INNOVATIONS JOURNALS

Case Report

Case Report: Nivolumab-Induced Autoimmune Pancreatitis

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ABSTRACT

Nivolumab is an anti-programmed cell death protein 1 monoclonal antibody. While an effective treatment for a variety of tumors, immune checkpoint inhibitors (ICI) can cause immune-related adverse events such as ICI-pancreatic injury (ICI-PI). Here we present a case of a 60-year-old man with metastatic acral melanoma treated with nivolumab and ipilimumab who developed ICI-PI. Changes in positron emission tomography images preceded symptom onset. However, this case is unique in that the patient presented with cholestatic liver disease. Magnetic resonance cholangiopancreatography showed a dilated extrahepatic bile duct that resolved with steroid therapy, similar to the clinical course of autoimmune pancreatitis. ICI-PI has variable presentations including obstructive jaundice with a clinical course mimicking autoimmune pancreatitis and prompt awareness and treatment of ICI-PI is clinically significant given increasing use of ICIs.

Keywords: immunotherapy, melanoma, pancreatitis

INTRODUCTION

Nivolumab is an immune checkpoint inhibitor (ICIs) that is effective treatment for a variety of tumors, including metastatic melanoma. ICIs block programmed cell death protein (PD-1) receptor and thus release the inhibitory effect on the T-cell effector mechanisms.[1] This boosts antitumor immune responses but also can lead to immune-related adverse events (irAEs), such as ICI-pancreatic injury (ICI-PI). ICI-PI is uncommon and often presents with incidentally elevated pancreatic enzymes. We present the first case of ICI-PI mimicking autoimmune pancreatitis (AIP) with obstructive jaundice.

CASE DESCRIPTION

According to institutional policy, this report was exempt from ethical review and the patient provided consent to publish the case. A 60-year-old man with acral melanoma metastatic to the liver was treated with four cycles of combination nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. After three cycles of maintenance monthly nivolumab 480 mg, surveillance positron emission tomography-computed tomography (PET-CT) revealed diffuse fluorodeoxyglucose (FDG)-avidity of the pancreas with peripancreatic fat stranding (Fig. 1).

He noted mild abdominal pain with an elevated lipase that was 10 times the upper limit of normal (Fig. 2). He had no gallstones on imaging and drank alcohol socially. Antinuclear antibody was negative with normal immunoglobulin (Ig)G4. He was diagnosed with ICI-PI and treated with intravenous fluids and corticosteroids (methylprednisolone 0.5 mg/kg/day) and discharged on a 14-day oral steroid taper with regular laboratory monitoring.

Three weeks after completing the steroid taper, he presented with worsening abdominal pain and gray-colored stool, for which he was admitted. Laboratory work was significant for elevated liver tests, consistent with a cholestatic obstructive pattern. Computed

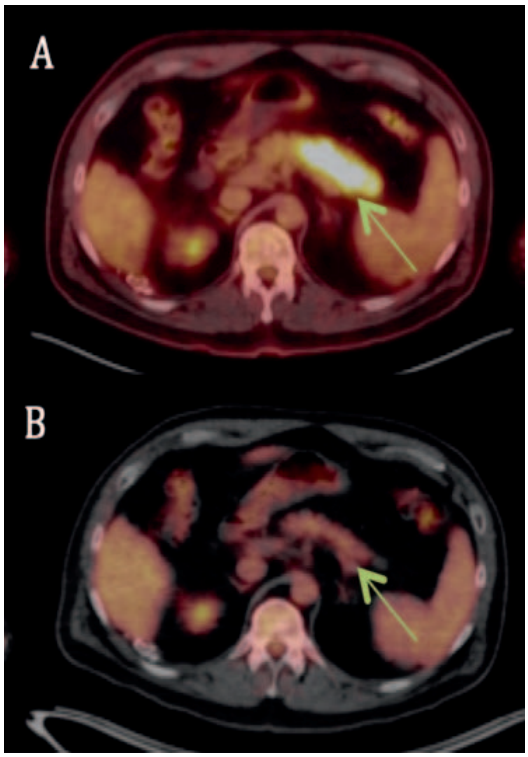

Figure 1. Positron emission tomography - computed tomography (PET - CT) imaging. (A) After three cycles of maintenance nivolumab. (B) After high-dose oral steroids and normalization of liver enzymes. Arrow points to the pancreas.

tomography (CT) revealed mild diffuse enlargement of the pancreas. Magnetic resonance cholangiopancreatography (MRCP) showed a dilated extrahepatic bile duct, measuring 11 mm, with an intrapancreatic stricture (Fig. 3).

Endoscopic ultrasound showed a diffusely lobular pancreas with hypoechoic areas and intervening hyperechoic standing. The pancreatic duct was not dilated. The bile duct was dilated and abruptly narrowed as it entered the pancreatic head. Fine needle aspiration of the pancreatic head with a 25G needle revealed pancreatic acini and focal findings suggestive of chronic pancreatitis without metastatic melanoma. Immunohistochemical stains for HMB45, MART1, and SOX10 were performed and negative.

A diagnosis of ICI-PI mimicking AIP was made. The modified Naranjo score was 5, indicating possible ICI-PI.[2] Of note, per the International Consensus Diagnostic Criteria for AIP, our patient met the following diagnostic criteria for AIP: imaging features of pancreatic parenchyma, histopathology, and response to steroid therapy.[3] He received high-dose oral steroids (prednisone 1 mg/kg/day) with a long taper over 9 weeks. Steroid course was complicated by mild hyperglycemia, controlled with metformin alone. His liver function tests normalized and repeat PET showed interval resolution of pancreatic FDG-avidity and peripancreatic fat stranding with continued remission of melanoma 8 months after completion of nivolumab and ipilimumab therapy.

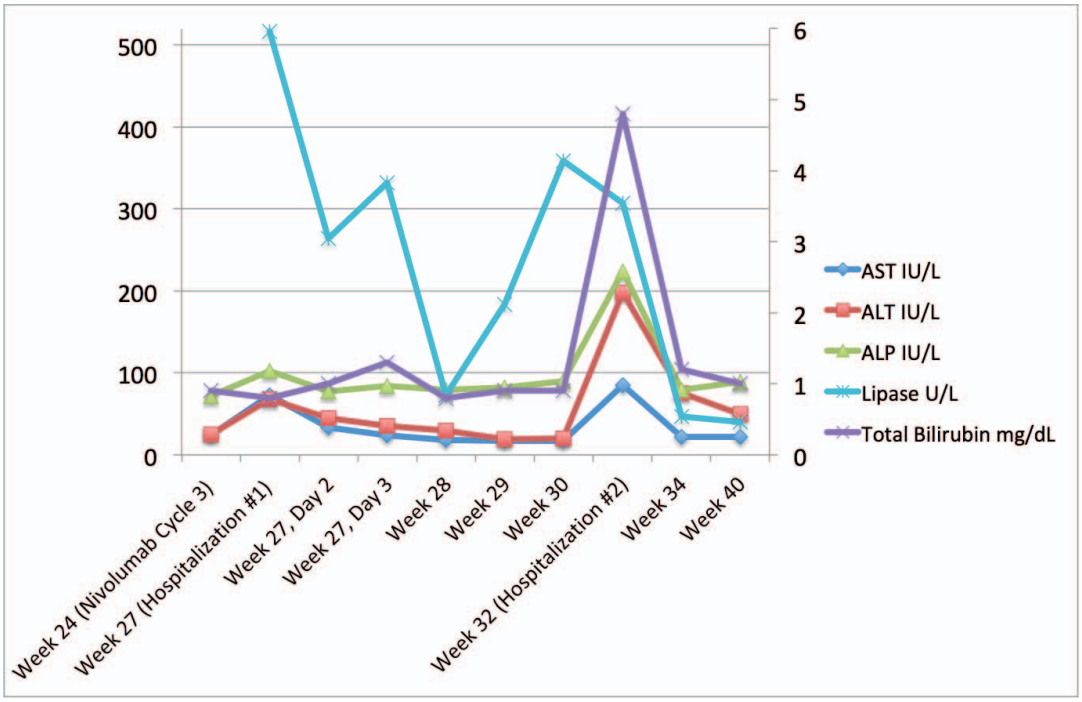

Figure 2. Liver enzymes, total bilirubin, and lipase from the last cycle of nivolumab therapy through both hospitalizations. Of note, steroids were initiated for a 14-day course on hospitalization #1 and for a 9-week course on hospitalization #2. Normal aspartate aminotransferase (AST) is 0 to 40 IU/L. Normal alanine aminotransferase (ALT) is 0–32 IU/L. Normal alkaline phosphatase (ALP) is 39 to 117 IU/L. Normal total bilirubin is 0–1.2 mg/dL. Upper limit of normal lipase is 51 U/L.

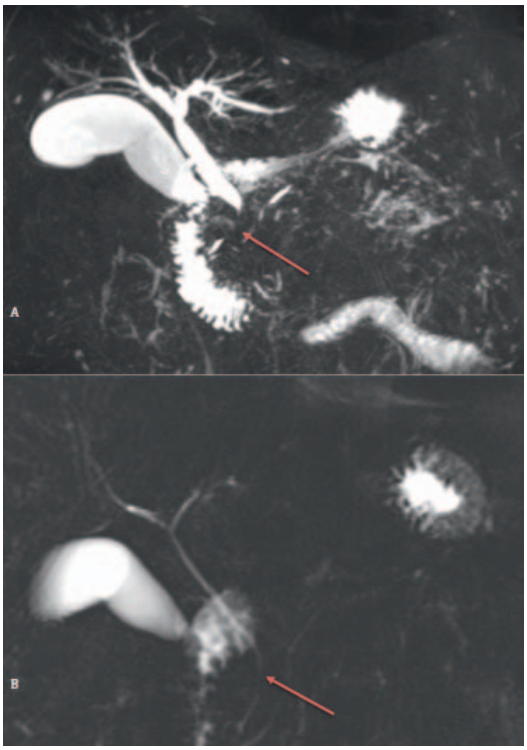

Figure 3. (A) Initial magnetic resonance cholangiopancreatography (MRCP) image. Red arrow points to intrapancreatic stricture noted after nivolumab therapy. (B) MRCP after steroid therapy. Red arrow points to site of prior intrapancreatic stricture that is now resolved.

DISCUSSION

By "releasing the breaks" on the immune system, checkpoint blockade can cause irAEs. The risk of an irAE is increased and time of onset is earlier if more than one ICI is used.[4] These side effects commonly affect the gastrointestinal tract, endocrine glands, skin, and liver. The mechanism underlying irAEs is likely related to the role that immune checkpoints play in immunologic homeostasis; irAEs typically develop in the first few weeks to months after treatment initiation. [5]

A single-center analysis of more than 2200 patients found the incidence of ICI-PI to be 4% for anti-PD-1 therapy and 8% for combination anti-PD-1 and anti-CTLA-4 therapy; however, only 39% of patients with grade 3-4 elevations of lipase exhibited symptoms of pancreatitis.[6] The clinical spectrum ranged from asymptomatic lipase elevation to typical symptoms of pancreatitis, including nausea, vomiting, and abdominal pain.

Dehghani et al[7] reported a case of focal AIP of the distal pancreatic tail without jaundice complicated by diabetes in a patient who received nivolumab for metastatic melanoma. In this case report, AIP was diagnosed via PET-CT combined with magnetic resonance imaging of the pancreas before the development of diabetes. Autoimmune biomarkers, such as antinuclear antibody, rheumatoid factor, antilactoferrin antibody, type 2 anti-carbonic anhydrase antibody, antitransglutaminase IgA and IgG, anti-gastric parietal cell, antithyroperoxidase, and antithyroglobulin antibody, were not found. This case suggested that pancreatitis could be identified before clinical or biological manifestations using 18F-FDG-PET/CT findings.

Our case supports this finding, as abnormal PET imaging preceded symptom onset in our patient. This highlights the importance of maintaining a broad differential when interpreting PET imaging to avoid misidentifying immunotherapy-related complications as tumor progression. In addition, biomarkers of autoimmune pancreatitis may not always be reliable, as they are often negative in such cases. Early detection of immunotherapy-related adverse effects can change management, and thus it is important for clinicians across multiple specialties to be aware of them given increasing use of anti-PD1 antibodies. Resolution of pancreatitis was noted on PET imaging after treatment with steroids. Furthermore, the intrapancreatic stricture noted on MRCP also resolved after treatment of ICI-PI (Fig. 1).

Most irAEs are treated with temporary immunosuppression with oral glucocorticoids or additional immunosuppressants in more severe cases. Although most irAE cases can be treated with corticosteroids alone, a minority of patients may not respond to steroids. In cases of ICI-mediated colitis (ICI-C) that are not responsive to steroids, Infliximab has been used. Infliximab is thought to work via several mechanisms, including opposing the activation of T cells by CTLA-4 antibodies, enhancing FOXp3+ regulatory T cells, as well as preventing tumor necrosis factor-alpha from binding to its receptor.[8] Further studies are needed to evaluate the role of biological agents and other steroid-sparing agents in the management of ICI-C. Given the similar pathophysiology of ICI-C and ICI-PI, biologics and steroid-sparing agents may potentially be used to manage ICI-PI as well.

Following resolution of an irAE, an important decision needs to be made about whether the ICI should be resumed. There are limited prospective data regarding this topic. One retrospective study described patients with non–small-cell lung cancer who were treated with anti-PD-1 or anti-PD-L1 therapy after resolution of an irAE.[9] Among the 38 patients included in the study, 50% had no further irAEs, 24% had recurrence of initial event, and 26% had a new event.

This unique case of ICI-PI evolving into obstructive jaundice treated with steroids alone had an imaging and clinical course mimicking AIP. Both ICI-related adverse events and AIP are T-cell driven processes suggesting a similar pathogenesis.[10] The incidence of ICI-PI will likely rise with the increasing use of ICIs; thus, awareness of ICI-PI and its variable presentation are clinically salient.

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