunctiva were pale. She had multiple ecchymoses, mostly on her lower and upper extremities, without any other signs of bleeding. The physical examination was normal, except for sinus tachycardia (heart rate of 105 beats/minute) along with a systolic murmur, which was interpreted to be present in the context of severe anemia. Blood pressure was normal (120/90 mmHg), and oxygen saturation was 99% on room air.

The patient declared herself sexually active and denied any history of sexually transmitted diseases. Also, her menstrual cycle was regular, the last one being two weeks

before the presentation. She had no children, denied any history of miscarriage, and was not pregnant at the time of the examination. Also, the patient declared no allergies, denied taking any home medications, including oral contraceptive pills or antibiotics, and did not smoke or use alcohol. She worked as an accountant and had no toxic exposure to ionizing radiation.

Further review of the paraclinical investigations revealed pancytopenia: leukopenia with neutropenia, severe macrocytic anemia, severe thrombocytopenia (Table 1) with increased inflammatory markers. Iron levels, ferritin, renal and hepatic function tests, coagulation, electrolytes, uric acid level, and total protein were normal. The peripheral blood smear showed aniso-poikilocytosis along with many macrocytes and very few platelets. Thus far, the preliminary diagnosis was medullary aplasia (aplastic anemia). For a certain diagnosis, bone marrow cytology (aspiration) and a bone marrow biopsy were performed, with needle aspiration. They both showed hypocellularity with a decrease in all cell elements, without megakaryocytes, malignant infiltrates, or fibrosis. These morphological findings matched perfectly with the diagnosis of medullary aplasia.

Once the medullary aplasia diagnosis was established, our target was to identify the etiology. Therefore, different causes of acquired aplastic anemia were taken into account. Infectious agents, such as human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, hepatitis B or C, *Toxoplasma gondii*, and tuberculosis, were negative. Given the pandemic situation, we have also thought of coronavirus disease, but the reverse transcriptase-polymerase chain reaction testing for SARS-CoV-2 was negative. Folic acid, vitamin B12, and tumor markers, such as CA125, CA15.5, CA19.9, carcinoembryonic antigen, or  $\alpha$ -fetoprotein, were within normal limits. Chest radiography, abdominal ultrasound, electrocardiography, and echocardiography showed no changes. Systemic lupus erythematosus or other autoimmune diseases have been excluded, as the antinuclear antibodies (ANA), anti-dsDNA antibodies, and the panel of ANA were all negative. Pregnancy, toxic environment, or drug-induced aplasia

**TABLE 1.** The evolution of biological findings

	Normal range	On admission	1 month after the initiation of the IST	6 months after the initiation of the IST
Hemoglobin	12–15.5 g/dL	4.8 g/dL	5.7 g/dL	4.1 g/dL
Platelet count	150,000–300,000/mm <sup>3</sup>	9,000/mm <sup>3</sup>	1,000/mm <sup>3</sup>	4,000/mm <sup>3</sup>
Leukocytes	4,000–9,000/mm <sup>3</sup>	3,200/mm <sup>3</sup>	2,000/mm <sup>3</sup>	1,500/mm <sup>3</sup>

have also been excluded. Based on clinical and paraclinical data, the patient was diagnosed with idiopathic medullary aplasia.

The patient immediately received supportive treatment including blood transfusions and vitamin therapy. We have also started combining immunosuppressive therapy (IST) with horse anti-thymocyte globulin (h-ATG) and cyclosporin A (CsA). On day 7, in the presence of severe thrombocytopenia, recurrent episodes of spontaneous nosebleeds and bleeding gums occurred, but the signs and symptoms secondary to anemia disappeared and Hb increased to 9.7 g/dL. One month after the initiation of IST, the patient's general condition and paraclinical markers had not improved. Severe anemia had reemerged, and the level of platelets and leukocytes had dropped to 2,000/mm<sup>3</sup> and 1,000/mm<sup>3</sup>, respectively (Table 1). Given the increased risk of life-threatening bleeding and because, in that case, an allogeneic bone marrow transplantation was planned, administration of irradiated platelet concentrates was indicated. The patient also received another blood transfusion. Moreover, taking into account the insufficient response to the initial IST, we added eltrombopag to the combination of h-ATG and CsA.

The patient's paraclinical findings from the most recent follow-up in the hematology department, at five months after the initiation of eltrombopag along with h-ATG and CsA, were unsatisfactory, with the persistence of severe pancytopenia (Table 1). The patient and the institution agreed with the study. All study procedures were in line with the principles stipulated in the Declaration of Helsinki. Because personal data was published, an informed signed consent for publication was obtained from the patient.

## DISCUSSIONS

Most patients with aplastic anemia present signs and symptoms secondary to the development of anemia (asthenia, dyspnea, dizziness, pallor), thrombocytopenia (petechiae, purpura, ecchymosis, hematomas, epistaxis or bleeding gums), or leukopenia (infections). The symptoms that brought this patient to the hospital were caused by the development of anemia, and soon after her admission, spontaneous epistaxis and bleeding gums occurred.<sup>1</sup> Fortunately, the patient did not develop any septic state secondary to bacterial, viral, or fungal infection.

The current standard of care for most patients includes supportive treatment such as blood transfusions, platelet concentrates, and prevention of infections. Even though leukopenia can cause severe bacterial infections, the ad-

ministration of broad-spectrum antibiotics should be used only in the presence of fever, severe neutropenia, or other signs and symptoms of infections. The use of prophylactic antifungal, antibiotic, or antiviral therapy had no clear recommendations, and there is no study to prove their effectiveness.<sup>8-13</sup> First-line therapy for definitive treatment in patients under the age of 40 years is represented by allogeneic bone marrow transplantation, if a human leukocyte antigen (HLA)-compatible family donor exists. In these cases, irradiated blood products as a supportive treatment are indicated if needed.<sup>11,13,14</sup> There are many sources reporting that an allogeneic transplant from a matched sibling donor heals most patients and has a high survival rate.<sup>11,13,15,16</sup> For patients over 40 years of age or when there is no histocompatibility with sibling donors, immunosuppressive therapy remains the first-line regimen. Since the 1990s, studies have shown that the combination of horse anti-thymocyte globulin and cyclosporin A has a hematological response rate of 60% to 70%. However, there is a small number of patients that remain refractory or have an insufficient response to IST.<sup>17-22</sup> Since its approval in 2014, the addition of eltrombopag, an oral synthetic thrombopoietin receptor agonist, to the standard IST for aplastic anemia, has resulted in an increased hematologic response rate. Studies revealed that patients who receive eltrombopag, horse anti-thymocyte globulin, and cyclosporin simultaneously, from the first day of treatment, present a substantial increase in complete recovery, with excellent long-term survival and lower rate of complications or development of a second malignant tumor.<sup>23-27</sup> The literature also describes the case of a patient with aplastic anemia treated with front-line eltrombopag in monotherapy.<sup>28</sup> Further emphasizing these results, the primary endpoint of the RACE study, a large, prospective, randomized multicenter study conducted by the European Group of Blood and Marrow Transplantation [NCT02099747], is to demonstrate if eltrombopag added to standard IST (h-ATG + CsA) increases the rate of complete recovery in untreated aplastic anemia patients.<sup>26,29</sup> Based on the results of a study conducted by the National Heart, Lung and Blood Institute of the National Institutes of Health, patients in the RACE study receive eltrombopag on day 14 after IST.<sup>26</sup>

Considering all the available treatment data on aplastic anemia, our patient received the standard proper treatment according to clinical and laboratory investigations. Despite all therapeutic measures applied, the prognosis of this patient remained reserved. The vital prognosis of the disease is related to the severity of the leukopenia and thrombocytopenia leading to an increased risk of bleeding or overwhelming generalized systemic infection. The age

of the patient can also be an important prognostic factor, with patients over the age of 40 having a higher mortality rate. Another important predictor for survival is related to the interval between diagnosis and the initiation of different interventions such as supportive care, bone marrow transplantation, or IST.<sup>1,2,6</sup> In our case, the patient was young (23 years), with no inherited or acquired hematologic or malignant disorders, no toxic exposures or exogenous risk factors that may have led to acquired aplastic anemia. Despite these positive points, the onset of the disease was fulminant and the evolution unfavorable due to the absent response to immunosuppressive treatment. In this situation, the only option for definitive treatment was bone marrow transplantation. The patient had been informed of the need for transplantation. We have requested the HLA typing of the family members. Sadly, because of the severe leukopenia, it was not possible to determine the HLA type of the patient, further delaying the bone marrow transplant.

## CONCLUSIONS

Medullary aplasia is a hematologic condition associated with a high prevalence of mortality and morbidity. Every effort should be made in order to diagnose and initiate treatment as soon as possible and long-term monitoring is mandatory. Despite new therapies developed for the treatment of aplastic anemia, there are still patients that present insufficient response to the initial immunosuppressive treatment. In this case report we presented a case of unresponsive severe aplastic anemia after 6 months of eltrombopag associated with the horse anti-thymocyte globulin and cyclosporin in a very young patient.

## CONFLICT OF INTEREST

Nothing to declare.

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