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Case Report

Severe Bone Marrow Hypoplasia in a Combined Treatment with Anti PD 1/CTLA-4 in a Patient with Melanoma: A Case Report and Literature Review

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Abstract

Immunotherapy with monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen 4 and the programmed death-1 receptor and its ligand PD-L1 has become standard of care for an increasing number of indications [1]. In recent years, an increasing number ofpatients have been exposed to these drugs with a chance of developing toxicities from these treatments [2]. Severe-hematological toxicities have been rarely reported in the literature. We reported a case of a severe bone marrow hypoplasia associated with immunotherapy. The diagnosis was confirmed with bone marrow biopsy after ruling out other pathologies associated with this entity.

Keywords: Immunotherapy; Nivolumab; Ipilimumab; Bone marrow hypoplasia.

Introduction

Immunotherapy has been positioned as an effective treatment for many tumors. Its effectiveness lies in enhancing antitumor immunity. Although it is usually well tolerated by patients, various adverse effects of autoimmune etiology may appear in approximately 10%, the most frequent being rash, hepatotoxicity, diarrhea, pneumonitis and thyroiditis, among others [3].

Severe bone marrow hypoplasia associated with immunotherapy is a complication rarely reported in the literature and its management poses a therapeutic challenge. In pivotal studies, the incidence of severe hematological adverse effects was low (1 to 3%), with aplastic anemia being a rarely reported event [4,5].

In a multicentric retrospective study, including 7626 patients treated with checkpoint inhibitors, only 50 developed immune-related hematologic adverse events and aplastic anemia represented only 2% of the events [6]. In another study including 437 patients diagnosed with melanoma, the incidence of hematological disorders was 0.9%, and the median of adverse events was 94 days after the onset of treatment [7].

Two meta-analyses that collected patients with aplastic anemia secondary to immunotherapy showed that the incidence of the event was mainly related to melanoma and lung cancer. The median age of onset of the adverse effect was between 59 and 65.6 years [8,9].

The recognition of immune-related hematological toxicities are important because the establishment of an early treatment is crucial to mitigate its severity [10]. We report a case of a patient diagnosed with bone marrow hypoplasia refractory to immunosuppressive treatment.

Case Report

A 57-year-old female patient with a history of locally

advanced amelanotic melanoma of the anal canal is presented. On day 0, systemic immunotherapy with ipilimumab and nivolumab was started.

On day 79, she presented to the emergency room with acute proctorrhagia and abdominal pain. Its intensity was 5/10 according to the Eva scale. She denied allergies and drug use. Her ECOG PS was one. Her usual medication was methadone 5 mg/day, paracetamol 1 g/12hrs., pantoprazole 40 mg/day, iron polymaltosate 100 mg/day and prednisone 10 mg/day. On admission, she was afebrile, hemodynamically stable. She had a soft, depressible, distended abdomen, slightly painful on deep palpation, without defense or peritoneal reaction. She presented petechiae, predominantly in the lower limbs and non-palpable purpura in support sites.

Renal function, liver function tests, and intrinsic and extrinsic coagulation pathway times were within normal values. The stool smear was reactive for Clostridium Difficile.

A contrast-enhanced abdominal CT was requested, which showed thickening of the right colon, sigmoid, and rectum. Due to severe clostridial diarrhea, treatment was started with oral vancomycin and intravenous metronidazole. The patient completed 14 days of treatment, with clear improvement of her symptoms within the first 48 hours, but without resolution of the laboratory abnormality that led to her hospitalization.

Due to persistent tricytopenia, it was decided to continue with other complementary studies in order to clarify the differential diagnoses. (Table 1)

Viral serologies	Non-reactive HIV (by 4th generation ELISA and P53 Western Blot); HCV non-reactive, HBV non-reactive, EBV non-reactive. CMV and EBV ruled out acute infection, VDRL negative. Negative parvovirus
Autoimmunity	Negative antinuclear and anticytoplasmic antibodies.
Ferrokinetic profile	Iron: 76 ug/dl Transferrin: 154 ug/d., Transferrin saturation: 35% Ferritin: 681.40 ng/ml
Hemolysis parameters	Indirect bilirubin: 0.53mg/dl. Lactate dehydrogenase. 312 IU/.l Direct Coombs: Positive (Requested after the first transfusion). Haptoglobin: 274 mg/dl No schistocytes on peripheral blood smear.
Vitamins B12 and B9	Normal values according to age.

Table 1: Complementary studies for differential diagnoses.

As the patient did not have any evident cause and suspecting an immune-related adverse event meprednisone 1 mg/kg was started without response in the usual expected time. She required poly transfusions of platelets throughout the hospitalization without achieving any increase in number (<10,000 mm3). A total of eighteen units of red blood cells and sixty-nine plasma concentrate by apheresis were transfused. Figure 1a,1b and 1c shows the time line and variation of the hemogram.

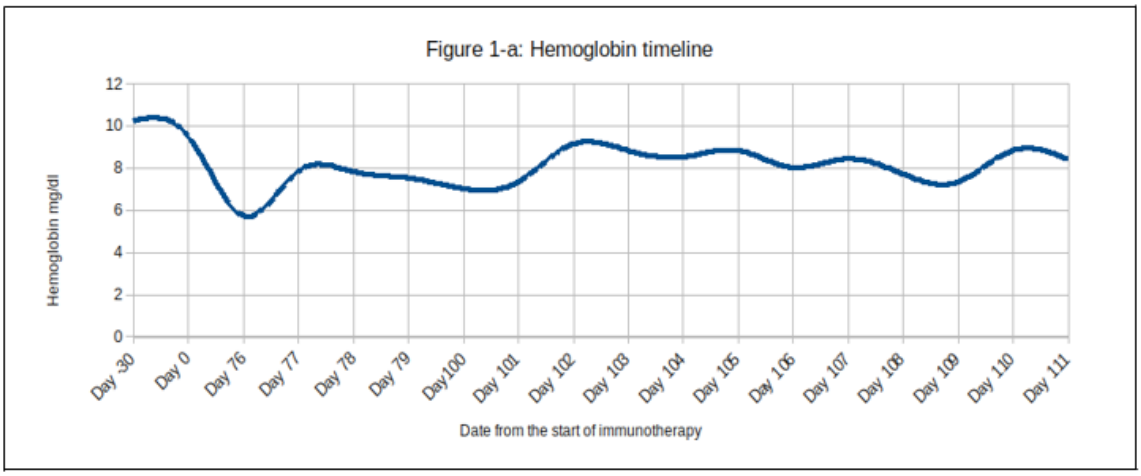

Figure 1a: Hemoglobin timeline. Day 0 (zero) represents the beginning of immunotherapy.

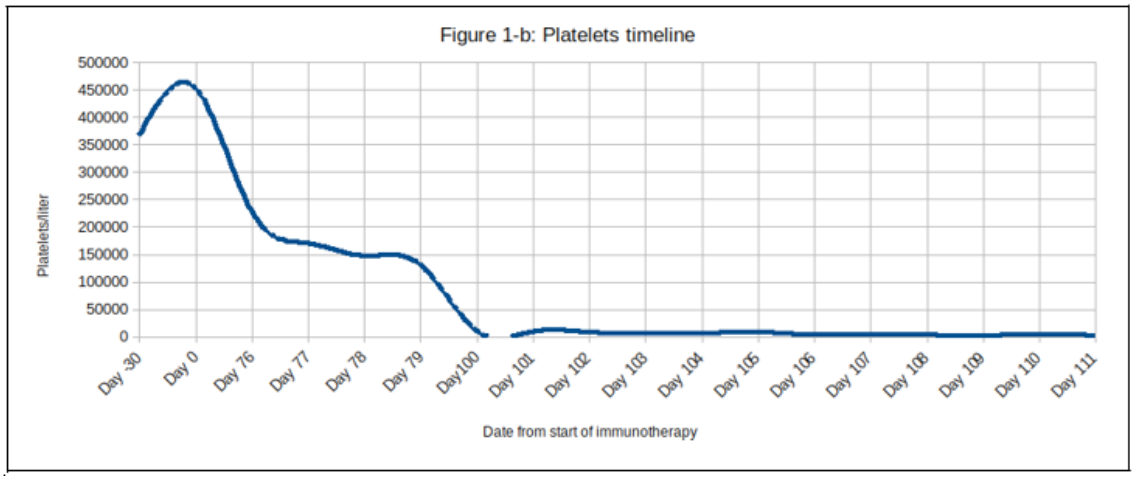

Figure 1b: Platelets timeline. Day 0 (zero) represents the beginning of immunotherapy.

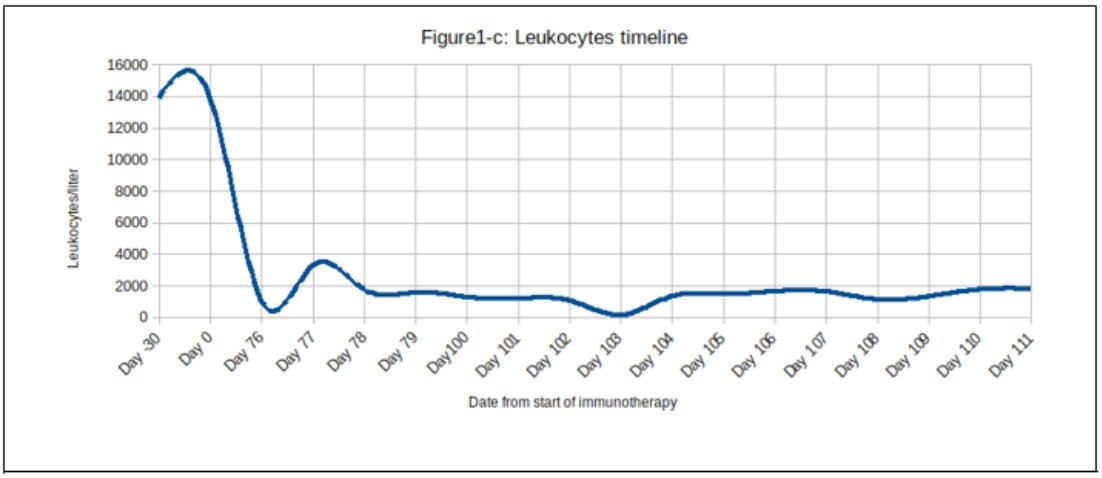

Figure 1c: Leukocytes timeline. Day 0 (zero) represents the beginning of immunotherapy

Positive direct Coombs was requested after the first transfusion, and it was interpreted as a false positive.

A bone marrow aspiration was performed, in order to study marrow function. The medullogram showed scant cellularity, a very reduced erythroid series and an absence of myeloid and megakaryocytic series. Most of the marrow spaces had adipose tissue and blood. The biopsy was interpreted as severe hypoplasia.

The patient continued with severe tricytopenia requiring platelet and red blood cell transfusions. He was treated with eltrombopag and filgrastim, concomitantly, in a daily scheme, without improvement.

As above mentioned, having ruled out the most relevant differential diagnoses, we concluded that the diagnosis was an immune-related bone marrow hypoplasia.

Discussion

Immunotherapy has become the first line treatment in a significant number of solid tumors, including melanoma. Although it usually has a favorable toxicity profile, compared to chemotherapy, with the increase in the number of patients treated, we had begun to observe infrequent adverse effects.

Dual therapy with PD-1 and CTLA 4 inhibitors has shown benefit in progression-free survival and overall survival in the management of advanced melanoma. However, the combination increases the risk of immune-mediated adverse effects [11].

In our case, the coexistence of diarrhea due to Clostridium and tricytopenia led us to think of secondary bone marrow failure. However, tricytopenia persisted with the infectious condition resolved, for which we opened the range of differential diagnoses. After we had ruled out the main causes of severe bone marrow hypoplasia, the strong temporal relationship between the start of immunotherapy and tricytopenia maked us conclude that this histopathological diagnosis was related to the use of the ipilumab-nivolumab combination.

After carrying out a bibliographic review, we confirmed the rarity of the adverse effect that the patient presented. To date, there is no clear recommendation on how to act against bone marrow hypoplasia. Although, there is uniformity in discontinuing treatment and starting corticosteroids [6,12]. In the absence of clinical resolution, immunomodulators and antithymocyte globulin could be useful [9].

The absence of response to suspension of treatment and initiation of corticosteroids leads to death in most case reports. So we can conclude that it is an adverse effect that carries a poor prognosis and is usually refractory to treatment.

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