DOI: 10.46765/2675-374X.2021v2n2p88

ALLOGENEIC TRANSPLANTATION IN AUTOIMMUNE DISEASE AND BONE MARROW APLASIA - CASE REPORT

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Running title: APLASIA AND ALLOGENEIC TRANSPLANTATION

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ABSTRACT

Ulcerative rectocolitis (UC) is an inflammatory bowel disease of unknown etiology that mainly affects the mucosa of the rectum and colon. Anemia is the most common hematological disorder in patients with UC and may be due to multiple causes such as blood loss, malabsorption, chronic illness and infection. We present a case report, in which UC and severe aplastic anemia (ASA) occur concomitantly, suggesting a common immune compromise between such pathologies.

Key words: Transplantation, Homologous. Transplantation, Haploidentical. Bone marrow aplasia. Proctocolitis.

INTRODUCTION

Ulcerative retocolitis (UC) is an inflammatory bowel disease of unknown etiology that mainly affects the mucosa of the rectum and colon. Anemia is the most common hematological disorder in patients with UC and may be due to multiple causes such as blood loss, malabsorption, chronic disease and infection[1]. Other rare hematological manifestations associated with UC include myelodysplastic syndromes (MDS) and leukemia[2].

Bone marrow aplasia is considered a rare disorder, with an estimated incidence of 2 per 1,000,000 inhabitants per year in Western countries. In Asia, this rate is about 2 to 3 times higher[1,2.] Half of the cases of aplastic anemia occur in the first three decades of life.

Several researchers suggest a clinical association between inflammatory bowel disease and MDS, since they share an immune dysfunction that impairs the activity of T lymphocytes[2,3] Some few case reports suggest an association between UC and severe aplastic anemia[4,5].

Aplastic anemia is a disease of bone marrow stem cells characterized by ineffective hematopoiesis, leading to pancytopenia. Although aplastic anemia is often idiopathic, immune-mediated suppression of hematopoiesis can occur in at least 50% of patients, since more than half of them achieve hematological remission in response to immunosuppressive therapy[6].

We report here a case of UC associated with pancytopenia requiring blood transfusion in a young patient whose bone marrow examination was compatible with aplastic anemia. A common pathogenic association between UC and aplastic anemia is suggested in this patient and can be explained based on an underlying immune compromise shared in both diseases.

LITERATURE REVIEW

Bone marrow aplasia is defined as pancytopenia, associated with aplasia or spinal hypoplasia, with a

consequent significant decrease in hematopoietic and progenitor stem cells[7].

Severe aplastic anemia (SAA) evolved from a disease with a high lethality rate in the 1960s to one in which long-term survival can be achieved in most patients after diagnosis. Current clinical and laboratory evidence defines an immunological pathophysiology in which effector cells and related cytokines recognize and destroy bone marrow precursor elements[8]. Among the associated immune diseases, most cases do not have a clear cause and are defined as idiopathic[8].

Aplastic anemia is also associated with histocompatibility antigens. The presence of "escape clones" (granulocytes with loss of chromosome 6 region that includes HLA alleles) in 10 to 15% of patients is impressive; selected cells due to the absence of HLA, acquired by 6p loss of heterozygosity (LOH) or somatic mutations support hematopoiesis by means of clonal expansion[9].

The HLA-DRB1 15 and HLA-DRB1 15:01 polymorphisms may be associated with an increased risk of SAA in Asians. Immunosuppressive therapy may be more effective in Asian patients with HLA-DRB1 15 and HLA-DRB1 15:01 polymorphisms than in Asian patients without such polymorphisms[10].

The immunosuppressive therapy of choice in AAS is with horse thymoglobulin associated with cyclosporine, which produces hematological recovery in 60 to 70% of cases and very good long-term survival, particularly among responders. However, hematological recurrence occurs in 30 to 40% of responders and clonal evolution to myelodysplasia in 10 to 15%. In Brazil, there is still a limitation regarding immunosuppressive therapy, since rabbit thymoglobulin is not available[9].

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For aplastic immune anemia in a young patient, transplantation is always the treatment of choice. When performed immediately after diagnosis, using a graft from a histocompatible donor brother, the results are excellent, with an estimated long-term survival rate of more than 90% among children and greater than 80% among adolescents, with a low rate of short- and long-term complications[8].

Haploidentical transplantation has been advocated in China as first-line treatment for children. In Europe, with an average 1-year survival rate of around 74%, haploidentical transplantation is recommended as second-line therapy. The current results are promising, but due to the relatively limited number of reported cases and the unknown long-term effects of complicated regimes and an incompatible immune system, haploidentical transplantation is considered experimental in the United States and Europe[8].

Ulcerative Retocolitis is an inflammatory bowel disease of unknown etiology that mainly affects the mucosa of the rectum and colon. Immunological mechanisms play an important role in UC, and immunogenetic factors are related to the development of the disease.

In this patient, the justification for the coexistence of ulcerative colitis and aplastic anemia is suggested based on an underlying immune compromise shared in both diseases[11].

CASE REPORT

A 23-year-old patient presents in September 2019 with abdominal pain associated with diarrhea. He had a colonoscopy performed and showing a diagnosis of ulcerative colitis. It was prescribed Mesalazine therapy (3.2 g / day) and dietary guidelines were started.

He developed headache and intermittent fever. Clinical and laboratory investigation of the condition showed severe pancytopenia.

In December 2019, he was referred for hematological investigation. Bone marrow biopsy was performed, showing hypoplasia, with a diagnosis of marrow aplasia. PNH research (02/2020) with the presence of a clone in 3% of red blood cells // 94.8% of granulocytes // 91% of monocytes. Negative DEB test.

At that time, he also had abdominal pain and severe diarrhea, despite the use of Mesalazine. An investigation was carried out with a new colonoscopy showing descending colitis, affecting the descending and sigmoid colon; in addition to an active ileum ulcer.

He was maintained n supportive therapy with platelet transfusions and red blood cell concentrates. Using Danazol.

After three months, despite dose adjustments of Danazol, due to the lack of response he started immunosuppressive therapy with Ciclosporin 200mg / day.

In this context, he already had partial improvement in diarrhea and abdominal pain.

Control colonoscopy was performed in July 2020, which maintained diagnostic characteristics, with edema and enantematous rectal mucosa, from the distal segment to the anal mucosa. Erosions, friabil-

ity, edema and enanthema even in the anal canal. There was no longer an ileal ulcer.

Search for bone marrow donor started, considering young patient, with adequate performance status. It was not found any unrelated compatible donor.

At that time, he remained with red blood cells and platelets transfusions, presenting different kinds of reactions, with the need for washed components.

He was referred to the Bone Marrow Transplant service, maintaining severe pancytopenia (Hb 7.9g / dL; Neutrophils: 740; Platelets 35,000).

The patient was submitted to an allogeneic transplant, with haploidentical donor. Female donor, 25 years old, ABO compatible, CMV status discordant (IgG + donor / IgG receptor -). Anti HLA negative.

Conditioning protocol was used with Cyclophosphamide (14.5mg / kg), Fludarabine (30mg / m^2) and Total Body Irradiation (TBI - 400cGy dose), associated with the dose of Cyclophosphamide (50mg / kg) in D + 3 and D + 4 for prophylaxis of GVHD. He received hematopoietic stem cells from the bone marrow (mononuclear cells 4.5 x 10 ^ 8 / kg).

Neutrophil and platelet uptake occurred on September 9th (D + 18). Transplantation underwent without major complications, he was discharged at D + 20 for outpatient follow-up, without acute GVHD.

Currently, 4 months after transplantation, using Tacrolimus, in an immunosuppressive dose, controlled by weekly dosage of the serum level of the drug. Hematimetric indices within normal values (Hb 12g / dL; leukometry 3030; neutrophils 1970; platelets 143,000), with no signs of chronic GVHD. He denies any gastrointestinal complaints.

DISCUSSION

The case in question reports a young patient, with a recent diagnosis of severe bone marrow aplasia, associated with Ulcerative Colitis.

It is known that allogeneic transplantation is indicated as the initial strategy to approach ASA in young patients, with a related donor available.

However, currently, there are no robust data in the literature regarding haploidentical transplantation in severe aplastic anemia. Despite that, this type of transplantation has been widely used, considering the advantage of having a related donor available immediately. In addition, recent studies have shown response rates similar to transplants from related and unrelated donors.

Another issue to be considered for allogeneic pre-transplant evaluation is the response to thymoglobulin. In Brazil, difficulties are encountered in the treatment of marrow aplasia, since rabbit thymoglobulin is not available. Such medication is not marketed in the country, only horse thymoglobulin, which is known to have much lower efficacy results.

In addition, most of the Hematology services, related to the public health care system (SUS), do not have anti-thymocytic therapy.

In the reported case, a young patient with a high transfusion need and consequent exposure to various pathologies has been admitted to a transplant service, including a positive HBsAg antibody dosage during treatment. In addition, he already had indication to use only washed hemoconcentrates, due to the high incidence of transfusion reactions.

No 10/10 compatible donor, related or unrelated, had been found, despite extensive search on REDOME (National Registry of Bone Marrow Donors).

It was also known that the patient has HLA-DRB1 15 and HLA-DRB1 15:01 polymorphisms that may be associated with increased risk of AA; while the haploidentical donor did not have it.

Thus, it was considered a young patient, with very severe marrow aplasia, without the availability of adequate immunosuppressive therapy, in need of frequent hospitalizations, due to infection or transfusion reaction. A few months after the diagnosis of AAS, the COVID-19 pandemic began, which made it even more difficult for the patient to have immediate access to health service.

Despite limited data involving haploidentical transplantation in AAS, we opted for such alternative since the patient's imminent risks at that time justified our choice.

With bone marrow transplantation, it was possible to treat both ongoing diseases: Ulcerative Colitis and Severe Bone Marrow Aplasia.

It is known that currently in Brazil, the transplantation of hematopoietic stem cells is very little used in the approach of autoimmune pathologies, despite presenting quite satisfactory results in international studies. With the development of new techniques and improvements in care, such therapy is increasingly safe and is the only one that can offer an improvement in the quality of life of young patients, who would naturally be exposed to various immunosuppressive therapies, and their respective risks, to the throughout life.

FINAL CONSIDERATIONS

The aim of this report was to discuss the curative approach to both bone marrow aplasia and ulcerative colitis, through allogeneic transplantation in a young patient. In addition, the modality of haploidentical transplantation is also addressed, which has been increasingly used, considering greater chances of finding a compatible donor.

It was not possible to compare our results with other studies, since there is little data in the literature evaluating patients whose incidence of such pathologies already considered rare, occurring in concomitance, becomes even more limited.

Thus, we exhibit a case of cell therapy, with haploidentical bone marrow transplantation, capable of achieving remission of AAS and UC. The patient in question is being followed up on an outpatient basis. At the present moment, immunosuppressive therapy has been suspended, the patient does not present any gastrointestinal symptoms or cytopenias, with hematimetric indices within normal values.

Cases like this one encourage both hematologists and gastroenterologists to consider bone marrow transplantation as a curative therapeutic possibility for their patients.

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