Clinical Oncology: Case Reports

A Case Report of Acute Myeloid Leukemia in a Patient Treated with Pembrolizumab

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Abstract

We report the case of a 68-year old male who presented with worsening epigastric pain and complaints of early satiety. CT abdomen indicated widespread hepatic metastatic disease. The primary malignancy was diagnosed as unresectable cholangiocarcinoma. The patient underwent various conventional chemotherapy and localized radiotherapy, all of which proved ineffective in reducing disease burden. Checkpoint inhibitor pembrolizumab (Keytruda®) was eventually administered. While treatment was effective in decreasing disease burden, fourteen months into treatment with the anti-PD-1 therapy, signs of bone marrow insufficiency became apparent. Bone marrow biopsy revealed leukemic blast cells leading to a suspicion of therapy-related Acute Myeloid Leukemia (AML). We suspect pembrolizumab resulted in the development of leukemia, recognizing this patient received various chemotherapy agents, but only one dose of a drug irinotecan that is known to be associated with therapy-induced AML, In this case report, we suspect AML developed as an adverse event related to immunotherapy.

Keywords

Epigastric; CT; Metastatic disease; Inhibitor; Acute myeloid leukemia

Introduction and Case Reports

We present the case of a 68-year old male who presented with worsening epigastric pain and complaints of early satiety. A Computed Tomography (CT) scan of the abdomen performed in November 2016, showed widespread hepatic metastatic disease with a dominant mass in the left hepatic lobe measuring 18.3 cm × 10.6 cm. Tumor markers, CEA and CA19-9, were both elevated. Based on tumor markers, pathology, and diagnostic imaging, a diagnosis of cholangiocarcinoma was made. Chemotherapy was initiated in December, 2016, with completion of 3 cycles of gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2, based on the ABC-02 trial [1]. CT scans performed in February 2017 indicated disease progression. The patient then proceeded with the 3 cycles of FOLFOX (folinic acid, fluorouracil, and oxaliplatin), with further progression of disease observed. Next, the patient underwent local radiotherapy with Y-90 with no appreciable effect on disease burden. Following Y-90 treatment, the patient completed one cycle of FOLFIRI (Folinic Acid, Fluorouracil, and Irinotecan Hydrochloride) but further treatment

was withheld due to intolerance. Foundation one testing showed mutations in TP53, BRCA1, BRCA2, and loss of MLH1. Loss of MLH1 impairs DNA mismatch repair, resulting in subsequent microsatellite instability leading to the accumulation of mutational load of oncogenes and increased expression of tumor neoantigens [2]. Given these findings, checkpoint inhibitor pembrolizumab (Keytruda®) 200 mg, was initiated and administered intravenously every 3 weeks. CT scan performed in December 2017, indicated partial disease response to the checkpoint inhibitor treatment, with significant disease regression. Pembrolizumab was continued and by December 2018, the dominant left hepatic lobe mass measured 8.6 cm × 4.6 cm.

Unfortunately, fourteen months into treatment with pembrolizumab, signs of bone marrow insufficiency became evident. The patient presented with worsening dysgranulopoiesis, leukopenia, thrombocytopenia, and neutropenia, as shown in Table 1. A bone marrow biopsy collected in February 2019, indicated grade 2 hypocellular marrow for age (20% cellularity) with left-shifted myeloid precursors, decreased granulopoiesis, decreased megakaryocytes, and 35% atypical monocytes cells of uncertain lineage (increased monocytes). A peripheral blood smear confirmed absolute leukopenia (1,600/µL), absolute neutropenia (720/µL) with, dysgranulopoiesis, absolute lymphopenia (800/µL), decreased absolute eosinophils (48/µL), absolute monocytopenia (16/µL) and thrombocytopenia (133,000/µL). Flow cytometry was diagnostically negative for a neoplastic disorder. The patient's chromosome analysis was negative for FLT3 mutation and positive for chromosome 8 polysomy. Further, flow cytometric analysis of the bone marrow specimen indicated T-cells with a decreased CD4+/CD8+ ratio of 1:1.2, indicating insufficient immunologic capacity necessary for an immune surveillance and response to malignancy [3]. A repeat peripheral smear showed progressive bone marrow failure with pancytopenia [leukopenia (1,570/µ), thrombocytopenia (137,000/µ), and anemia]. Bone marrow aspirate indicated hypocellular marrow with increased myeloid blasts (57% by immunophenotyping) as shown in Figure 1. This blast population expressed CD4, CD11c, bright CD33 (79.97%), dim CD45, bright CD64 (75.83%), dim CD71, partial CD117, dim CD123, and bright HLA-DR (63.80%). Following additional testing, a diagnosis of Therapy-Related Acute Myeloid Leukemia (t-AML) was reached (Figure 1). Pembrolizumab was discontinued on February 2019, due to the development of bicytopenia. Treatment with azacitidine 75 mg/m^2 was initiated in March 2019, in response to the development of t-AML. Upon follow up, patient reported significant nausea, coupled with the loss of appetite, and an inability to eat and drink. Patient eventually elected to forgo azacitidine treatment after 1 cycle (3/25/19 to 6/2/19) and proceeded with hospice care.

Immunotherapy with checkpoint inhibitors such as anti-CTLA-4 and anti-PD-1 monoclonal antibodies provides an exciting and promising frontier for oncology. Many malignancies previously thought to be unresponsive to treatment now show appreciable response when administered with pembrolizumab (Keytruda®) and other immunotherapeutics [4]. Furthermore, an ever-growing number of oncologic patients may require such therapy for prolonged periods of time. This enthusiasm for immunotherapy must be balanced with an element of caution, as there may be secondary adverse effects yet to be fully identified. With this report, we demonstrate the importance

of remaining vigilant in the care of patients and staying informed of the growing list of possible adverse effects one may encounter as the indications for immunotherapy grows. The mechanism of immunotherapy rests on its ability to upregulate the immune response, specifically T-cells, to recognize and clear malignancies that would have otherwise evaded the host response. Current generation immunotherapies target two receptors on T-cells named Cytotoxic T-Lymphocyte-Associated Antigen 4 (CTLA-4) and Programmed Cell Death-1 (PD-1) receptors, pathways exploited by malignant cells to downregulate the host's immune response to cancer.

As tumor cells evolve via immunoediting and clonal selection via therapy-related selective pressure, cancer cells expressing PD-L1 ligands are able to avoid such immune recognition and the subsequent activation of cytotoxic T-cells leading to their unfettered proliferation. This downregulation of the immune system manifests via the coupling of the PD-L1 ligand on cancerous cells to the PD-1 receptor on activated T-cells. This coupling forces activated T-cells into anergy,

allowing cancer cells to proliferate, undeterred by any meaningful activation of the immune system. This forced anergy represents the exploitation of a regulatory mechanism normally utilized by the body as a means to modulate and avoid both immune system exhaustion and autoimmunity related bodily damage. It is now postulated that in periods of chronic inflammation, T cells upregulate a variety of inhibitory receptors as a means to reduce their own effectiveness or potency and avoid deleterious effects. This immune exhaustion is normally seen in cases in which the patient is no longer able to clear a pathogen. However, this has also been displayed and associated with the chronic inflammation seen in malignant states [5,6]. Once this T-cell regulatory mechanism is targeted and inhibited by immunotherapy, a hyperreactive response by T-cells is now possible. With immunotherapy, we are able to upregulate T-cell function, but upon activation we are unable to control the selectivity of which cell lines T-cells wage their attack. This hyperreactive immune response constitutes the bulk of adverse events linked to checkpoint inhibitor therapy.

Table 1: Blood count results over the course of immunotherapy pembrolizumab (Keytruda).

	12/20/18	1/16/19	2/6/19	2/27/19	2/28/19	3/6/19	3/11/19	3/25/19
WBC	4.7	2.7	2.6	1.7	1.6	1.6	1.6	1.4
HGB	14.8	14.6	14.4	14.1	13.6	13.9	13.1	13.3
HCT	42.1	41.6	41.4	39.7	39.2	39.6	36.1	37.4
PLT	137	139	130	144	133	139	137	123

Table 2: Immunotherapy induced bone marrow insufficiency.

| Disease	Immunotherapy	Type of Cytopenia
Lung adenocarcinoma x[3]	Nivolumab	Pancytopenia
Metastatic melanoma	Ipilimumab, pembrolizumab	Thrombocytopenia, anemia
Melanoma	Pembrolizumab	Idiopathic thrombocytopenia purpura
Metastatic melanoma	Nivolumab	Thrombocytopenia
Metastatic melanoma	Nivolumab	Autoimmune hemolytic anemia
Metastatic melanoma	Pembrolizumab	Lymphopenia, anemia
Metastatic melanoma	Pembrolizumab	Pancytopenia
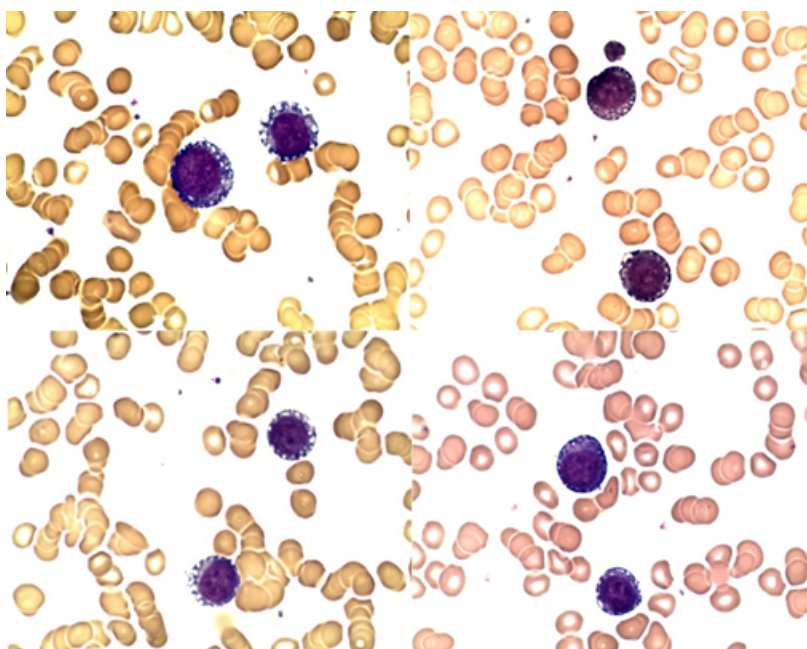
Figure 1: Bone marrow smear. Bone marrow aspiration revealed a population of morphologically distinct leukemic blast cells: Wright-Giemsa stain.

The majority of adverse effects related to immunotherapy are fatigue, dermatologic toxicity, gastrointestinal toxicity, hepatotoxicity, pulmonary toxicity, and various endocrinopathies [7,4]. Upon an exhaustive review of literature, we are now aware of a subset of hematologic toxicities related to immunotherapy [8]. These hematologic effects alter various cell lineages, causing various forms of bone marrow insufficiency [9]. To our knowledge, this is the first case reporting on suspected checkpoint inhibitor pembrolizumab involvement in therapy-induced AML. In our case, the patient developed t-AML approximately 17 months after initiation with pembrolizumab. This induction time is on par with times related to t-AML arising from treatment with conventional chemotherapy agents such as alkylating agents and epipodophyllotoxin agents [10]. However, as this patient only received a single cycle of irinotecan (as part of a regimen that also included 5FU and oxaliplatin, FOLFIRI), we believe it is reasonable to postulate a link between immunotherapy and the subsequent development of AML.

Discussion

Currently, there is not a clear understanding of the pathogenesis of immunotherapy-related acute myeloid leukemia. However, research shows t-AML and MDS following conventional chemotherapy is correlated with having a high prevalence of TP53 mutations thought to be caused by the mutagenic effects of therapy. It is believed that loss of function mutations in the tumor suppressor gene TP53 of these clonal populations leads to chemoresistance and the selective pressure of chemotherapy-induced DNA damage acting on pre-existing preleukemic cells, which allows for transformation to leukemic cells. Thus, chemotherapy contributes to the formation of myeloid tumors by promoting the expansion of pre-existing preleukemic clones under the selective pressure of genotoxic stress. However, the role checkpoint inhibitors and the subsequent hyperactivation of cytotoxic T cells occupy in this paradigm, is yet to be understood.

A comprehensive search of the literature has yielded a fair number of other reports of bone marrow insufficiency post-treatment with checkpoint inhibitors (Table 2) [11-13]. Modern immunotherapy relies on the upregulation of activated T-cells and the subsequent anti-tumor effect carried out by the patient's own immune system. In the process of stimulating this activated T-cell population, immunotherapy can cause hyperactivation leading to an autoimmune barrage on host cells, including those of bone marrow cell lineages. Hematologic complications due to immunotherapy have been reported, as listed in the table. Michot JM et al. reports three patients who presented with bone marrow failure and immune-related aplastic anemia following anti-PD-1 therapy with nivolumab [9], Le Roy A et al. presents two cases with thrombocytopenia and anemia, in which both ipilimumab and pembrolizumab were administered prior to bone marrow changes developing [14], Kanameishi S et al. presents one case of Grade IV thrombocytopenia [15] Kong BY et al. reports the development of autoimmune hemolytic anemia following approximately 5 cycles of nivolumab for metastatic melanoma [16]. One phase 2 study with 41 patients with progressive metastatic melanoma with or without mismatch repair deficiency [17]. Approximately 20% (n=8) reported Grade 3-4 lymphopenia and 17% (n=7) Grade 3-4 anemia [6] and Atwal D et al, reports a metastatic melanoma patient who developed severe pancytopenia following 18 cycles of pembrolizumab treatment [18].

Conclusion

In this case, we reported upon a patient who developed t-AML following immunotherapy, pembrolizumab, for the treatment of metastatic cholangiocarcinoma. To our knowledge, this is the first case of acute myeloid leukemia following anti-PD-1 treatment. Further research is necessary to elucidate the mechanism for this process; nonetheless, we believe it is crucial that physicians are aware of the possible hematologic adverse effects arising from the use of pembrolizumab and other potential immunotherapies.

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