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CASE REPORT | PANCREAS

Immunomodulators for Steroid-Dependent Recurrent Acute Pancreatitis After Immune Checkpoint Inhibitor Therapy: A Case Series

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ABSTRACT

One to 2% of patients undergoing immune checkpoint inhibitor (ICI) therapy develop ICI-induced pancreatitis (ICI-IP). A small subset of these patients develop recurrent pancreatitis, even after discontinuation of ICI therapy. This case series presents 2 patients with recurrent steroid-responsive ICI-IP who were managed with immunomodulators as steroid-sparing agents. Both patients were maintained on immunomodulators for approximately 2 years before discontinuation of the agents, with no further recurrence or complications of pancreatitis. This case series highlights the use of mycophenolate mofetil and azathioprine for the management of recurrent ICI-IP.

KEYWORDS: immune checkpoint inhibitor; acute pancreatitis; immunomodulators

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of cancer. They function by blocking inhibitors of the intrinsic immune system and activating tumor-specific $CD8^+$ T cells, resulting in improved antitumor activity of the T cells.[1,2] However, this response can cause immune-related adverse effects (irAEs) in nontarget tissues. While the exact pathophysiology remains unclear, studies suggest involvement of cell-mediated, antibody, and cytokine responses.[2] These irAEs can affect any organ system, with gastrointestinal, hepatic, and dermatologic toxicities being the most common. Colitis and hepatitis are the more common gastrointestinal irAEs, while pancreatitis is rare.[1]

Most clinical trials report <1% incidence for ICI-induced pancreatitis (ICI-IP), with higher incidence in those treated with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors compared with programmed cell death protein 1 (PD1) inhibitors (3.98% vs 0.94%) and increased risk from combined therapy (10.60%; 95% confidence interval 7.89–13.32).[1,3,4] The median time to onset of pancreatitis varies (PD-1/PD-L1 inhibitors: 146 days; CTLA-4 inhibitors: 69 days).[1] Symptoms of ICI-IP include epigastric pain, nausea, vomiting, and diarrhea.[3,4] Diagnosis requires ruling out alternative etiologies including gallstones, alcohol, hypertriglyceridemia, hypercalcemia, and drugs with established pancreatic toxicity.[4]

The American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines recommend treating acute episodes with intravenous fluids, high-dose steroids, and potentially discontinuing the ICI based on adverse event severity.[2,5–8] There is no consensus on treating patients with recurrent ICI-IP after completion of a steroid course.

This case series presents 2 patients diagnosed with steroid responsive recurrent ICI-IP and discusses their management with steroid-sparing immunomodulating agents: mycophenolate mofetil (MMF) and azathioprine.

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CASE REPORT

Case 1: A 63-year-old woman presented with metastatic poorly differentiated adenocarcinoma of the left lung. The patient had a 13 pack-year smoking history and consumed alcohol infrequently. She underwent induction chemotherapy with carboplatin, pemetrexed, and pembrolizumab. After 6 cycles, maintenance of pemetrexed/pembrolizumab was initiated. After 1 year of maintenance therapy, the patient developed abdominal pain, postprandial nausea, and vomiting. Lipase level was elevated 6-fold (349 U/L, reference range 13–60 U/L) (Figure 1). Cross sectional imaging revealed changes consistent with acute pancreatitis. The patient had no prior episodes of pancreatitis. Extensive evaluation did not reveal alternate etiology for pancreatitis.

She was diagnosed with ICI-IP and treated with prednisone 60 mg daily. Pembrolizumab was held. Symptoms improved within 5 days of starting prednisone at 1 mg/kg per day. Prednisone was tapered by 10 mg weekly. The patient continued maintenance pemetrexed alone for 5 more cycles but subsequently experienced recurrent acute pancreatitis. High-dose prednisone was initiated.

After a multidisciplinary consultation, azathioprine was started with plans to titrate to 1.5 mg/kg/day. However, 6 weeks later, the patient developed transaminitis from azathioprine-induced hepatitis. Thiopurine methyltransferase enzyme activity was 29.1 unit/mL (reference range 24–44 unit/mL). She was switched to MMF and titrated to 2,000 mg daily. Prednisone was tapered completely. The patient continued maintenance

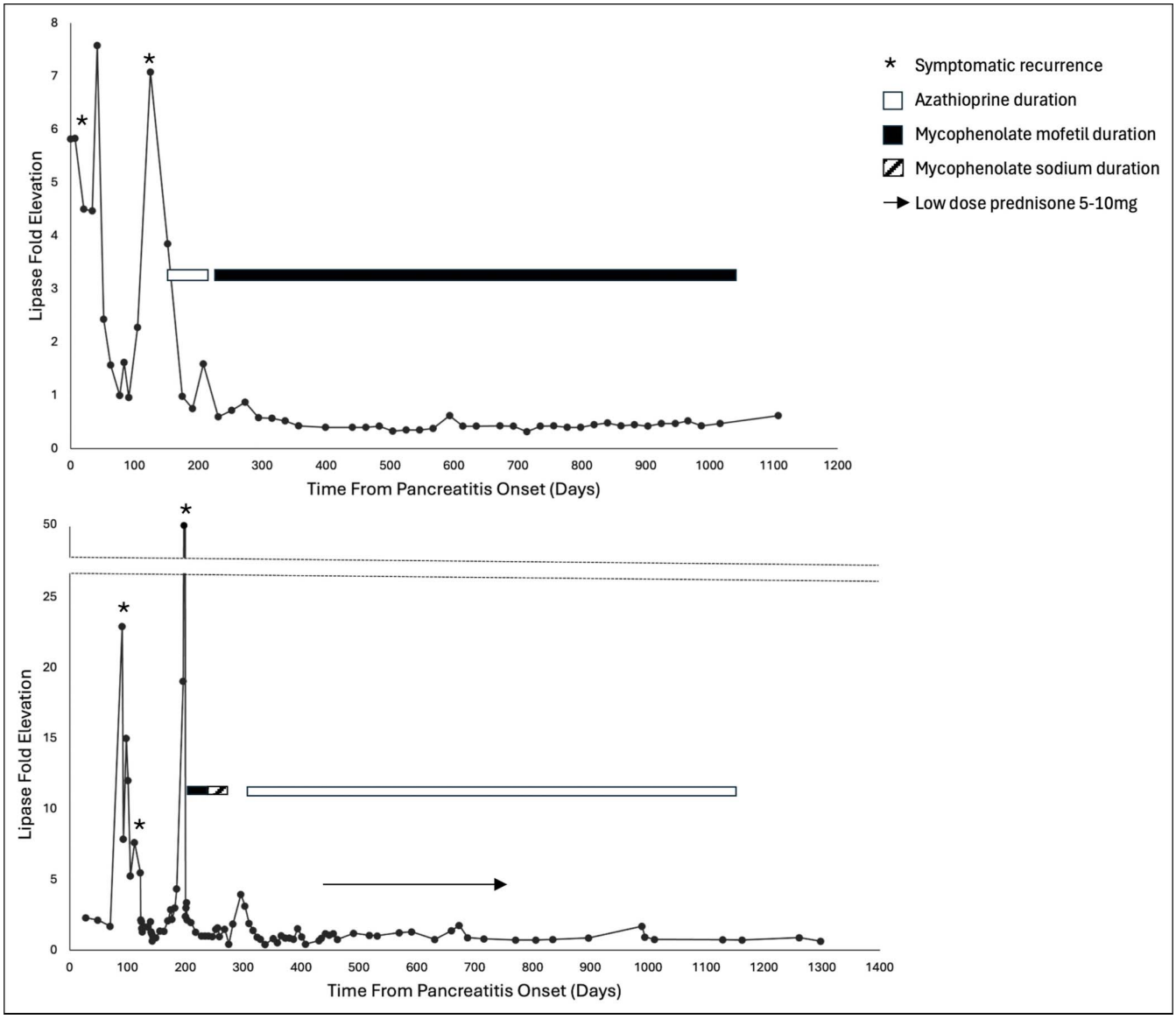

Figure 1. Longitudinal monitoring of lipase levels in case 1 (top) and case 2 (bottom) with timeline of key clinical events. Lipase fold elevation was calculated using percent of upper normal limit.

pemetrexed without complications. MMF was discontinued after 2 years of therapy. The patient has not had recurrent pancreatitis during 14 months of follow-up.

Case 2: A 50-year-old woman presented with a history of sclerosing epithelioid fibrosarcoma with lung and bone metastases. She underwent wide-field resection and radiation. Combination therapy with nivolumab and ipilimumab was started 1 year later due to disease progression on imaging.

Two months into therapy, she had mild elevation of serum lipase level without symptoms. Her treatment was continued. After 5 cycles, she experienced nausea and abdominal pain. The patient was a nonsmoker with moderate alcohol consumption (3–4 drinks weekly). Her lipase levels were elevated more than 10-fold (1,375 U/L, reference range 13–60 U/L), and abdominal computed tomography (CT) showed interstitial pancreatitis (Figure 1). The patient had no prior episodes of pancreatitis. Evaluation for alternate etiologies was unrevealing. ICI-IP was diagnosed, and she was started on prednisone 1 mg/kg per day. ICI therapy was held. Her symptoms improved with high-dose prednisone, subsequently tapered over 1 month.

One month later, the patient was admitted with abdominal pain and a significant elevation of lipase (2,998 U/L, reference range 73–393 U/L). Cross-sectional imaging showed interstitial pancreatitis. Prednisone 1 mg/kg per day was initiated, leading to improvement in 3 days. Prednisone was tapered slowly. However, 2 months later, she returned with acute pancreatitis while on prednisone 20 mg per day, prompting an increase to 60 mg daily. After a multidisciplinary conference, MMF was initiated as a steroid-sparing agent. She developed pedal edema, which was attributed to MMF, prompting a switch to mycophenolate sodium titrated to 720 mg twice daily.

She had recurrent pancreatitis 1 month after starting mycophenolate sodium when prednisone was tapered to 30 mg daily, indicating inadequate response. She transitioned to azathioprine, titrated to 1.5 mg/kg/day. The patient initially had recurrent abdominal pain and elevated serum lipase levels when prednisone was weaned below 10 mg per day. Low-dose oral prednisone was continued at 5–10 mg per day along with azathioprine for 13 months before discontinuation. Azathioprine was continued for 2 additional years and then tapered off. She remained symptom free 2 months after discontinuing azathioprine.

DISCUSSION

ICIs have transformed the treatment of cancer. They function by modifying the T cell response to tumor cells. However, this immune activation can also lead to systemic immune-related adverse events. ICI-IP is traditionally managed with high-dose steroids followed by a slow taper, with discontinuation of ICI therapy considered in more severe cases. Recurrent pancreatitis, a rare subtype of irAE, presents a unique challenge as patients experience multiple episodes of steroid-responsive acute pancreatitis that recur after steroid discontinuation. This condition is likely due to persistent alterations in the immune response.

Maintaining these patients on prolonged high-dose systemic steroids carries a significant risk of adverse effects. This case series describes the successful use of mycophenolate and azathioprine as steroid-sparing agents for steroid-dependent ICI-IP. Both cases achieved symptom control and steroid discontinuation. Eventually, they stopped immunomodulator therapy without further recurrence of pancreatitis.

Historically, immunomodulators have been used as steroid-sparing agents in other immune-mediated disorders like inflammatory bowel disease and rheumatoid arthritis. We propose that for patients with recurrent pancreatitis following ICI therapy, immunomodulators can be introduced as steroid-sparing agents. This approach is supported by several case reports of ICI-IP managed with immunomodulators.[9–12] However, it is important to note that these medications carry their own side effect profile and require careful monitoring for drug-induced adverse events.

DISCLOSURES

Author contributions: H. Peck, W. Pagani, A. Smith: writing, editing, reference management. S. Madhavan: editing, obtaining patient consent. S. Madhavan is the article guarantor.

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Informed consent was obtained for this case report.

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