Pembrolizumab-Induced Diabetes Mellitus Presenting as Diabetic Ketoacidosis in a Patient With Metastatic Colonic Adenocarcinoma

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Abstract

Immunotherapy drugs are gaining popularity in the treatment of certain malignancies due to the success of these agents in recent clinical trials. Pembrolizumab is an immune checkpoint inhibitor that acts via binding to programmed cell death 1 (PD-1) receptors on T-cells, allowing for the constitutive activation of T-cells to fight malignant tumor cells. Immune checkpoint molecules such as PD-1 act to inhibit T-cell function, promoting tolerance to self-antigens. Inhibition of these molecules may lead to increased T-cell activation against cancer cells, but also against healthy tissue, leading to the side effects of these medications known as immune-related adverse events. In this article, we present the case of a 77-year-old female with a history of metastatic colonic adenocarcinoma presenting with new-onset diabetes mellitus and diabetic ketoacidosis in the setting of receiving pembrolizumab chemotherapy. Our patient was treated with hydration, insulin therapy, and management of her electrolytes, ultimately being discharged with the need for home insulin therapy to manage her new-onset diabetes. There are no current guidelines for the management or surveillance of patients receiving pembrolizumab chemotherapy, and further research should be done to determine which patients are at highest risk to developing this rare but potentially lethal side effect.

Keywords

immunotherapy, pembrolizumab, diabetic ketoacidosis

Case Report

A 77-year-old female presented to the emergency department with 1 week of lethargy and fatigue. Over the past several days, she had been experiencing worsening polyuria, polydipsia, nausea, and multiple episodes of emesis daily. In August 2018, she had been diagnosed with Stage IV, TxN2M1, BRAF-positive, mismatch repair (MMR) stable, p53-positive colonic adenocarcinoma of the left sigmoid colon with axillary and supraclavicular nodal metastases. She had been following regularly with oncology and had undergone 12 cycles of FOLFOX (leucovorin, fluorouracil, oxaliplatin) chemotherapy between September 2018 and April 2019. Positron emission tomography computed tomography scan was performed in April 2019 showing resolution of her axillary and supraclavicular nodal metastases; however, a new hypermetabolic mediastinal lymph node in the right pre-tracheal space concerning for chemotherapy

refractory metastasis was discovered. In June 2019, the patient was started on second-line, single-agent treatment with pembrolizumab due to difficulty tolerating FOLFOX treatment. She received 200 mg of pembrolizumab every 3 weeks, for 16 cycles, between June 2019 and June 2020. The most recent dose was administered 4 weeks prior to presentation. During the course of her treatment, the patient followed monthly with her oncologist. She had regular laboratory

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draws including complete blood count (CBC), comprehensive metabolic panel (CMP), and thyroid-stimulating hormone. Hemoglobin A1C level 6 months prior to presentation was 5.7%. One regular follow-up visit for blood work, at 12 weeks, 8 weeks, and 4 weeks prior to presentation with diabetic ketoacidosis (DKA), the patient's fasting glucose values were 152 mg/dL, 162 mg/dL, and 169 mg/dL, respectively. The patient's thyroid-stimulating hormone levels were also within normal limits during each of the regular oncology follow-up visits.

On arrival to the emergency department, the patient was alert and oriented; however, she appeared distressed and clinically dehydrated. Initial laboratory evaluations included a CBC, CMP, urinalysis, urine culture, blood cultures, chest X-ray, and electrocardiogram. The CMP revealed a corrected sodium of 137 mEq/L, potassium of 6.1 mmol/L, chloride of 87 mmol/L, as well as a bicarbonate level of 11 mmol/L and an elevated anion gap of 24 mmol/L. The patients fasting glucose was 747 mg/dL. Urinalysis revealed the presence of both glucose and ketones. CBC, cultures, chest X-ray, and electrocardiogram were unremarkable. A venous blood gas and β-hydroxybutyrate level were ordered, revealing a pH of 7.14 and β-hydroxybutyrate level of >46.00 mg/dL (normal <2.81 mg/dL). Based on her clinical signs and symptoms along with hyperglycemia, anion gap metabolic acidosis, and the presence of urine and serum ketones, the diagnosis of DKA was made and the patient was admitted to the hospital for DKA management. Further testing for anti-islet cell antibodies (normal <7.4 units/mL) and anti-glutamic acid decarboxylase antibodies (normal <5.0 IU/mL) were performed during hospitalization but were undetected. Hemoglobin A1C level was ordered on admission and found to be 8.8%. After 4 days of treatment including rehydration, insulin therapy and dose titration, and management of electrolytes, the patient recovered and was discharged home with basal and mealtime insulin therapy.

Discussion

The success of immune checkpoint inhibitors in the field of cancer immunotherapy has been well documented.[1] There are 3 classes of immune checkpoint inhibitors currently approved for use in patients with a variety of malignancies. These include the cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor ipilimumab, the programmed cell death 1 (PD-1) inhibitors nivolumab and pembrolizumab, and the PD ligand 1 (PD-L1) inhibitors atezolizumab, avelumab, and durvalumab.[2] The immune checkpoint molecules CTLA-4 and PD-1 work by inhibiting T-cell function to promote tolerance to self-antigens, which is important in the prevention of autoimmune disorders.[2] While inhibition of these molecules may lead to an increased T-cell response against cancerous cells, it also inhibits the ability of these molecules to prevent autoimmunity. The side effects of these medications have been referred to as immune-related adverse events and have been

shown to affect many organ systems, including the endocrine system.[3] Side effects specific to pembrolizumab therapy that have been described include thyroid dysfunction, hypophysitis, pneumonitis, colitis, hepatitis, diabetes mellitus, and primary adrenal insufficiency.[4]

Pembrolizumab-induced diabetes is rare, being reported to occur in 0.4% of patients according to a systematic review by de Filette et al.[3] The initial presentation is often consistent with classical diabetes, including polyuria, polydipsia, weight loss, fatigue, and dehydration.[3] A small number of cases have also been documented in which the patients initially presented with diabetic ketoacidosis, much like the current case.[5] The time from initiation of therapy to development of frank diabetes varies, with some cases being reported in as little as 4 weeks while others have been reported >12 months after initiation of anti-PD-1 immunotherapy.[5,6] The mechanism for the development of diabetes in patients on this immunotherapy is hypothesized to be due to the activation of autoreactive T-cells secondary to inhibition of PD-1, leading to T-cell destruction of pancreatic islet cells.[7] It has been hypothesized that the initiation of pembrolizumab therapy and blockade of the PD-1 molecules leads to autoreactive CD8+ T-cells that are unable to be bound by the PD-L1 molecules of the pancreatic β cells due to their blockade by pembrolizumab, allowing for destruction of the β cells and development of insulin deficient type 1 diabetes mellitus, or as in this case, acute worsening of preexisting pre-diabetes or type 2 diabetes mellitus.[7]

An interesting phenomenon is that the presence of autoantibodies has only been shown in about half of the documented cases of PD-1 inhibitor–induced diabetes.[3,6] This is significant because of the fact that in patients who develop type 1 diabetes mellitus unrelated to PD-1 inhibitor use, >90% will have at least one positive autoantibody.[8] That is what makes the development of frank diabetes in these patients so unique. Expanding on this further, Quandt et al evaluated whether patients without the presence of autoantibodies develop them in the months after the acute initial presentation.[8] Despite the hypothesis that autoantibodies will likely develop, they found that in follow-ups as long as 32 months from diagnosis, autoantibodies remained negative in the setting of persistent diabetes in these patients.[8] This is important and leads to the consideration that while half of these patients may be developing autoimmune diabetes as a consequence of PD-1 inhibitor therapy, the other half may simply have ketosis-prone type 2 diabetes. This is why regular monitoring of chemistries in patients beginning PD-1 inhibitor therapy is so important. In our case, the patient had an A1C of 5.7% 6 months prior to presentation; however, it is possible that anemia secondary to the patient's prolonged course of chemotherapy may cause an unreliable A1C value. In the months leading up to her admission, fasting glucose values ranged from 152 to 169 mg/dL. On admission, the patient had an A1C of 8.8%, which is significantly higher than her nondiabetic A1C level 6 months prior. This, along with negative autoantibodies is consistent

with likely evolving type 2 diabetes that was worsened secondary to β-cell destruction as a consequence of PD-1 inhibitor therapy. This insidious worsening led to the profound hyperglycemia, which manifested as a hyperosmolar state and ultimately the development of ketoacidosis.

There are no currently established guidelines for clinicians to implement with regard to monitoring patients beginning pembrolizumab therapy, and this is a critical area that warrants further attention.[4] It is well known that the risk of development of diabetes increases with age. As discussed previously, patients undergoing immune checkpoint inhibitor therapy are at risk for both the precipitous development of type 1 diabetes as well as insidious worsening of preexisting diabetes. Untreated, these conditions can develop into ketoacidosis or severe hyperosmolar states that may be associated with significant morbidity and mortality. Therefore, when patients are undergoing these therapies, clinicians should be wary of even mild alterations in fasting glucose levels. If these changes are noted, clinicians should consider more aggressive monitoring strategies such as the prescription of glucometers and providing patients with education regarding diabetes. It may be necessary to consider initiation of hypoglycemic agents in some cases. Furthermore, it is not known whether patients who have positive autoantibodies developed these prior to the initiation of pembrolizumab therapy. If this is the case, physicians could screen patients for the presence of these autoantibodies prior to beginning pembrolizumab therapy to determine whether a patient is at increased risk of developing diabetes.[8]

Conclusion

In the current case, we describe the presentation of diabetes mellitus in a 77-year-old woman undergoing pembrolizumab immunotherapy for metastatic colonic adenocarcinoma. The development of diabetes mellitus in the context of undergoing pembrolizumab immunotherapy is rare, and a lack of guidelines for monitoring patients for this complication places this vulnerable patient population at risk for significant morbidity and mortality. It is important for clinicians to recognize this side effect, and patients should receive education regarding signs and symptoms to monitor for the development of diabetes or diabetic ketoacidosis. Regular monitoring of glucose levels and hemoglobin A1C levels may be beneficial. Further research is needed to identify patient risk factors that may predispose patients to the development of this complication.

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