Management of Acute Pancreatitis Associated With Checkpoint Inhibitors

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Abstract

Pancreatitis is a rare immune-related adverse event (irAE) associated with the use of immune checkpoint inhibitors (ICIs). It is more often associated with combined immunotherapy than by any single agent. Early signs of pancreatitis may only include elevation of lipase and amylase. Additional symptoms associated with pancreatitis include symptoms such as severe epigastric abdominal pain (that may radiate to the back, chest, or flank), nausea and/or vomiting, or dyspnea, and may indicate more advanced disease. Some researchers note that the presence of symptoms is not an indicator of more severe pancreatitis or long-term adverse outcomes. Radiologic changes can be useful in the diagnostic workup of ICI-associated pancreatitis, but radiologic tests may not show any changes in some patients with active pancreatitis. The management of ICI-associated pancreatitis can include those interventions used to manage acute pancreatitis (e.g., IV fluids, holding the agent, antibiotics, and steroids). The National Comprehensive Cancer Network Guidelines only recommend intervention for moderate to severe pancreatitis. Holding the associated ICI(s) is the most commonly used intervention when patients experience pancreatitis that is thought to be related to ICIs. Steroids are usually used in the management of irAEs associated with checkpoint inhibitors; however, there are no studies available at this time to indicate that this is the best method to treat pancreatitis associated with ICIs. Additional studies are needed to determine if steroids are the best method to manage irAE-associated pancreatitis or if additional management strategies are important in the management of pancreatitis in patients receiving checkpoint inhibitors.

CASE STUDY

KG is a 55-year-old male who was diagnosed with stage IIIB squamous cell lung cancer (non–small cell lung cancer) in 2017. His medical history includes hypertension, diabetes, and hyperlipidemia, all of which have been under control for the past 5 years through medication. His type 2 diabetes is managed with diet and medications, including metformin at

1,000 mg po bid, nateglinide at 120 mg three times daily taken 30 minutes prior to meals, and linagliptin at 5 mg po daily in the morning. Additional medications include losartan for hypertension and atorvastatin for hyperlipidemia. He is currently receiving treatment with the programmed cell death ligand 1 (PD-L1)-blocking antibody durvalumab (Imfinzi), which was initiated in January 2018. His prior treatment history includes chemotherapy with paclitaxel and carboplatin along with radiation therapy.

KG was tolerating treatment well and had not experienced any immune-related adverse events (irAEs); however, he was noted to have a slowly progressive rise in his blood sugars without any change in his diabetes medications. His blood glucose levels ranged from 106 to 284 mg/dL (average blood sugar: 194 mg/dL). No HbA1c level was available. He reported that he was adherent in taking his medications as prescribed. Due to KG's history of diabetes and labile blood glucose readings, pancreatic enzymes were monitored in addition to complete blood count, renal, liver, and thyroid function. On July 30, 2018, prior to cycle 15 of durvalumab, routine pretreatment labs indicated elevated serum amylase and lipase levels (amylase level 3 × upper limit of normal [ULN]; lipase level ≥ 3 × ULN). He reported having some upper abdominal discomfort that was worse when he leaned forward and was new for him. He indicated he was having episodes of nausea but no vomiting. The altered amylase/lipase results are considered grade 2 enzyme elevations (according to Common Terminology Criteria for Adverse Events) or moderate enzyme elevations (according to the National Comprehensive Cancer Network). Prior results were within normal range. Other abnormal lab results included a blood glucose level of 166 mg/dL. KG had no recent medical, surgical, or medication changes. He does not have a history of prior pancreatitis.

The clinical diagnosis for KG was immune checkpoint inhibitor–associated pancreatitis. The durvalumab therapy was held and KG's abdominal discomfort resolved. He did not develop any additional symptoms of pancreatitis. Subsequent labs performed 2 weeks later showed normal serum amylase and lipase levels, and KG's treatment with durvalumab was restarted. KG went on to receive 1 full year of durvalumab and did not experience any additional irAEs or pancreatic lab abnormalities.

Acute pancreatitis is an inflammation of the pancreas (Figure 1). Whereas mild pancreatitis occurs when there is no organ dysfunction, severe pancreatitis is complicated by multiple organ dysfunction. Pancreatitis initially occurs with cell damage and results in trypsinogen activation that results in the recruitment of macrophages and neutrophils. Trypsinogen causes activation of trypsin that leads to further cell injury. In addition, there is activation of other digestive enzymes that ultimately results in massive destruction of pancreatic tissue (Waller, Long, Koyfman, & Gottlieb, 2018). This feedback loop usually stops spontaneously; however, in some patients, there is progression of the disease, which leads to a more serious illness. This results in diffuse pancreatic necrosis and possibly infection (Waller et al., 2018). Infected pancreatic necrosis can develop within a few days following the onset of symptoms but is more common later in the course of the disease (Waller et al., 2018). Chronic pancreatitis is a syndrome with endocrine and exocrine gland dysfunction. Chronic pancreatitis develops due to progressive inflammation and chronic fibrosis of the pancreatic acini and causes permanent structural damage. Chronic pancreatitis can develop due to recurrent attacks of acute pancreatitis. It is thought that acute and chronic pancreatitis are separate entities (Hammad, Ditillo, & Castanon, 2018).

The incidence of pancreatitis has been increasing over the past few decades and affects between 14 and 45 per 100,000 people. It remains difficult to predict which patients with pancreatitis will develop pancreatic necrosis. The mortality rate is approximately 15% in those with pancreatic necrosis and 30% in those with infected pancreatic necrosis (Waller et al., 2018). In addition, approximately 1% of all patients admitted to the hospital with acute pancreatitis die while in the hospital.
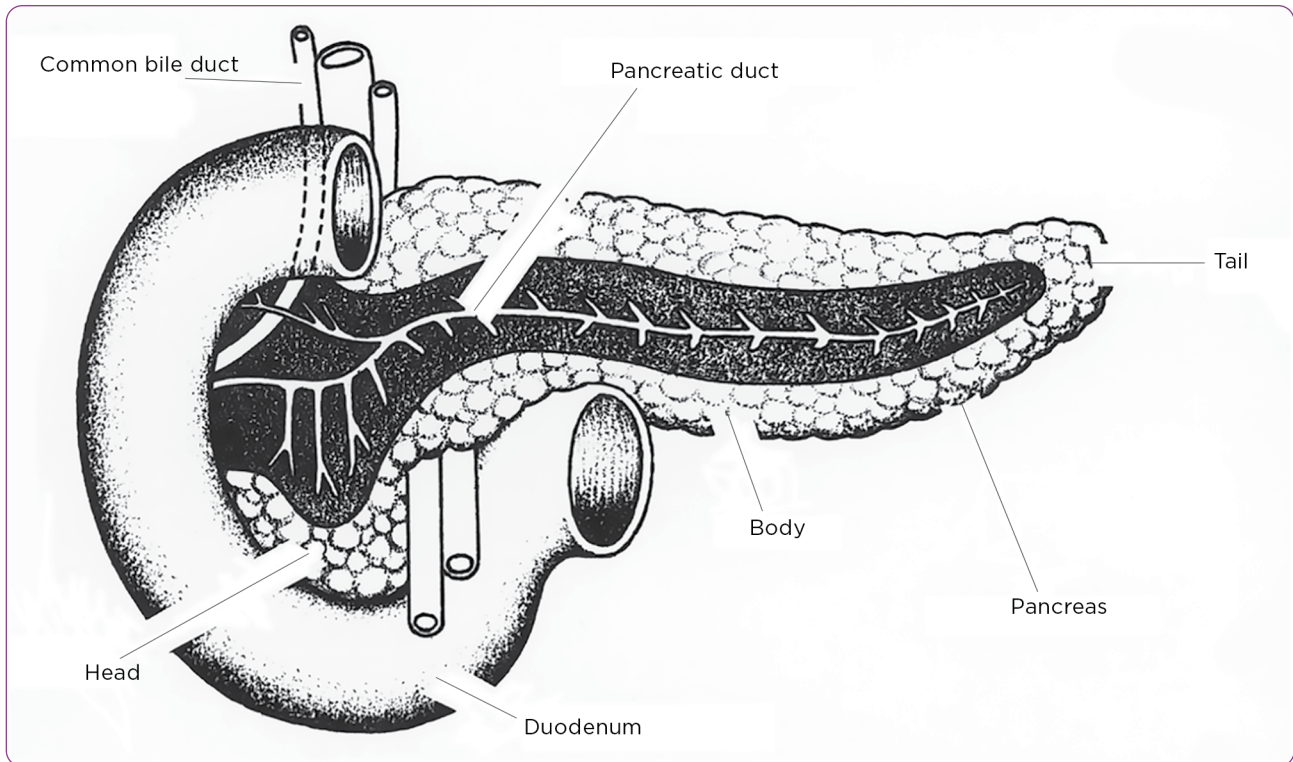
Figure 1. Pancreas. From the National Institutes of Health (2001).

The most common causes of pancreatitis include gallbladder disease and alcohol use. Additional causes include hypertriglyceridemia and medications. In patients with malignancy, pancreatitis can occur due to the malignancy itself or agents used in the treatment of the malignancy (Friedman, Proverbs-Singh, & Postow, 2016). There are additional causes of pancreatitis, including hypercalcemia, fibrosis, autoimmune etiologies, toxins, scorpion stings, and congenital etiologies. In approximately 25% of cases of pancreatitis, no definitive cause is identified (Nesvaderani, Eslick, Vagg, Faraj, & Cox, 2015).

The presence of gallstones is thought to be the most common cause of pancreatitis, with an estimated 40% to 70% of cases thought to be related to gallstones. Gallstones cause pancreatic duct obstruction, which increases the intrapancreatic duct pressure. This causes acid to efflux into the pancreas and activates trypsinogen inside the pancreas, which leads to cell damage. Mechanical obstruction (from pancreatic cancer, sphincter of Oddi dysfunction, or postendoscopic retrograde cholangiopancreatography [ERCP]) likely cause similar events to occur.

Alcohol intake is the second most common cause of pancreatitis and represents 25% to 41% of cases with pancreatitis (Waller et al., 2018). Pancreatitis associated with binge drinking usually occurs 12 to 24 hours after the cessation of the intake of alcohol (Waller et al., 2018). Individuals who binge drink often have a history of chronic alcohol abuse of more than 3.5 drinks per day for more than 5 years. Pancreatitis occurring in alcohol-naive individuals is much less common than in those who binge drink. There is no established threshold at which alcohol use will cause pancreatitis, but it has been noted that individuals who are dependent on alcohol develop pancreatitis only less than 5% of the time (DiMagno, 2011; Waller et al., 2018).

The third most common cause of pancreatitis worldwide is hypertriglyceridemia; pancreatitis is usually associated with triglyceride levels over 1,000 mg/dL. It accounts for up to 10% of all cases of pancreatitis overall and about 50% of pancreatitis cases in pregnancy (Ewald, Hardt, Kloer, 2009). Inflammation in the pancreas is caused by free fatty acids produced by the breakdown of triglycerides (Waller et al., 2018).

Acute pancreatitis can also occur following an ERCP, with approximately 35% to 70% of patients developing hyperamylasemia following the procedure. If the hyperamylasemia occurs along with severe abdominal pain and nausea and vomiting, it is diagnosed as post-ERCP pancreatitis. The risk of ERCP-associated acute pancreatitis is higher when the ERCP is used to treat dysfunction of the sphincter of Oddi but lower if the procedure is used to remove gallstones. The incidence of acute pancreatitis associated with diagnostic ERCP is approximately 3% (Hammad et al., 2018; Wang, Gao, Wei, Wang, & Ding, 2009).

It is estimated that 0.1% to 2% of acute pancreatitis is associated with drugs (see Table 1 for a list of drugs reported to be associated with pancreatitis). The classes of medications that have been noted to be associated with pancreatitis include chemotherapy agents, agents that cause hypertriglyceridemia, hepatic embolization, hyperthermic intraperitoneal chemotherapy, proteasome inhibitors, immune-modulating agents, tyrosine kinase inhibitors, antibody-toxin conjugates, and immune checkpoint inhibitors (Clamon, Patel, & Mott, 2017; Gandhi et al., 2014; Jones, Hall, Kaye, & Kaye, 2015; Muzaffar, Jia, Liles, Naveed, & Kumari, 2016; Sakhri, Ben Salem, Harbi, Fathallah, & Ltaief, 2010; Trivedi & Pitchumoni, 2005).

CHECKPOINT INHIBITORS

The signaling of immune checkpoint inhibitors (ICIs; including cytotoxic T-lymphocyte–associated protein 4 [CTLA-4], programmed cell death protein 1 [PD-1], and programmed cell death ligand 1 [PD-L1]) is important in the process in which cancer cells escape surveillance by the immune system. Immune checkpoint inhibitors increase antitumor immunity by blocking regulators of T-cell function. The T-cell regulators are present on both immune and tumor cells. Checkpoint inhibitors are effective in reversing the blocking of immune responses to malignancy as well as main-

Table 1. Medications Associated With Pancreatitis	
Drug classification	**Examples of specific drugs**
Anticancer chemotherapy agents	Asparaginase, mercaptopurine, cytosine arabinoside, cisplatin, interferon alfa-2b, doxorubicin, gefitinib, vinorelbine, oxaliplatin, levamisole, methotrexate, azathioprine, 5-fluorouracil, capecitabine, ifosfamide, paclitaxel, everolimus, all-*trans* retinoic acid
Hormones	Tamoxifen
Proteasome inhibitors	Bortezomib
Immune-modulating agents	Thalidomide
Tyrosine kinase inhibitors	Sunitinib, sorafenib, axitinib, vandetanib, pazopanib, nilotinib
BCR-ABL targeted TKI	Ponatinib, imatinib
BRAF inhibitors	Vemurafenib, dabrafenib
Bruton tyrosine kinase inhibitors	Ibrutinib
Antibody conjugates	Brentuximab vedotin, ado-trastuzumab emtansine
CD3 T-cell engager	Blinatumomab
Immune checkpoint inhibitors	Ipilimumab, nivolumab, pembrolizumab, atezolizumab
Hyperthermic intraperitoneal chemotherapy	–
Transarterial chemoembolism	–
Radioembolization with ^{90}Y microspheres	–

Note. TKI = tyrosine kinase inhibitor. Information from Amgen (2019); Artac et al. (2002); Blum et al. (2012); Butt et al. (2010); Chung et al. (2008); Cortes et al. (2012); Elisaf et al. (2000); Elouni et al. (2010); Engel et al. (2013); Genentech (2019); Ghatalia et al. (2015); Hofmann et al. (2016); Ibrahim et al. (2011); Kawakubo et al. (2015); Merchant et al. (2012); Muluneh et al. (2013); Muzaffar et al. (2016); Novartis (2019); Özçınar et al. (2009); Palandri et al. (2009); Péron et al. (2014); Peterson et al. (2013); Piso et al. (2011); Rünzi & Layer (1996); Russano et al. (2015); Subramaniam et al. (2013); Sakhri et al. (2010); Sevin et al. (2012); She et al. (2016); Tirumani et al. (2013); Urru et al. (2014); Varma et al. (2010); Wolchok et al. (2013); Yucel & Warmerdam (2010).

taining control of immunity to tumor cells. The majority of adverse effects of ICIs are immune-related adverse events (irAEs) and are caused by the activation of T cells (Michot et al., 2018). In general, the agents that block CTLA-4 have a higher rate of irAEs as compared to those that block PD-1 or PD-L1 (George, Yoo, Joshi, & Farrell, 2018).

The incidence of ICI-associated pancreatitis is rare. Most clinical trials involving checkpoint inhibitors (single agents) have reported a less than 1% incidence of grade 3 to 4 pancreatitis. Michot and colleagues (2018) reported an incidence of immune-related lipase elevation associated with anti–PD-1 or anti–PD-L1 to be 2.3% and the overall incidence of immune-related pancreatitis at 0.3%. However, specifically in patients who have immune-related lipase elevation, the incidence of pancreatitis was 14%. It has been noted that the incidence of pancreatitis associated with CTLA-4 agents is higher than that associated with PD-1 agents (George et al., 2018). The incidence of pancreatitis associated with PD-1 agents is approximately 1.8% to 2.6%; however, in combined immunotherapy (ipilimumab [Yervoy] and nivolumab [Opdivo]), the incidence can be as high as 6% (Clamon et al., 2017; George et al., 2018; Hofmann et al., 2016).

In a meta-analysis by George and colleagues (2018), no deaths associated with pancreatitis have been reported with the use of ICIs; however, the same authors reported that the incidence of grade 3 to 5 pancreatitis is approximately 1.7%. El Majzoub and colleagues (2018) reported that emergency department visits related to pancreatitis were more often associated with combination therapy and nivolumab than pembrolizumab (Keytruda) or ipilimumab. In addition, patients with melanoma who are treated with an ICI have a higher incidence of pancreatitis (3.7% vs. 1.2%) as compared to other malignancies (George et al., 2018). The onset of pancreatitis is unclear and varies widely between studies, from 2 to 16 weeks (Alabed, Aghayev, Sakellis, & Van den Abbeele, 2015; Hofmann et al., 2016). The median time from the start of ICI therapy to peak lipase elevation was longer in patients who received PD-1/PD-L1 monotherapy than in patients who received CTLA-4–based regimens (median 146 days vs. 69 days).

The resemblance between pancreatic injury associated with ICIs and traditional acute pancreatitis has not yet been studied. In addition, there is the potential that there are various factors that can be potential causes for elevated serum lipase (Abu-Sbeih et al., 2019a). Immune checkpoint inhibitor–associated pancreatitis is usually asymptomatic, usually with imaging of the pancreas found to be normal and the elevation of lipase levels found incidentally (Abu-Sbeih et al., 2019a). These authors feel that current guidelines regarding the monitoring, diagnosis, and management of ICI-associated pancreatitis are based on minimal evidence.

CLINICAL SIGNS AND SYMPTOMS

Patients with acute pancreatitis usually present with severe epigastric abdominal pain that may radiate to the back, with approximately 50% of patients experience pain radiating to the chest or flank (Hammad et al., 2018). Associated symptoms may include nausea and/or vomiting, fever, and diarrhea (Banks et al., 2013; Hammad et al., 2018; Tenner, Baillie, DeWitt, & Vege, 2013). Some patients experience more than one symptom, whereas other patients may experience none. Physical examination findings may include tenderness upon palpation of the abdomen, abdominal distention, hypoactive bowel sounds, or jaundice. In addition, patients may experience hypotension (Clamon et al., 2017). In severe cases, patients may exhibit tachypnea, hypoxemia, tachycardia, or hypotension (Vege, 2018). If an ileus is also present, the patient may have abdominal distention with hypoactive bowel sounds (Hammad et al., 2018). Patients with infected pancreatic necrosis often present with tachycardia, hypotension, fever, and leukocytosis (Banks & Freeman, 2006; Waller et al., 2018).

In a study reported by Abu-Sbeih and colleagues (2019a), symptoms associated with ICI-related pancreatic injury include epigastric pain, nausea and vomiting, fever, and diarrhea, with approximately a quarter of patients experiencing more than one of these symptoms. However, they also reported that some patients are completely asymptomatic but have CT findings suggestive of pancreatitis. Typical pancreatitis presentation is observed in approximately one third of patients receiving ICI therapy who develop pancreatitis. In the study, half of the patients experienced grade 2 pancreatitis with enzyme elevation or radiologic findings only, whereas the remainder of

the patients experienced grade 3 pancreatitis with symptoms that included pain and vomiting, and intervention was indicated. Fever was more likely to be experienced by patients who experienced atypical symptoms of pancreatitis than those who had asymptomatic lipase elevation (Abu-Sbeih et al., 2019a). Patients with a prior history of pancreatitis had an increased risk of experiencing pancreatitis associated with the ICI that presented with clinical symptoms.

Gallstones have been noted to be the most common cause of acute pancreatitis. Until recently, the presence of gallstones was not reported as part of the symptoms seen in patients receiving ICI. However, a few case studies have recently been reported in patients receiving ICI therapy who developed cholecystitis (Abu-Sbeih et al., 2019b). Several mechanisms can increase the likelihood of cholecystitis, such as the presence of liver metastasis with potential for biliary stone formation, rapid weight loss, altered immunity with potentially increased susceptibility to infections, and risk factors such as advanced age, obesity, smoking, and a high-fat diet (Abu-Sbeih et al., 2019b). Symptoms associated with cholecystitis are similar to those seen in ICI-associated pancreatitis and include abdominal pain, nausea and vomiting, diarrhea, and fever. Approximately 8% of patients with ICI-associated cholecystitis had a positive infection workup at the time of cholecystitis onset. The cause of ICI-associated cholecystitis requires microscopic confirmation (Abu-Sbeih et al., 2019b).

Patients have developed diabetes after receiving treatment with ICI. The reported incidence of immunotherapy-induced type 1 diabetes is approximately 0.4%, but the actual incidence may be higher due to onset long after treatment is completed (Galligan et al., 2018). In reviewing 27 patients who developed insulin-dependent diabetes mellitus after receiving treatment with checkpoint inhibitors, the average time of onset was found to be after 20 cycles of immunotherapy, but the range was from 1 to 78 cycles (Stamatouli et al., 2018). The majority of patients presented with diabetic ketoacidosis. Approximately 42% of patients diagnosed with immunotherapy-induced diabetes exhibited evidence of pancreatitis, and 32% of these with elevated lipase and/or amylase (2–10 × upper limit of normal [ULN]; Stamatouli, et al., 2018). Pancreatic edema was noted on the CT scan of one patient, which suggests the role of pancreatic inflammation in the development of diabetes. Two patients with preexisting type 2 diabetes developed insulin dependence or worsened glucose control (Stamatouli et al., 2018). Immunotherapy-induced diabetes is more common with PD-1 and PD-L1 inhibitors as compared to other checkpoint inhibitors (Haanen et al., 2017; Stamatouli et al., 2018). Regular blood glucose monitoring is recommended in order to detect any changes as soon as possible (Haanen et al., 2017).

Labs

Lab results in evaluating patients for pancreatitis include elevated serum amylase and lipase levels, with lipase being a more sensitive indicator of acute pancreatitis (Hammad et al., 2018). Patients with clinical symptoms are more likely to develop higher mean peak values of serum lipase than patients who are asymptomatic with their checkpoint inhibitor–associated pancreatitis (Abu-Sbeih et al., 2019a). There is no difference between the level of amylase in those who experience symptoms with pancreatitis and those who do not (Abu-Sbeih et al., 2019a). The National Comprehensive Cancer Network Guidelines (NCCN, 2020) separate the asymptomatic elevation in amylase/lipase elevation into mild (< 3 × ULN amylase and or lipase), moderate (> 3–5 × ULN amylase or lipase), or severe (> 5 × ULN amylase or lipase). In addition to immunotherapy-related enzyme elevations, other possible etiologies of elevated pancreatic enzymes should be considered. These include malignancy, biliary obstruction, alcohol-related pancreatitis, gallstone pancreatitis, renal failure, or T cell-mediated inflammation of other organs (Friedman et al., 2016; Grover, Rahma, Hashemi, & Lim, 2018).

Other abnormalities may be leukocytosis, elevated blood urea nitrogen, hypocalcemia, or hyper- or hypoglycemia. Hematocrit may be elevated due to hemoconcentration with third spacing. C-reactive protein may also be elevated. Interleukin 6, interleukin 8, interleukin 10, tumor necrosis factor, polymorphonuclear elastase, and trypsinogen activation peptide have been found to be useful in clinical trials but are not currently suitable or readily available for clinical practice

(Banks & Freeman, 2006; Hammad et al., 2018; Waller et al., 2018).

DIAGNOSIS

The diagnosis of acute pancreatitis requires two of the following three features: clinical symptoms, radiographic findings of an inflamed pancreas, or elevated pancreas enzyme levels (amylase and lipase). Serum amylase or lipase should be higher than three times the ULN to be characterized as acute pancreatitis (Banks et al., 2013; Friedman et al., 2016). Elevated serum amylase and/or lipase levels may occur without symptoms or radiologic abnormalities; therefore, routine monitoring of pancreatic enzyme levels at baseline or during treatment with ICI therapy is not recommended in the NCCN Guidelines (2020). However, in the study reported by Abu-Sbeih and colleagues (2019a), clinical symptoms of pancreatitis were evident in 39% of patients who had grade 3 or higher lipase elevation. They indicated that ICI-associated pancreatic injury is usually asymptomatic and yields normal pancreas imaging findings. In addition, the elevated serum lipase is detected incidentally in many patients who develop ICI-associated pancreatic injury. Abu-Sbeih and colleagues (2019b) also found that ICI-associated pancreatic injury was more common in patients who experienced other adverse events. Therefore, they recommend that lipase values be obtained in patients who are diagnosed with nonpancreatic-associated adverse events. The recommended evaluation for potential pancreatitis associated with ICIs includes amylase and lipase levels, and abdominal imaging (NCCN, 2020). Further study is needed to determine if pancreatic enzymes should be monitored during ICI therapy or only in certain situations.

Radiology Evaluation

Radiology studies such as x-ray, ultrasound, CT, or MRI may be obtained and may show pancreatic inflammation, acute peripancreatic fluid collection, gallstones, bowel gas due to ileus, pancreatic edema, diffuse enlargement of the pancreas, or pancreatic necrosis (Vege, 2018). Imaging findings of acute pancreatitis from any cause include fat stranding, enlargement of the pancreas, and decreased attenuation (Widmann, Nguyen, Plaick-ner, & Jaschke, 2016). Specific CT or MRI findings related to pancreatitis from checkpoint inhibitors include evidence of pancreatic enlargement, decrease in attenuation, and surrounding fat stranding (Widmann et al., 2016). Intense fluorodeoxyglucose uptake in the pancreas may be seen on PET/CT. Abu-Sbeih and colleagues (2019a) reported that abnormal CT findings were more likely to be found in patients who developed ICI-associated pancreatitis with clinical symptoms than patients who did not exhibit symptoms. In their study, only 13% of patients with elevated lipase levels also had abnormal CT findings; therefore, these authors indicate that CT is not useful in the evaluation of ICI-associated pancreatic injury.

RISK STRATIFICATION AND GRADING

The most commonly used system for grading the severity of adverse events in oncology is the Common Terminology Criteria for Adverse Events (CTCAE), currently in version 5.0 (see Table 2). In this system, grading for pancreatitis begins at grade 2, which is defined as asymptomatic enzyme elevation and/or radiologic findings only. Grade 3 pancreatitis is classified as symptomatic with severe abdominal pain/vomiting requiring medical intervention. Grade 4 pancreatitis is life-threatening, requiring urgent intervention. Grade 5 is death (NCI, 2017). The NCCN includes a grading of pancreatitis in their Guidelines for the management of immunotherapy-related toxicities. These vary somewhat from the CTCAE grading scale (see Tables 2–4). The NCCN Guidelines include a separate grading in asymptomatic amylase/lipase elevation. The Guidelines include a separate grading of pancreatitis that is based on the elevation of amylase/lipase, radiologic findings, or clinical findings.

However, some authors do not agree with these grading scales. For example, Abu-Sbeih and colleagues (2019b) indicated that almost half of the patients in their study who were diagnosed with ICI-associated pancreatitis had no symptoms at all. Typical pancreatitis presentation was observed in about one third of patients, whereas the other two thirds of patients did not have typical pancreatitis symptoms. Additional studies are needed to clarify the grading of ICI-associated pancreatitis and how these grades impact management strategies.

Table 2. Common Terminology Criteria for Adverse Events (CTCAE) Grading of Pancreatitis

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pancreatitis	–	Enzyme elevation; radiologic findings only	Severe pain, vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death
Pancreatic necrosis	–	–	Tube feeding or TPN indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Amylase	> ULN–1.5 × ULN	> 1.5–2.0 × ULN; > 2.0–5.0 × ULN and asymptomatic	> 2.0–5.0 × ULN with signs or symptoms; > 5.0 × ULN and asymptomatic	> 5.0 × ULN and with signs or symptoms	–
Lipase	> ULN–1.5 × ULN	> 1.5–2.0 × ULN; > 2.0–5.0 × ULN and asymptomatic	> 2.0–5.0 × ULN with signs or symptoms; > 5.0 × ULN and asymptomatic	> 5.0 × ULN and with signs or symptoms	–

Note. TPN = total parenteral nutrition; ULN = upper limit of normal. Information from National Cancer Institute (2017).

Risk stratification scoring tools are available for acute pancreatitis to help the provider determine the need for admission and whether the patient would be best suited in an intensive care unit (ICU). The bedside index of severity in acute pancreatitis score (BISAP score) is simpler than earlier developed tools and is able to be completed with information gathered at initial assessment (Waller et al., 2018). Its use helps to predict mortality associated with pancreatitis and may help to determine if the patient requires care in the ICU (see Table 5 for BISAP index).

An additional scoring system has been developed by Whitlock and colleagues (2011) that helps to evaluate the patient's risk at discharge from the hospital for readmission. The important factors at discharge include inability to tolerate solid diet,

gastrointestinal symptoms (nausea, vomiting, diarrhea), pancreatic necrosis, antibiotic use, or pain. Based on this scale, the presence of zero to one criteria equates to a readmission rate of 5%, two to three criteria with a readmission rate of 18%, and four or more criteria a readmission rate of 68% (Whitlock et al., 2011).

MANAGEMENT OF ICI-ASSOCIATED PANCREATITIS

Numerous guidelines have been developed for the management of immunotherapy-related adverse events; however, other than the NCCN Guidelines, most have not addressed pancreatitis individually given its low incidence (Brahmer et al., 2018; Haanen et al., 2017; Puzanov et al., 2017). Other authors, such as Abu-Sbeih and colleagues (2019b), indicate that the management of ICI-associated cholecystitis should be similar to the recommended care for the traditional management of cholecystitis (see Table 6 for an outline of the major components of management strategies for immunotherapy-associated pancreatitis).

The NCCN Guidelines (2020) for the management of ICI-related toxicities do not recommend interventions for asymptomatic pancreatic enzyme elevations. Based on the NCCN Guide-

Table 3. NCCN Grading of Immune Checkpoint Inhibitor–Associated Asymptomatic Amylase/Lipase Elevation

Mild	≤ 3 × ULN amylase and/or ≤ 3 × ULN lipase
Moderate	> 3–5 × ULN amylase and/or > 3–5 × ULN lipase
Severe	> 5 × ULN amylase and/or > 5 × ULN lipase

Note. Information from NCCN (2019).

Table 4. National Comprehensive Cancer Network Grading of Immune Checkpoint Inhibitor–Associated Pancreatitis

Grading	Description
Mild (grade 1)	Elevation of amylase/lipase > 3 × ULN or radiologic findings on CT or clinical findings consistent with pancreatitis
Moderate (grade 2)	Two of three: elevation of amylase/lipase > 3 × ULN + radiologic findings on CT + clinical findings concerning for pancreatitis
Severe (grades 3–4)	Elevation of amylase/lipase + radiologic findings + severe abdominal pain or vomiting and hemodynamically unstable

Note. Information from NCCN (2019).

lines, unless the patient is symptomatic, treatment with immunotherapy may continue with ongoing monitoring of pancreatic enzymes. Permanent discontinuation of ICI therapy is recommended for severe acute pancreatitis associated with the ICI. The Guidelines recommend the use of steroids (prednisone/methylprednisolone at 0.5–1 mg/kg/day) for moderate to severe ICI-associated pancreatitis. Some authors (Ikeuchi, Okuma, & Tabata, 2016) indicate that some cases of severe pancreatitis associated with ICI therapy may require doses of prednisone as high as 4 mg/kg/day. Once symptoms resolve, the prednisone should be tapered slowly over 4 to 6 weeks.

However, in the study reported by Abu-Sbeih and colleagues (2019a), they did not find that steroids had any value in the management of ICI-associated pancreatitis. They indicated that they did not see that the use of steroids prevented short-term (pseudocyst, symptoms) or long-term (chronic pancreatitis, diabetes) adverse effects, nor did they improve survival in patients who experienced ICI-associated pancreatitis. In addition, in a study reported by Abu-Sbeih and colleagues (2019b), in patients who developed ICI-associated cholecystitis, they indicated that the use of steroids was unclear.

Therefore, the usefulness of steroids in patients with ICI-associated pancreatitis remains in question. For many ICI-associated adverse events, if improvement is not noted within 48 hours with the use of steroids, the use of infliximab is recommended (NCCN, 2020). It is given as a single dose that can be repeated 14 days later. However, the specific use of infliximab for the management of pancreatitis is not included in the available guidelines nor in studies that have thus far been reported on the management of irAEs.

Inpatient admission and supportive care with IV hydration, pain control, and bowel rest should be considered in highly symptomatic patients (Working Group IAP/APA Acute Pancreatitis Guidelines, 2013). The inflammatory mediators associated with acute pancreatitis contribute to increased vascular permeability and third spacing of fluid. In addition, patients may have developed dehydration due to the nausea and vomiting that can occur with acute pancreatitis. Therefore, the administration of IV fluids is the mainstay of treatment of acute pancreatitis (Waller et al., 2018). The current version of the NCCN Guidelines now includes the use of IV hydration in all levels of pancreatitis associated with ICIs (2020).

Table 5. Bedside Index of Severity in Acute Pancreatitis Score (BISAP)[a]: Risk Stratification for Pancreatitis

	No	Yes
BUN > 25 mg/dL	0	1
Altered mental status (Glasgow coma scale score < 15)	0	1
≥ 2 systemic inflammatory response syndrome (SIRS) criteria • Temp > 38°C (100.4°F) or < 36°C (96.8°F) • Heart rate > 90 beats/min • Respiratory rate > 20 breaths/minute or arterial carbon dioxide tension (PaCO$_2$) < 32 mm Hg • Abnormal WBC count (> 12,000/µL or < 4,000/µL or > 10% immature [band] forms)	0	1
Age > 60 years	0	1
Pleural effusion present	0	1

Note. BUN = blood urea nitrogen. Information from Waller et al. (2018).
[a]0–2 points: low mortality (< 2%); 3–5 points: higher mortality (> 15%)

Table 6. Major Components of Management Strategies for Immunotherapy-Associated Pancreatitis		
Management of acute pancreatitis	**Management of ICI-associated pancreatitis**	
	NCCN	**Abu-Sbeih and colleagues**
IV fluids	IV fluids	IV fluids
Antibiotics	–	–
Analgesics	Analgesics	–
Hold/discontinue offending agent	Hold/discontinue ICI	Hold/discontinue ICI
Steroids (po or IV)	Steroids	–

Note. ICI = immune checkpoint inhibitor. Information from Abu-Sbeih et al. (2019a); Mao et al. (2009); NCCN (2019); Waller et al. (2018).

Rapid, large-volume IV fluid administration has been found to be associated with sepsis and decreased survival; therefore, controlled fluid replacement (5–10 mL/kg/h or less than 4.1 L over initial 24 hours) is recommended (de-Madaria et al., 2011; Mao et al., 2009). The specific type of IV fluid to use remains a controversy. Normal saline can lead to a hyperchloremic metabolic acidosis when administered in large amounts. The acidosis can increase the activation of trypsinogen, which can potentially exacerbate the pancreatitis. Therefore, balanced solutions such as Lactated Ringer's may be preferred (Waller et al., 2018).

Abu-Sbeih and colleagues (2019a) indicated in their report that there is significant usefulness of aggressive IV fluid repletion in the treatment of ICI-associated pancreatitis. The IV fluids seemed to decrease the risk of long-term adverse events associated with pancreatitis. The authors felt that IV fluid administration should be considered for a lipase elevation of grade 3 or higher, even in those patients who are asymptomatic. The most critical timepoint is within the first 48 hours after the onset of the indication of pancreatitis.

Antibiotics and analgesics may be needed for some patients. The routine administration of antibiotics for patients with pancreatitis is not recommended. However, if patients present with cholangitis, cholecystitis, or another infection, antibiotics may be necessary (Waller et al., 2018). There is no indication for the use of antibiotics in either the guidelines or in any of the manuscripts published by researchers who have looked at ICI-associated pancreatitis. However, Abu-Sbeih and colleagues (2019b) reported that there was no difference in the duration of symptoms, hospitaliza-

tion, resumption of ICI therapy, or death in patients who received antibiotics.

Patients may be in severe pain from ICI-associated pancreatitis and therefore may need analgesics for pain control. Patients with mild symptoms may be discharged with oral acetaminophen or opioids. Gülen and colleagues (2016) reported that IV acetaminophen provides equianalgesia to IV tramadol. If nonopioids do not provide significant relief of pain, IV opioids are effective (e.g., fentanyl, morphine, hydromorphone).

Previously, bowel rest was the standard of care for the management of acute pancreatitis; however, that is no longer the case. There is no information regarding bowel rest in the management of ICI-associated pancreatitis, and recommendations are to start feeding as soon as the patient can tolerate food. However, in patients with moderate to severe acute pancreatitis, oral feeding might not be tolerated due to nausea and vomiting or pain. In patients who can tolerate oral foods, feeding should be initiated with a low-fat diet. Early enteral nutrition is related to decreased incidence of infection, with the recommendation for the patient to eat during the first 24 to 48 hours of hospitalization (Li et al., 2013; Waller et al., 2018).

At times, surgical intervention may be useful in the management of acute pancreatitis, primarily when associated with gallstones. Current treatment guidelines do not include the management of cholecystitis associated with ICI therapy since it is a rare event and only recently has been a reported adverse event associated with ICIs. Endoscopic retrograde cholangiopancreatography is useful in patients with pancreatitis associ-

ated with gallstones with concurrent acute cholangitis, common bile duct (CBD) obstruction, dilatation of the CBD, or increased liver enzyme levels without cholangitis. Patients who present with mild acute pancreatitis with gallbladder stones may require a cholecystectomy. Early laparoscopic cholecystectomy in the management of acute pancreatitis has been associated with shortened hospital stay (Gurusamy, Nagendran, & Davidson, 2013; Hammad et al., 2018). However, Abu-Sbeih and colleagues (2019b) reported that surgery or antibiotics in the management of ICI-associated cholecystitis did not accompany any difference in duration or symptoms, duration of hospitalization, resumption of ICI therapy, or death (from any cause).

Patients undergoing treatment for immunotherapy-associated pancreatitis should be monitored for the development of pancreatic exocrine insufficiently and/or diabetes mellitus. Following resolution of pancreatitis and normalization of pancreatic enzymes, there has been one case report in a retrospective study by Hofmann and colleagues (2016) of pancreatic insufficiency requiring oral repletion of pancreatic enzymes.

DISCUSSION

Pancreatitis is a rare irAE associated with the use of checkpoint inhibitors. It is more often associated with combined immunotherapy than by any single agent. Since therapy is not warranted in patients with elevated pancreatic enzymes alone, monitoring of these levels is not recommended at this time. However, patients who experience symptoms of pancreatitis should have lipase and amylase levels evaluated. Radiologic changes can be useful in the diagnostic workup of irAE-associated pancreatitis, but patients with active pancreatitis may not have any changes noted on radiologic tests. The NCCN Guidelines only recommend intervention for moderate to severe pancreatitis. Steroids are usually used in the management of irAEs associated with checkpoint inhibitors; however, there are no studies available at this time to indicate that this is the best method to treat immunotherapy-related pancreatitis. Additional studies are needed to determine if steroids are the best method to manage irAE-associated pancreatitis and the recom-

mended treatment in those patients who develop immunotherapy-associated pancreatitis that is refractory to steroids. In addition, it is unclear if other strategies used in the management of acute pancreatitis are useful in the management of ICI-associated pancreatitis. Additional studies are needed to determine the best management strategies for ICI-associated pancreatitis.

ROLE OF THE ADVANCED PRACTITIONER

Pancreatitis associated with checkpoint inhibitors can be difficult to diagnose. Clinicians need to be aware of the risk of pancreatitis associated with immunotherapy, but also of the lack of data to support the use of frequent monitoring of pancreatic enzymes (lipase and amylase). Patients may also have other risk factors for the development of pancreatitis, and providers should be aware of the patient's increased risk for pancreatitis associated not only with ICIs but also with other potential causes such as medications, gallstones, alcohol, and hypertriglyceridemia. In many cases, the advanced practitioner is the first provider to evaluate a patient who comes in for new symptoms while receiving therapy and can identify potential symptoms associated with pancreatitis. Advanced practitioners need to be educated on the potential symptoms of pancreatitis and appropriate workup of these symptoms. They need to remain current in the recommended treatment for this adverse event and monitor any updates to the guidelines that are available for the management of irAEs. ●

Disclosure

Ms. Rogers has served on advisory boards for Cardinal Health, Celgene, Daiichi Sankyo, Genentech, Merck, Mylan, and Sanofi Genzyme, and on speakers bureaus for AbbVie, Coherus BioSciences, Genentech, and Seattle Genetics. The other authors have no conflicts of interest to report.

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