CASE REPORT PEER REVIEWED | OPEN ACCESS

Ipilimumab-nivolumab combination therapy leads to biopsy proven immune-mediated pancreatitis

Joshua B. French, Eizaburo Sasatomi, Lisa M. Gangarosa

ABSTRACT

Introduction: Oncologic therapies are continuing to expand and include classes of medications whose primary mechanism of action results in targeted immunotherapy. As with any new therapy, these medications have side effects. In particular, nivolumab and ipilimumab have been associated with side effects involving the gastrointestinal tract, including asymptomatic elevations in pancreatic enzymes as well as rare cases of overt acute pancreatitis. Case Report: We present a case of combination nivolumab and ipilimumab induced acute pancreatitis during which an endoscopic ultrasound guided fine needle biopsy was obtained. The biopsy demonstrated a T cell rich inflammatory infiltrate, consistent with an immune-mediated acute pancreatitis. This is the first report to include histologic findings. Conclusion: Checkpoint inhibitors can cause acute pancreatitis via an immune mediated mechanism with lymphocytic infiltration.

Keywords: Checkpoint inhibitors, Ipilimumab, Nivolumab, Pancreatitis

Joshua B. French[1], Eizaburo Sasatomi[2], Lisa M Gangarosa[1]

Affiliations: [1]MD, Department of Medicine: Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]MD, PhD, Department of Pathology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.

Corresponding Author: Lisa M. Gangarosa, MD, University of North Carolina at Chapel Hill, 130 Mason Farm Road CB# 7080, Chapel Hill, NC 27599; Email: lisa_gangarosa@med.unc.edu

Received: 07 September 2017
Accepted: 20 September 2017
Published: 09 October 2017

How to cite this article

French JB, Sasatomi E, Gangarosa LM. Ipilimumab-nivolumab combination therapy leads to biopsy proven immune-mediated pancreatitis. J Case Rep Images Med 2017;3:46–49.

Article ID: 100041Z09JF2017

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doi: 10.5348/Z09-2017-41-CR-13

INTRODUCTION

Over the last several years cancer therapies have continued to expand in regards to mechanisms of action and number of therapies available. One such area of growth has been that of targeted immunotherapy. Checkpoint Inhibitors such as the immunomodulatory antibodies nivolumab and ipilimumab were developed to specifically target certain receptors to enhance the immune system and ultimately provide a novel treatment modality for certain malignancies. These therapies have demonstrated activity and shown to be viable for treating patients with advanced melanoma [1]. Despite improvement in clinical oncologic endpoints, these medications have led to a variety of unwanted side effects including dermatologic, endocrine, and gastrointestinal side effects [2–8].

CASE REPORT

A 49-year-old male with a history of melanoma, with known metastasis to the brain and lung, presented with acute interstitial pancreatitis and was referred for gastroenterology consultation. At that time he was in a study protocol receiving combination nivolumab and ipilimumab for his metastatic melanoma. When he

presented to oncology clinic for his fourth infusion he complained of epigastric abdominal pain with associated nausea and a few episodes of vomiting. A laboratory panel was sent and this demonstrated a normal total bilirubin as well as normal aspartate and alanine aminotransferases but did show an elevated lipase at 1957 U/L (Reference Range: 44–232 U/L) as well as an elevated amylase at 211 (Reference Range: 30–110). He had previously had some intermittent minimally elevated lipase values after starting his therapy but these normalized on recheck and were not associated with symptoms of pancreatitis. His last lipase measurement, the month prior to this episode, was within the normal range. A computed tomography (CT) scan of abdomen and pelvis was obtained and demonstrated a normal pancreas, uncomplicated cholelithiasis, and a normal biliary ductal system. His fourth infusion of immunotherapy was withheld due to his symptoms. A week later his symptoms persisted and a magnetic resonance cholangiopancreatography (MRCP) scan was ordered and obtained a few days later. This study demonstrated cholelithiasis without choledocholithiasis or biliary duct dilation but did demonstrate a mildly enlarged and edematous pancreatic body and tail consistent with moderate acute pancreatitis (Figure 1). At this time his Lipase was rechecked and found to be 5674 U/L and he was admitted to the hospital for acute pancreatitis.

During this hospitalization, he had some mild improvement of his symptoms with supportive care. General surgery was consulted regarding possible cholecystectomy but ultimately this was deferred given that gallstone disease was felt to be a less likely cause of pancreatitis based on labs. Three days after his admission he was discharged and a referral was placed to gastroenterology clinic. Ten days later in gastroenterology clinic, he denied any alcohol or tobacco use and his triglycerides and calcium levels were normal. He denied a family history of pancreatitis. He still had some intermittent epigastric pain and his lipase remained elevated at 4062 U/L. An endoscopic ultrasound (EUS) was ordered which was performed (linear echoendoscope at 7.5 MHz) a few weeks later and demonstrated cholelithiasis, a normal common bile duct, and pancreatic parenchymal changes consisting of diffuse echogenicity, hyperechoic strands, and hyperechoic foci throughout the entire pancreas consistent with inflammatory changes (Figure 2). Fine needle biopsy (FNB) of the pancreatic body was performed under endoscopic ultrasound (EUS) guidance with a 25-gauge core biopsy needle with six total passes. The histology from the tissue obtained demonstrated multiple samples of pancreatic parenchyma with edema and a predominantly lymphocytic infiltrate with ongoing acinar cell injury/dropout and mild early fibrosis. There was no evidence of significant duct epithelial injury or periductal inflammation. There were no plasma cell clusters or neutrophilic aggregates seen. Immunohistochemical stains were obtained demonstrating positivity for S100, CD45, CD3, CD4, CD8, CD68, and Oscar keratin. CD20 was noted to be rare and IgG4 was rarely seen with only 2 positive cells per high power field. Overall, the histologic features demonstrated an active lymphocyte and histiocyte rich pancreatitis with ongoing acinar injury and early fibrosis. The presence of only rare IgG4 positive plasma cells made the diagnosis of type I autoimmune pancreatitis unlikely and the histologic features did not support a diagnosis of type 2 autoimmune pancreatitis. Furthermore, there was no evidence of metastatic melanoma. Concomitant hematopathology demonstrated a polymorphic population of predominantly T cells (74%) and polytypic B cells (4%) (Figure 3).

During the time that his workup was ongoing, his symptoms slowly improved as study drugs continued to be withheld. At the time of the pancreas biopsy, his last infusion was approximately two months prior. Shortly after the pancreatic biopsy he experienced worsening of chronic peripheral neuropathy and was started on a course of steroids (prednisone 60 mg daily), which was continued for 10 days total. Two weeks after the biopsy his abdominal pain had resolved and his lipase at that time on recheck was 420 U/L.

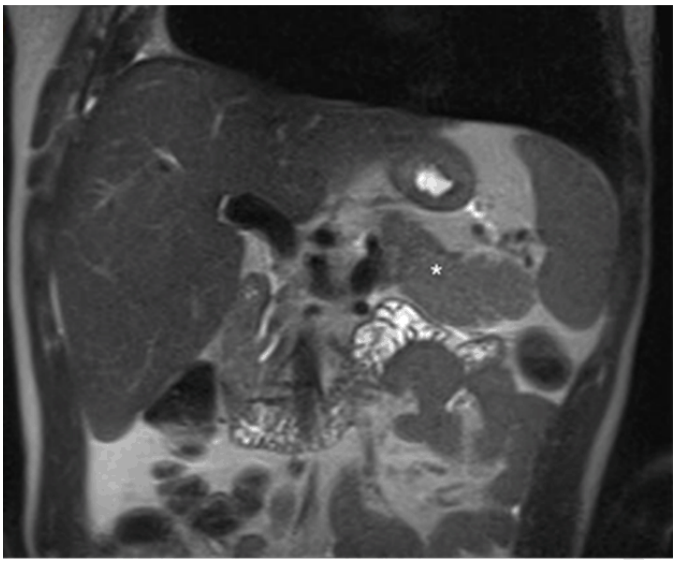

Figure 1: Magnetic resonance cholangiopancreatography demonstrating an edematous pancreatic tail consistent with mild acute pancreatitis.

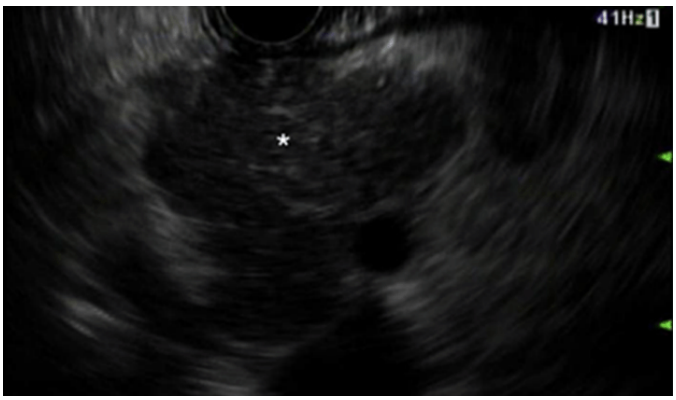

Figure 2: Endoscopic ultrasound demonstrating pancreatic parenchymal changes consistent with inflammation.

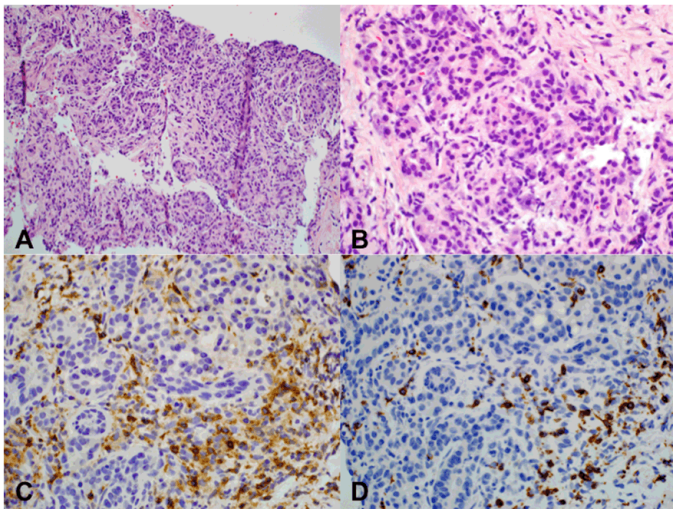

Figure 3: (A) A core biopsy of the pancreas shows diffuse lymphocytic infiltrate with edema and mild interstitial fibrosis (H&E stain, ×20), (B) At higher magnification lymphocytic acinar inflammation with ongoing acinar cell injury and dropout is appreciated (H&E stain, ×40), (C) An immunohistochemical stain for CD4 is positive in many scattered lymphocytes (×40), and (D) An immunohistochemical stain for CD8 also shows many scattered CD8 positive T lymphocytes (×40).

Due to his pancreatitis, neuropathy and pneumonitis, he did not receive further therapy with ipilimumab and nivolumab.

DISCUSSION

Nivolumab is a Programmed Cell Death (PD-1) receptor antibody and ipilimumab is a cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody that are employed to enhance the immune system and treat advanced melanoma [2, 3]. While these medications have successfully treated melanoma and other cancers, side effects involving dermatologic, endocrine, and gastrointestinal systems have been noted [2–8]. The United States National Cancer Institute developed the Common Terminology Criteria for Adverse Events to be utilized in adverse event reporting [9]. This grading system, consisting of adverse events being assigned Grade 1 to Grade 5 with increasing severity, is commonly used for reporting adverse events in chemotherapy and oncologic immunotherapy trials. Both PD-1 and CTLA-4 antibody treatments were associated with Grade 3–4 elevated lipase levels individually, and when used in combination to treat advanced melanoma, an elevated lipase was noted to be the most common Grade 3 or 4 adverse event [8].

While elevations in lipase have been well described, overt pancreatitis occurs less frequently [4, 5]. Pancreatitis is diagnosed based on the revised Atlanta Classification requiring any 2 of 3 components to be present: elevations in amylase or lipase to 3x the upper limit of normal, severe epigastric pain consistent with pancreatic pain, and/or CT, MRI, or ultrasound evidence of acute pancreatitis [10]. Thus, elevations in amylase or lipase alone do not meet the clinical diagnostic criteria for acute pancreatitis. Friedman et al. described a retrospective analysis of 119 patients receiving nivolumab and ipilimumab in combination for melanoma and found that 32 patients (26.9%) had Grade 3 or higher elevations in lipase and 10 patients (8.4%) had Grade 3 or higher elevations in amylase. However, only two patients (1.7%) were actually shown to develop pancreatitis based on the Atlanta Classification definition of acute pancreatitis [5]. Similarly, other case reports have described confirmed pancreatitis, typically elevated pancreatic enzymes with associated imaging changes of acute pancreatitis, when using these agents and other immunotherapies within the CTLA-4 and PD-1 medication classes [4, 6, 11].

The case presented here adds further to literature describing the histology of acute pancreatitis associated with the use of combination nivolumab and Ipilimumab in patients with melanoma. To our knowledge, this is the only case of acute pancreatitis associated with the use of these agents in which a biopsy was performed and the pathologic findings demonstrated a lymphocytic predominant acute pancreatitis.

Autoimmune side effects related to immunotherapy are treated with stopping or delaying the subsequent doses of the medications and for more severe effects, systemic steroids are used [7]. This method of therapy has been used in many of the reported cases of pancreatitis and other adverse effects with positive results and resolution of the acute pancreatitis [4, 5, 8, 11]. Similarly, the patient in our case recovered well without signs of ongoing or definitive recurrent acute pancreatitis after his therapy was withheld. The patient described in this case did receive oral steroids for significant peripheral neuropathy associated with his therapy during the course of his pancreatitis. The symptoms attributable to his pancreatitis were beginning to improve prior to the initiation of oral steroids. It is unclear if the 10-day course of oral 60 mg prednisone played a role in the recovery of his pancreatitis, but it may have aided in the resolution of his symptoms.

CONCLUSION

While the exact etiology of acute pancreatitis can occasionally be difficult to determine, in patients on nivolumab and ipilimumab drug induced, immune mediated pancreatitis should be considered. In the absence of other common etiologies, we do not necessarily advocate routine pancreatic biopsy in patients meeting diagnostic criteria for acute pancreatitis while on combination therapy. However, in certain clinical settings, if the exact mechanism remains unclear, pancreatic biopsy can demonstrate findings of lymphocytic pancreatitis, providing evidence of an immune mediated pancreatitis.

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Author Contributions

Joshua B. French – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Eizaburo Sasatomi – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Lisa M. Gangarosa – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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