Pembrolizumab-Induced Pancytopenia: A Case Report

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ABSTRACT

Introduction: Programmed death receptor-1 blockade with pembrolizumab is approved by the US Food and Drug Administration to treat patients with metastatic melanoma. Activating T cells to fight cancer may cause immune-mediated adverse events. Pembrolizumab-induced pancytopenia has not been previously reported in the medical literature, to our knowledge.

Case Presentation: A 52-year-old Caucasian woman with a diagnosis of metastatic melanoma of the rectum experienced multiple adverse events along her course of therapy with pembrolizumab, ranging from colitis, hepatitis, gastritis, and vitiligo after the fifth cycle of pembrolizumab; to knee synovitis after the 14th cycle; and to severe pancytopenia after the 18th cycle of pembrolizumab. Severe pancytopenia improved after high-dose corticosteroids and a 5-day course of intravenous immunoglobulin therapy.

Discussion: In our case, pembrolizumab-induced Grade 4 pancytopenia resolved via a combination of corticosteroids and intravenous immunoglobulins. Pancytopenia reached a nadir in 10 weeks, and it took 16 weeks for meaningful recovery.

INTRODUCTION

Since the mid-1990s, the medical community has witnessed the birth of immunotherapy to fight cancer. The tremendous discovery of the efficacy of immunotherapy in melanoma paved the way for its application in other types of cancers such as non-small cell lung cancer, head and neck cancers, renal cell carcinoma, and urothelial carcinoma of the bladder.[1] The US Food and Drug Administration approved 3 different immunotherapeutic drugs for the treatment of advanced melanoma: ipilimumab, which is a monoclonal antibody against the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and nivolumab and pembrolizumab, which are monoclonal antibodies against the programmed cell death-1 (PD-1) receptor.[2,3] These monoclonal antibodies are also referred to as "immune checkpoint inhibitors" because they remove the brakes (the checkpoints) from the immune system and activate T cells.[1-3] With activation of the T cells to fight cancer, there is always a chance that these activated T cells might attack normal tissues, leading to immune-related adverse events such as colitis, hepatitis, pneumonitis, endocrinopathies, skin rash, and rarely encephalitis.[1-3] Immune-mediated hematologic toxicity could vary from anemia, thrombocytopenia, and leukopenia to rarely pancytopenia (Table 1).[4-14] We present the first case, to our knowledge, of pembrolizumab-induced pancytopenia to be reported in the literature.

CASE PRESENTATION

Presenting Concerns

A 52-year-old Caucasian woman presented with episodes of bright red blood per rectum for 1 month. Colonoscopy showed an ulcerated mass in the distal aspect of the rectum. Pathologic analysis confirmed malignant melanoma. The initial positron emission tomography-computed

Table 1. Immunotherapy-induced cytopenia reported in the literature

Author, year	Disease	Immunotherapy	Type of cytopenia	Treatment
Le Roy et al, 2016[4]	Metastatic melanoma	Pembrolizumab	Thrombocytopenia	Steroids and IVIG
Langer et al, 2016[5]	Non-small cell lung cancer	Pembrolizumab	Anemia, thrombocytopenia, neutropenia	Unknown
Nair et al, 2016[6]	Metastatic melanoma	Pembrolizumab	Autoimmune hemolytic anemia, pure red cell aplasia	Steroids and IVIG
Weber et al, 2015[7]	Metastatic melanoma	Nivolumab	Anemia	Steroids
Sharma et al, 2016[8]	Metastatic urothelial carcinoma	Nivolumab	Anemia, thrombocytopenia	Unknown
Schwab et al, 2016[9]	Squamous cell skin cancer	Nivolumab	Autoimmune hemolytic anemia	Steroids
Kong et al, 2016[10]	Metastatic melanoma	Nivolumab	Autoimmune hemolytic anemia	Steroids
Inadomi et al, 2016[11]	Metastatic melanoma	Nivolumab	Anemia, thrombocytopenia	Steroids, RBC and platelet transfusion
Di Giacomo et al, 2011[12]	Metastatic melanoma	Ipilimumab	Pancytopenia	Steroids
Zimmer et al, 2015[13]	Metastatic melanoma	Ipilimumab	Pancytopenia	Steroids
du Rusquec et al, 2014[14]	Metastatic melanoma	Ipilimumab	Autoimmune pancytopenia	Steroids, IVIG, hematopoietic growth factors

IVIG = intravenous immunoglobulins; RBC = red blood cell; steroids = corticosteroids.

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tomography (CT) scan, obtained on October 28, 2014, revealed a rectal mass (3 cm × 2.8 cm × 5.8 cm) along with pelvic and retroperitoneal lymphadenopathy. Figure 1 shows a timeline of the case with relevant history and interventions. Figure 2 shows a timeline of relevant laboratory test results. We received written informed consent from the patient for treatment and inclusion in this case report.

Therapeutic Intervention and Treatment

The patient completed 2 cycles of ipilimumab, 3 mg/kg intravenously every 3 weeks, but severe colitis developed that was resistant to corticosteroids. However, she responded well to infliximab, with a total of 2 doses 4 weeks apart.

Follow-up and Outcomes

A follow-up CT scan of the abdomen and pelvis revealed disease progression, so a regimen of pembrolizumab (2 mg/kg intravenously every 3 weeks) was initiated. After 5 cycles of pembrolizumab, severe gastritis and pancolitis developed, confirmed by biopsy. *Clostridium difficile* antigen and toxin test results were negative. In addition, the patient developed potentially immune-mediated hepatitis and vitiligo. Pembrolizumab therapy was withheld, and prednisone treatment was initiated at 60 mg/d, with a quick taper in dosage by 10 mg/d every week during the next 4 weeks.

A CT scan of the abdomen and pelvis two months after the fifth cycle of pembrolizumab showed a complete response. Five months after her fifth cycle of pembrolizumab, the patient developed retroperitoneal lymphadenopathy, so pembrolizumab treatment was restarted.

After the 14th cycle of pembrolizumab, low-grade fever developed along with right knee stiffness, swelling, and pain. The patient underwent laparoscopic right knee surgery for repair of a suspected acute medial meniscal tear seen on magnetic resonance imaging; however, during the surgery the synovium was inflamed and was completely excised. Final pathologic results were consistent with acute synovitis, which was believed to be caused by pembrolizumab. The patient responded to a short course of prednisone, 60 mg/d orally, which was used for only 2 days. She refused to continue the medication regimen because of fear of adverse events. Therefore, a single dose of infliximab was given.

Cycle 15 of pembrolizumab was resumed on July 7, 2016, and a month later the patient presented with left knee swelling and pain. She responded well to a course of corticosteroids and resumed pembrolizumab therapy. After Cycle 18 of pembrolizumab, severe pancytopenia developed. Pembrolizumab therapy was again withheld, and the patient received prednisone, 1 mg/kg orally daily, with a tapering dosage over 6 weeks. She continued to have pancytopenia, after which she received a 5-day course of intravenous immunoglobulins (IVIG), 1 g/kg daily. The patient required red blood cell (RBC) and platelet transfusions as well. A bone marrow biopsy specimen was hypocellular for age (20% cellularity).

Results of a repeat bone marrow biopsy 6 weeks after the course of IVIG revealed normocellular bone marrow for age (40%

Dates	Relevant Past Medical History and Interventions		
April 20, 2015	**Chief complaint:** A 52-year-old woman presented with episodes of bright red blood per rectum for one month. **Physical examination:** normal. **Previous imaging:** PET-CT scan obtained October 28, 2014 revealed a rectal mass (3 x 2.8 x 5.8 cm) along with pelvic and retroperitoneal lymphadenopathy. **Previous intervention:** Colonoscopy dated November 7, 2014 revealed an ulcerated rectal mass and biopsy confirmed malignant melanoma.		
Dates	**Summaries from initial and follow-up visits**	**Diagnostic testing**	**Interventions**
November 4, 2014	No complaints	none	Received ipilimumab
November 25, 2014	Tolerating ipilimumab well	none	Received ipilimumab
December 12, 2014	Abdominal pain and diarrhea	Colonoscopy showed erythema and enlarged rectal mass	Patient received oral prednisone 60 mg/d and a dose of infliximab; ipilimumab was discontinued
December 15, 2014	Abdominal pain	none	Laparoscopic colostomy for near-obstructing rectal mass
January 18, 2015	Diarrhea while tapering down her prednisone	none	Infliximab
February 2015-April 2016	Follow-up every 3 wks for immunotherapy with pembrolizumab	PET-CT every 3 mos while on pembrolizumab	Received 14 cycles of pembrolizumab
May 4, 2015	Follow-up visit revealed hepatitis, vitiligo, diarrhea after her 5th cycle of pembrolizumab	CT chest/abdomen/pelvis showed an overall decrease in size and density of the metastatic liver lesions; interval decreased in size of rectal and pelvis masses	Pembrolizumab dose was held; received prednisone 60 mg with taper over 4 wks; after symptoms resolved, pemprolizumab was restarted
April 18, 2016	Patient completed 14 cycles of pembrolizumab but now presents with severe right knee pain	MRI right knee showed a complex tear of the posterior horn of her medial meniscus	Right knee arthroscopy dated April 20, 2016, revealed inflamed synovium; total synovectomy was done
May 17, 2016	none	none	Colostomy take down and removal of two periaortic lymph nodes; pathology confirmed melanoma
July 7, 2016	Patient has no complaints and presents to resume pembrolizumab	none	Patient resumed pembrolizumab (cycle 15)
July 28, 2016	Patient presents with severe left knee pain with effusions	PET-CT showed progression of disease with periaortic lymphadenopathy	Pembrolizumab was held; infliximab was given for acute left knee synovitis
September 12, 2016	No new complaints	none	Resumed pembrolizumab
October 3, 2016	Fatigue, pale	Complete blood count revealed severe pancytopenia	Pembrolizumab was held; patient treated with prednisone 1 mg/kg taper over 4 wks and IVIG.
February 6, 2017	Feeling good	PET-CT showed enlarged periaortic lymphadenopathy that has increased in size since holding pembrolizumab in October 2016	Pembrolizumab was resumed, and on February 11, 2017, she developed again severe pancytopenia (WBC 1.88, Hgb 7.4, PLT 46); decision was made to give 2 consecutive cycles of pembrolizumab and skip one

Figure 1. Timeline of the case with relevant medical history and interventions.

CT = computed tomography; Hgb = hemoglobin (g/dL); IVIG = intravenous immunoglobulins; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography; PLT = platelets (× 10^9/L); WBC = white blood cells (× 10^9/L).

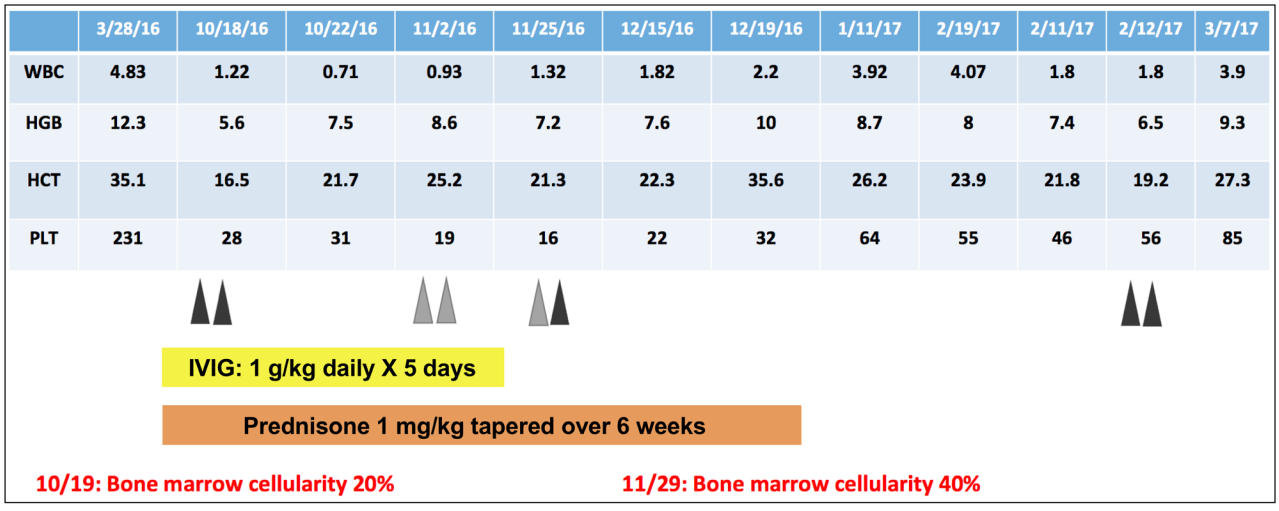

Figure 2. Screenshot from the patient's electronic medical record showing the timeline of the case with relevant laboratory tests results. Dates are month/day/year.

HCT = hematocrit (%); HGB = hemoglobin (g/dL); IVIG = intravenous immunoglobulins; PLT = platelets (× 10^9/L); WBC = white blood cells (× 10^9/L); ▲ = 1 U of red blood cell transfusion, ▲ = 1 U of platelet transfusion.

cellularity) with erythroid predominance. Her blood cell counts improved greatly, although remaining lower than normal, and she is doing fairly well at the time of this writing. A repeat positron emission tomography-CT showed complete response.

DISCUSSION

Pembrolizumab-induced anemia or thrombocytopenia has rarely been reported. To our knowledge, this is the first case to report the association of pembrolizumab with severe prolonged pancytopenia. In our case, pembrolizumab-induced Grade 4 pancytopenia successfully resolved via a combination of corticosteroids and IVIG. Pretreatment and posttreatment bone marrow biopsy specimens showed that recovery of the peripheral blood cell count lagged behind the bone marrow recovery in our case. A repeated bone marrow biopsy may be considered if pancytopenia does not improve despite treatment with IVIG and a corticosteroid course of 4 to 6 weeks. Le Roy et al[4] reported 2 cases of pembrolizumab-induced immune thrombocytopenia that resolved quickly after intravenous methylprednisolone and IVIG. In the KEYNOTE-021 study,[5] which is a randomized Phase 2 study of carboplatin and pemetrexed with or without pembrolizumab for treatment of advanced, nonsquamous non-small cell lung cancer, no cases of pancytopenia were reported. However, Grade 3 anemia, neutropenia, and thrombocytopenia were seen in 12%, 3%, and 4% of study subjects, respectively.[5] Nair et al[6] also reported a case of pembrolizumab-induced autoimmune hemolytic anemia with pure RBC aplasia that was successfully treated with corticosteroids and IVIG.

Few cases of cytopenias have been reported with use of nivolumab. A randomized controlled trial by Weber et al[7] described Grade 3 nivolumab-induced anemia in 1% of patients, and this anemia responded well to corticosteroids. Sharma et al[8] reported Grade 3 neutropenia in 3% of study subjects and Grades 1 to 2 anemia in 10%, but none of the subjects had Grade 3 or 4 anemia. Evidently, 1 patient experienced Grade 4 thrombocytopenia that resulted in death.[8] Schwab et al[9] and Kong et al[10] each described a case of autoimmune hemolytic anemia associated with nivolumab that responded appropriately to corticosteroids. Inadomi et al[11] described a patient in whom bicytopenia developed after nivolumab therapy: Grade 4 anemia and Grade 4 thrombocytopenia. The patient received intravenous methylprednisolone treatment and RBC and platelet transfusions, but his bicytopenia did not recover, and he eventually died.[11]

Contrary to the anti-PD-1 immunotherapy, pancytopenia has been well documented in association with ipilimumab (anti-CTLA-4 antibody). Di Giacomo et al[12] and Zimmer et al[13] each described a patient with Grade 4 pancytopenia associated with ipilimumab which resulted in the death of both patients. In addition, du Rusquec et al[14] reported a patient with metastatic melanoma who received ipilimumab and subsequently experienced Grade 4 pancytopenia. The patient received high-dose corticosteroids, IVIG, and hematopoietic growth factors and required RBC and platelet transfusions. The blood cell counts improved subsequently, but pancytopenia relapsed a few weeks after another infusion of ipilimumab and required another course of treatment with hematopoietic growth factors and IVIG.[14]

Immunotherapies are known to cause upregulation and proliferation of T cells and subsequently B cells. During this proliferative response, some of the autoreactive T cells and B cells may go unchecked and subsequently can lead to autoimmune side effects. Our study adds to the growing evidence that immunotherapy can lead to serious hematologic toxicity. Although a few cases of pancytopenia have been described in association with ipilimumab (anti-CTLA-4), none has been reported so far in association with anti-PD-1 inhibitors (nivolumab or pembrolizumab), until this case.

CONCLUSION

With the increased use of immunotherapy in the treatment of metastatic melanoma and other malignancies, physicians are finding themselves in uncharted territory, where we must learn from each other's experiences. It is extremely important to be familiar with the different immune-mediated adverse events that could occur during immunotherapy and to provide appropriate management. Blood cell counts must be closely monitored, and serious Grade 3 or 4 cytopenias should warrant immediate suspension of the treatment and early intervention with high-dose corticosteroids and IVIG if needed. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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The Humors

If the juices of the body were more chymically examined, … it is not improbable, that many things relating to the nature of the humors, and to the ways of sweetening, actuating and otherwise altering them, may be detected, and the importance of such discoveries may be discerned.

— Robert William Boyle, FRS, 1627-1691, Anglo-Irish natural philosopher, chemist, physicist, and inventor