Immunotherapy-Associated Pancreatic Adverse Events: Current Understanding of Their Mechanism, Diagnosis, and Management

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Immune checkpoint inhibitors (ICIs) such as anti-programmed death-1 (PD-1) and its ligand PD-L1 and anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) monoclonal antibodies, are involved in T cell-mediated immune response augmentation and promote anti-tumor immunity. Cancer patients treated with combination of immunotherapy, chemotherapy, radiotherapy, and targeted therapy exhibit superior clinical outcomes and tolerance compared with patients treated with monotherapies. However, immutherapy is associated with several concomitant immune-related adverse events (irAEs). For instance, IrAEs interferes with function of gastrointestinal tract, endocrine, dermatological, nervous system and musculoskeletal systems. ICIs-associated pancreatic injury might causes decrease in endocrine and exocrine pancreatic function, resulting in metabolic and nutritional disorders. Clinicians who administer immune checkpoint inhibitors to cancer patients are diagnosed with hyperglycemia, abdominal pain and steatorrhea. Currently, the precise mechanism of ICIs-associated pancreatic injury has not been fully explored. This paper summarizes incidence, diagnosis, clinical characteristics, potential mechanisms, and treatment management patterns of ICIs-associated pancreatic AEs based on previous studies. In addition, possible management approaches of these adverse effects are presented in this paper. in the findings summarized in this paper lay a basis for management of ICIs-associated pancreatic AEs and expanding future immunotherapy applications.

Keywords: immune checkpoint inhibitors, immune-related adverse events, ICIs associated with diabetes mellitus, amylase/lipase, pancreatitis, pancreatic exocrine insufficiency
INTRODUCTION

Programmed death 1 (PD-1) receptors bind to programmed death-ligand 1 (PD-L1), transport negative signals to T cells, and regulate functions of effector T cells. These receptors are expressed by T cells, B cells, and natural killer cells. In addition to normal T cells, several tumor cells upregulate PD-L1 on their surface, thus evading antitumor immune response and promoting immune tolerance by inactivating T cells through the PD-1/PD-L1 axis. These processes cause delay in the immune activation cycle. Cytotoxic T lymphocyte antigen 4 (CTLA-4) expressed on the surface of T cells downregulates immune responses against cancer cells in the early stages of the immune activation cycle. The mechanism of action is by interacting with the surface molecules B7.1 (CD80) and B7.2 (CD86) on antigen-presenting cells (1–5). These interactions promote tumor cells and aid in evasion of immunosurveillance. Therefore, use of immune checkpoint inhibitors (ICIs), including anti-PD-1 monoclonal antibodies (nivolumab and pembrolizumab), anti-PD-L1 monoclonal antibodies (atezolizumab, avelumab, and durvalumab), and anti-CTLA-4 monoclonal antibodies (ipilimumab and tremelimumab), triggers activation and expansion of T lymphocytes. These inhibitors act by blocking inhibitory signals of T cells and enhancing ability of the immune system to fight cancer cells (Figure 1).

Mechanisms of the 3 immunotherapy agents are different from each other and ICIs alone or in combination with chemotherapy are conventional first- or second-line therapies. This has been attributed to favorable survival durations and tolerance for many types of malignancies, including metastatic melanoma (6), advanced non-small cell lung cancer (7), Hodgkin lymphoma (8), metastatic renal cell carcinoma (9), and unresectable hepatocellular carcinoma (10). Despite the efficacy of immunotherapy, immune-related adverse events (irAEs), often involving endocrine tissues including pneumonitis, hypophysitis, thyroiditis, colitis, pancreatitis, and autoimmune diabetes, have emerged as potential challenges to patients (11, 12).

Incidence rate of ICIs-associated pancreatic AEs (pancreatitis, hyperglycemia, elevated amylase/lipase, and exocrine pancreatic insufficiency) is relatively low. Most of these events have been described as a case report (Table 1). Cancer patients treated with ICIs present with symptoms collectively described as ICIs-associated pancreatic AEs including abdominal pain, vomiting, dyspepsia, irregular stools, and large daily glucose fluctuations (7, 13, 32). ICIs-associated pancreatic AEs are rare, however they result in poor quality of life and affect safety of patients. This minireview retrieved data on ICIs-associated pancreatic AEs from several publications and summarizes different clinical and pathophysiological mechanisms and effective treatments for these effects (Table 2).

ICIS ASSOCIATED WITH DIABETES MELLITUS

The duration before onset of ICIs associated with diabetes mellitus (ICIs-DM) is between 3 weeks and 81 weeks after immunotherapy initiation, and most cases are reported in patients without pre-existing T2DM (11, 25, 47, 68–70). Drug administration significantly changes blood glucose level in cancer patients. HbA1C may be nearly normal or slightly elevated, C-peptide is low or undetectable, and severe cases are associated with diabetic ketoacidosis (DKA) (4, 32). A few ICIs-DM cases with pre-existing T2DM present with rapid hyperglycemia, however, DKA and undetectable C-peptide are uncommon (Table 1). Most ICIs-DM cases are observed during treatment with PD-1/PD-L1 inhibitors either alone or in combination with other immunotherapies. On the contrary, a few ICIs-DM cases are reported for patients exposed to CTLA-4 inhibitor monotherapy (7, 11, 70). Patients with advanced tumors are more likely to receive first-line systemic immunotherapy, and may receive combination of PD-1/PD-L1 inhibitors and CTLA-4 inhibitors. ICIs-induced DM incidence of combined therapy is 17%, which is significantly higher compared with that of single PD-1 or PD-L1 inhibitor treatment (6%) (11).

ICIs-DM are classified into 4 types based on the different clinical and biological profiles of ICIs-induced diabetes and their potential pathophysiology. These types include: acute autoimmune insulin-dependent DM, type 2 diabetes-like phenotype, diabetes-induced by autoimmune pancreatitis, and diabetes following autoimmune lipatrophy (5, 55).

Several studies report that acute autoimmune insulin-dependent DM type, an extremely rare irAE is associated with high mortality. Abrupt onset of hyperglycemia is associated with DKA, whereas hyperglycemia with a concomitant near-normal HbA1c level is an indicator of a fulminant disease. Marie-Lea Gauci et al., reported that among 132 patients suffering from melanoma, treatment with anti-PD-1 and anti-CTLA-4 resulted in T1D accompanied with high blood glucose levels and undetectable C-peptide concentrations in 3 cases. Furthermore, 2 patients presented with positive autoantibodies [glutamic acid decarboxylase (GAD) and tyrosine-phosphatase inhibitor (IA2)] before anti-PD-1 treatment and diabetes onset. These findings imply that these patients are likely to develop T1D (6). Positive autoantibodies are implicated in progressive insulinopenia and insulin-dependent DM, similar to cases of adult-onset autoimmune diabetes (71). CD8+ T cell clones promoted by
blocking PD-1 or PD-L1 are the primary cell types involved in destruction of insulin-secreting β-cells associated with DM, without affecting α-cells (6). PD-1/PD-L1 interaction plays a vital role in preventing onset of diabetes in animals. Notably, mice without antibodies develop diabetes, whereas other mice with autoantibodies are unnecessarily predicted to have diabetes (50). Kochupurakkal et al. reported some of the risk factors associated with anti-diabetic immune tolerance. For instance, upregulation of CTLA-4 and regulatory T cells (Treg) through low IL-2 production is correlated with high number of DCs and increased T cell stimulation and activation in the absence of negative costimulation induced by PD-1/PD-L1 pathway (51).

The period between start of ICIs therapy and onset of T1DM is linked to the presence or absence of GAD antibodies (GADA). Individuals with pre-existing positive GADA antibodies have high risk of developing T1DM in the first 2 months after initiation of treatment. Similarly, GADA-negative patients have a high risk of developing T1DM, however, this effect becomes evident after 2 months of treatment (37). High-risk human leukocyte antigen (HLA) type (HLA-DR4 allele) results in increased susceptibility of humans to T1D (52).

A few subjects exhibit pre-existing T2DM, which is effectively regulated without insulin. These patients experience a sharp increase in blood glucose levels after treatment initiation with
### Table 1: Published case reports and case series of immune checkpoint inhibitors associated with diabetes mellitus.

| Authors | Patient | Cancer type | Relevant History | Agent | Time to onset (weeks) | Clinical Presenting features | Autoantibodies | HLA (A/B/C) | Treatment | Discontinued ICI | Other iAEs | Outcome |
|---------|---------|-------------|-----------------|-------|-----------------------|-----------------------------|----------------|-------------|------------|-----------------|------------|----------|
| Kusuki et al. (13) | 72 M | NSCLC | Colon cancer | Pembrolizumab | 16 | DKA | 2.71 | 0.39 ng/ml | 8.1 | NR | DRB1*01:01, DOB1*03:03 | None | Yes | CR |
| Singh et al. (8) | 70 M | NSCLC | Lung cancer | Pembrolizumab + Ipilimumab | 14 | DKA | 4.41 | < 0.1 ng/ml | 6.5 | None | None | None | None | None | NR |
| Wan et al. (10) | 56 M | RCC | Chronic viral hepatitis | Nivolumab | 19.9 | Hyperglycemia | 2.4 | 0.1 mg/dl | 8.6 | None | None | None | None | None | NR |
| Falcao et al. (7) | 57 F | RCC | None | Pembrolizumab | 24 | DKA | 2.22 | 1.12 ng/ml | 7.8 | None | None | None | None | None | NR |
| Kotwal et al. (16) | 52 M | Melanoma | Type 2 DM | Pembrolizumab | 12 | DKA | 2.37 | NR | 11.2 | NR | None | None | None | None | NR |
| Mengbar et al. (18) | 55 M | Urothelial cancer | None | Nivolumab | 8 | DKA | 0.36 mg/kg q2w | Undetectable | 8.2 | None | None | None | None | None | NR |
| Sakaguchi et al. (20) | 68 F | Melanoma | Graves disease | Nivolumab | 81 | DKA | 2.23 | 0.3 mg/L | 7.8 | None | None | None | None | None | NR |
| Marchand et al. (22) | 55 M | Pleomorphic carcinoma | None | Nivolumab | 11 | DKA | 24.9 | NR | 11.6 | NR | None | None | None | None | NR |
| Li et al. (23) | 70 M | RCC | Type 2 DM | Nivolumab | 9 cycles | DKA | 2.71 | 0.12 mg/dl | 8.6 | None | None | None | None | None | NR |
| Li et al. (29) | 68 F | RCC | None | Pembrolizumab | 14 | DKA | 24.9 | 0.1 mg/dl | 8.6 | None | None | None | None | None | NR |
| Capalbo et al. (31) | 74 F | Lung cancer | Arterial hypertension | Pembrolizumab | 16 | DKA | 5.5 | 0.2 mg/dl | 8.7 | None | None | None | None | None | NR |

(Continued)


| Authors               | Patient | Cancer type | Relevant History | Agent | Time to onset (weeks) | Clinical Presenting Features | Glucose (mmol/L) | C-peptide | HbA1c (%) | Autoantibodies | HLA | Treatment | Discontinued ICI | Other irAEs | Outcome |
|-----------------------|---------|-------------|-----------------|-------|----------------------|-----------------------------|------------------|-----------|-----------|---------------|-----|-----------|------------------|------------|---------|
| Kumagai et al. (31)   | 73 M    | NSCLC       | None            | Nivolumab | 25                   | Hyperglycemia >1111.1   0.49 ng/ml   | 13.4            | None      | None      | None          |     |            |                    |            |         |
| Chang et al. (32)     | 42 M    | Melanoma    | None            | Nivolumab + Ipilimumab, Nivolumab | 12 | DKA   40.4 N R | 8.5 | None      | None      | None          |     |            |                    |            |         |
| Hickmott et al. (33)  | 57 F    | Urothelial cancer | None | Nivolumab | 15 | DKA 24 0.65 ng/ml | 7.5 | None      | None      | None          |     |            |                    |            |         |
| Minakata et al. (34)  | 72 M    | Hodgkin lymphoma | None | Nivolumab | 12 | F1DM 20.8 Urinary C-peptide 5.0 µg/dl | 7.3 | None      | None      | None          |     |            |                    |            |         |
| Chae et al. (35)      | 76 M    | NSCLC       | None            | Pembrolizumab | 3 | Asymptomatic 34.2 0.81 ng/ml 7.4 | GAD/IA-2 37.8 | AAD1,02 | None      | None          |     |            |                    |            |         |
| Godwin et al. (36)    | 34 F    | NSCLC       | None            | Pembrolizumab | 4 | DKA 739 <0.1 ng/ml 7.1 | GAD/IA-2/IAA A30,01,02 (A30) DQ1,04,07,07,07 (DQ1) | 2 mg/kg q2w | No |            |                |            |         |
| Changizzadeh et al. (37) | 42 M | Melanoma | None | Nivolumab + Ipilimumab, Nivolumab | 12 | DKA >1111.1 0.49 ng/ml 11.1 | 0.49 ng/ml 11.1 | 0.49 ng/ml 11.1 | 0.49 | None      | None          |     |            |                    |            |         |
| Changizzadeh et al. (38) | 42 M | Melanoma | None | Pembrolizumab | 3 | Asymptomatic 34.2 0.81 ng/ml 7.4 | GAD/IA-2 37.8 | AAD1,02 | None      | None          |     |            |                    |            |         |
| Changizzadeh et al. (39) | 42 M | Melanoma | None | Pembrolizumab | 3 | Asymptomatic 34.2 0.81 ng/ml 7.4 | GAD/IA-2 37.8 | AAD1,02 | None      | None          |     |            |                    |            |         |
| Changizzadeh et al. (40) | 42 M | Melanoma | None | Pembrolizumab | 3 | Asymptomatic 34.2 0.81 ng/ml 7.4 | GAD/IA-2 37.8 | AAD1,02 | None      | None          |     |            |                    |            |         |
| Changizzadeh et al. (41) | 42 M | Melanoma | None | Pembrolizumab | 3 | Asymptomatic 34.2 0.81 ng/ml 7.4 | GAD/IA-2 37.8 | AAD1,02 | None      | None          |     |            |                    |            |         |
| Changizzadeh et al. (42) | 42 M | Melanoma | None | Pembrolizumab | 3 | Asymptomatic 34.2 0.81 ng/ml 7.4 | GAD/IA-2 37.8 | AAD1,02 | None      | None          |     |            |                    |            |         |
| Changizzadeh et al. (43) | 42 M | Melanoma | None | Pembrolizumab | 3 | Asymptomatic 34.2 0.81 ng/ml 7.4 | GAD/IA-2 37.8 | AAD1,02 | None      | None          |     |            |                    |            |         |
| Changizzadeh et al. (44) | 42 M | Melanoma | None | Pembrolizumab | 3 | Asymptomatic 34.2 0.81 ng/ml 7.4 | GAD/IA-2 37.8 | AAD1,02 | None      | None          |     |            |                    |            |         |
| Changizzadeh et al. (45) | 42 M | Melanoma | None | Pembrolizumab | 3 | Asymptomatic 34.2 0.81 ng/ml 7.4 | GAD/IA-2 37.8 | AAD1,02 | None      | None          |     |            |                    |            |         |
| Changizzadeh et al. (46) | 42 M | Melanoma | None | Pembrolizumab | 3 | Asymptomatic 34.2 0.81 ng/ml 7.4 | GAD/IA-2 37.8 | AAD1,02 | None      | None          |     |            |                    |            |         |
| Changizzadeh et al. (47) | 42 M | Melanoma | None | Pembrolizumab | 3 | Asymptomatic 34.2 0.81 ng/ml 7.4 | GAD/IA-2 37.8 | AAD1,02 | None      | None          |     |            |                    |            |         |
| Changizzadeh et al. (48) | 42 M | Melanoma | None | Pembrolizumab | 3 | Asymptomatic 34.2 0.81 ng/ml 7.4 | GAD/IA-2 37.8 | AAD1,02 | None      | None          |     |            |                    |            |         |

**Note:** SCJ, Sarcomatoid squamous cell carcinoma of the Jaw; NSCLC, Non-small cell lung cancer; SCLC, Small-cell lung cancer; RCC, Renal cell carcinoma; MCC, Merkel cell carcinoma; HNSCC, Head and neck squamous cell carcinoma; HCC, Hepatocellular carcinoma; Type 2 DM, Type 2 diabetes mellitus; NR, Not reported; DKA, Diabetic ketoacidosis; GAD, Glutamic acid decarboxylase; IA-2, Islet-associated antigen-2; AAA, Insulin autoantibodies; ICA, Islet cell antibody; ZnT8, Zinc transporter B; F1DM, Fulminant type 1 diabetes; q2w, every two weeks; q3w, every three weeks.
| Type of pancreatic injury | Characteristics | Possible mechanisms | Treatment | References |
|---------------------------|-----------------|--------------------|-----------|------------|
| Acute autoimmune insulin-dependent DM | Hyperglycemia; FIDM; DKA; Undetectable C-peptide; Autoantibodies | 1. β-cells are destroyed by CD8+ T cells, but α-cells are not affected. 2. The period of onset hyperglycemia may link to the antibodies. | ♦️ New-onset hyperglycemia < 200 mg/dl and a history of T2D with low suspicion for DKA should continue ICIs, monitor serial blood glucose and modify diet and lifestyle; and consider endocrine consultation if patients are symptomatic or glucose levels are persistently uncontrolled. | (6, 37, 50–52) |
| Type 2 diabetes-like phenotype | Hyperglycemia; Pre-existing T2DM; Higher BMI; Older age; Hypertension; Detectable C-peptide; Higher HbA1c; CRP; Few with DKA | 1. β-cells are destroyed by CD8+ T cells, but α-cells are not affected. 2. T2D-like phenotype can be an insidious side effect on glycemia due to an abnormal chronic subclinical inflammatory state induced by long-term ICIs therapy. | ♦️ New-onset fasting glucose > 200 mg/dl, random blood glucose > 250 mg/dl, history of T2D with fasting/random glucose > 250 mg/dl, and workup negative for DKA should be given similar treatments and management. | (5, 6, 16, 25, 53, 54) |
| Diabetes induced by autoimmune pancreatitis | Hyperglycemia; Higher HbA1c; Pancreatitis; Pancreatic atrophy | 1. CD8+ T cells infiltrate in and around the pancreatic islets rather than CD4+ T cells. 2. It cause damage to pancreatic cells, including islet β-cells and acinar, thereby destroying exocrine and endocrine pancreatic tissues and resulting in pancreaticitis-related diabetes and pancreatic atrophy. | ♦️ DKA should hold ICIs, require inpatient care and endocrine consultation. DKA should be managed with institutional guidelines: IV fluids +/- potassium supplementation, IV insulin, and hourly monitoring of laboratory indicators (glucose, serum ketones, blood pH, and anion gap) to correct the anion gap and electrolyte disorder. | (22, 24, 55) |
| Diabetes following autoimmune lipoatrophy | Hyperglycemia; AGL; Central obesity; Higher HbA1c | 1. The histological analysis revealed CD3+ T cells infiltration and extensive fibroelastosis replacement. 2. The worsening of glycemic control is primarily related to the increased IR and concomitant with the progression of autoimmune lipoatrophy. | ♦️ Pancreatic enzyme monitoring is not recommended as a routine procedure unless pancreatitis is suspected. ♦️ ICIs can be continued. | (15, 55, 56) |
| Exocrine Asymptomatic pancreatic enzyme elevation | A mild increase in amylase and lipase levels | 1. The relationship between asymptomatically elevated amylase/lipase levels and pancreatitis is still vague. 2. This increase is likely related to T-cell-mediated inflammation present in other organs, a metastatic disease, or renal failure, but it is not linked to pancreatic inflammation. | ♦️ Once ICIs-P is confirmed with the criteria, hospital admission should be recommended. ♦️ For grade 2, ICIs should be discontinued, and 0.5–1 mg/kg/day prednisone/methylprednisolone should be given instead until symptoms improve to grade ≥ 1. Then, the dose should be tapered for 4–6 weeks, and IV hydration should be administered. ♦️ For grades 3–4, ICIs should be permanently discontinued, and treatment with a double daily dose of glucocorticosteroids than moderate grade and IV fluids should be provided. | (57–61, 62–65) |
| ICIs-P | Requires meeting ≥2 criteria: 1. significant symptoms of pancreatitis; 2. radiographic evidence; 3. changes in laboratory data. | 1. CD3+ T lymphocytes densely infiltrate the pancreatic islets in “healthy” areas, and the ratio of CD8+/CD4+ T lymphocytes in “unhealthy” areas increases. It suggests that immune T cell infiltrates may be the prevalent cytotoxic components of ICIs treatment. 2. Dense CD8+, TIA1+, and granzyme B+ lymphoid infiltrate within a biopsied lesion. | ♦️ For grade 2, ICIs should be discontinued, and 0.5–1 mg/kg/day prednisone/methylprednisolone should be given instead until symptoms improve to grade ≤ 1. Then, the dose should be tapered for 4–6 weeks, and IV hydration should be administered. | (57, 62–65) |
| ICIs-PEI | Abdominal pain; Good appetite; Irregular stools; Steatorrhea; Fecal pancreatic elastase-1 test | CD8+ T cells infiltrate inside and around the pancreas to damage ductal and acinar cells (exocrine pancreas) and even pancreatic atrophy. The alteration decreases the secretion of pancreatic enzymes and affects the release of bicarbonate, water, and enzymes into the duodenum. | ♦️ For grades 3–4, ICIs should be permanently discontinued, and treatment with a double daily dose of glucocorticosteroids than moderate grade and IV fluids should be provided. PERT, Pancreatic enzyme replacement therapy. | (66, 67) |

ICIs, Immune checkpoint inhibitors; DM, Diabetes mellitus; DKA, Diabetic ketoacidosis; FIDM, Fulminant type 1 diabetes; CRP, C-reactive protein; AGL, Acquired generalized lipoatrophy; ICIs-P, ICIs associated with pancreatitis; ICIs-PEI, ICIs associated with pancreatic exocrine insufficiency; PERT, Pancreatic enzyme replacement therapy.
ICIs. This outcome implies that ICIs can decompensate glucose control. Most of these patients have a higher BMI, relatively older age, hypertension, detectable C-peptide, and higher HbA1c compared with patients with acute autoimmune insulin-dependent DM. Interestingly, a few cases eventually develop diabetic ketoacidosis since most patients with pre-existing T2DM self-administer hypoglycemic drugs, therefore, they self-monitor their blood glucose levels (5, 6, 16, 25, 53). Kotwal et al. reported 9 cases with unexplained worsening of glycemic control for pre-existing T2D after they commenced ICIs therapy. Their HbA1c increased by 10% in 6 months, and most patients needed another antihyperglycemic agent or insulin. Consequently, they had underwent outpatient visits and inpatient admission due to poor blood glucose control (16). Interestingly, laboratory findings showed increased C-reactive protein (CRP) levels in a subset of patients at the time of presentation, implying that immunotherapy induced an inflammatory profile (6). CRP levels are negatively associated with insulin sensitivity, therefore, chronic subclinical inflammation causes insulin resistance (IR) in which is implicated in pathogenesis of T2D (54). Therefore, T2D-like phenotype is an insidious side effect on glycemia attributed to an abnormal inflammatory state induced by long-term ICIs therapy.

Previous studies report several cases of new-onset DM developed autoimmune pancreatitis after cancer immunotherapy. Dehghani et al. reported a 63-year-old Caucasian man without genetic history of diabetes or autoimmune disease, administered with nivolumab for treatment of advanced melanoma. The patient developed focal pancreatitis 15 months after initiation of nivolumab therapy. CT scans showed peripancreatic fatty infiltration around the pancreatic tail. However, he was asymptomatic with normal serum lipase, IgG4, and fasting blood glucose level (6.2 mmol/liter). After 3 more months, his blood lipase was threefold the normal level, fecal elastase-1 decreased to 58 mg/g (normal values > 200 mg/g), serum glucose increased to 11 mmol/liter, HbA1c was 9.3%, and diabetes-associated autoantibodies were negative. Despite these findings, the patent showed no clinical signs. MRI results showed a 50% decrease from the initial pancreatic volume (24). In addition, Marchand et al. reported a dynamic change in pancreatic volume similar to that reported in previous cases. Initially, pancreatic volume increased by 15% after 4 courses of nivolumab, pancreatic atrophy subsequently developed, and the initial volume significantly decreased (63%) 3 months later at the onset of DM (22). Activation of resident immune cells (CD8+ T cell clones) is promoted by immunotherapy infiltrates in and around pancreatic islets rather than CD4+ T cells. This phenomenon explains development of pancreatitis and increase in pancreatic volume before the onset of diabetes. Increased CD8+ T cells might damage pancreatic cells, including islet β-cells and acinar, thereby destroying exocrine and endocrine pancreatic tissues ultimately resulting in pancreatitis-related diabetes and pancreatic atrophy (22, 55).

Autoimmune lipoatrophy also known as acquired generalized lipoatrophy (AGL) causes significant reduction in whole-body fat. Absence of adipocytes promotes ectopic lipid droplet accumulation in other body parts. Abnormal adipose storage is frequently associated with insulin resistance and DM. Falcao et al. reported a case of immune-related AGL. A 57-year-old woman with well-managed T2D (HbA1c 6.7%) received nivolumab for clear cell renal carcinoma. On the 2nd month of treatment, she presented with loss of subcutaneous fat tissues in the facial neck, shoulders, arms, and buttocks. In addition, the patients showed an abnormal pattern of adipose tissues in her abdomen and calves, implying she had central obesity. Further, she was diagnosed with deterioration of glycemic control and HbA1c (10.5%). Her low-density lipoprotein-cholesterol and triglyceride levels increased, whereas the high-density lipoprotein-cholesterol levels decreased. Histological analysis of the subcutaneous biopsy of the medial surface of the arm showed chronic lobular panniculitis with CD3+ lymphocytic infiltration and extensive fibroelastosis replacement. Poor glycemic control was primarily attributed to increased IR and progression of autoimmune lipoatrophy (15, 56). Other studies report new-onset DM secondary to AGL in patients without personal or family history during immunotherapy (15, 55).

Several studies have reported ICIs-associated diabetes providing information for identifying individuals at risk. Routine measurement of HbA1c and blood glucose during treatment should be carried out in clinical work. Furthermore, testing biomarkers including cytokines, novel autoantibodies, and high-risk genetics before ICIs treatment could provide potential predictive valuable information for ICIs-DM (72). Currently, few biomarkers associated with irAE have been reported. Therefore, further studies are essential to identify more potential biomarkers, including proteins, lipids, mRNA, miRNA, and exosomes. National Comprehensive Cancer Network (NCCN) guidelines for management of ICIs-related toxicities (version 1.2020) are the most current comprehensive guidelines adopted in clinical practice, specifically, when symptoms including polyuria, polydipsia, nausea, and vomiting associated with changes in blood glucose levels occur after immunotherapy. Based on these guidelines, patients with (1) new-onset hyperglycemia < 200 mg/dl and (2) history of T2D with low suspicion for DKA should be continuously treated with ICIs. However, their serial blood glucose after administration of each dose should be monitored. The diet and lifestyle of these patients should be modified, and endocrine consultation should be considered if patients are symptomatic or if their glucose levels are persistently uncontrolled. Patients with (3) new-onset fasting glucose > 200 mg/dl, (4) random blood glucose > 250 mg/dl, (5) history of T2D with fasting/random glucose > 250 mg/dl, and (6) workup negative for DKA should be given similar treatments and management. Patients presenting with (7) DKA should have immunotherapy discontinued, however immunotherapy can be restarted once DKA is resolved. Patients requiring inpatient care and endocrine consultation should be administered with insulin as prescribed by a medical oncologist and an endocrinologist. DKA should be managed based on institutional guidelines, i.e., intravenous (IV) fluids +/- potassium supplementation, IV insulin therapy, and hourly monitoring of laboratory indicators (glucose, serum ketones, blood pH, and anion gap) to correct anion gap and electrolyte disorder (73).
ICIS ASSOCIATED WITH ASYMPTOMATIC PANCREATIC ENZYME ELEVATION

ICIs associated with pancreatic injury affect endocrine and exocrine functions of the pancreas (DM), and the effects may be asymptomatic or symptomatic. Diagnosis of acute pancreatitis depends on identification of at least 2 of the following features: (1) severe epigastric pain often radiating to the back; (2) elevated serum lipase/amylase levels (at least three times the upper normal limit); and (3) characteristic findings of acute pancreatitis on abdominal imaging. Imaging (CT, MRI, and PET/CT) of ICIs-associated pancreatitis shows any of the following: (1) new focal or diffuse pancreatic enlargement; (2) decreased enhancement and surrounding fat stranding without a focal lesion suspicious for metastasis; and (3) diffuse increased FDG uptake (62). Elevations in amylase/lipase are graded using the Common Terminology Criteria for Adverse Events (CTCAE 5.0) where by Grade 1 represents asymptomatic enzyme elevation or nonimmune-mediated causes of asymptomatically elevated pancreatic enzyme levels should be explored. For instance, this increase may be related to T cell-mediated inflammation present in other organs, a metastatic disease, or renal failure, and may not be related to pancreatic inflammation (61, 63). Pancreatic enzyme monitoring in asymptomatic patients is not recommended as a routine procedure unless for cases where pancreatitis is suspected. NCCN guidelines state that treatment with ICIs can be continued for patients with slight increase in amylase and lipase levels (at least 3 times the upper normal limit) if pancreatitis is excluded (73).

ICIS ASSOCIATED WITH PANCREATITIS

ICIs associated with pancreatitis (ICIs-P) are extremely rare irAEs, making diagnosis a clinical challenge. As previously described, diagnosis of ICIs-P requires at least 2 criteria among the significant symptoms of pancreatitis, including radiographic evidence, and changes in laboratory data. George et al. evaluated 33 trials in a meta-analysis and reported that incidence of pancreatitis in the CTLA-4 group was higher compared with that of the PD-1 group (4% vs. 1%). Moreover, incidence of grade 2 pancreatitis in CTLA-4-PD-1 combination group was 10.6%, significantly higher compared with that of mono-immunotherapy (58).

Kohlmann et al. reported a case of ICIs-P within the first 4 months of immunotherapy. The patient manifested a belted-shaped epigastric pain 106 days after immunotherapy initiation. Laboratory findings showed that serum lipase and serum amylase levels increased to 394.2 and 318 U/l, respectively. Pancreatic computed tomography showed edematous swelling within the tail of the pancreas. Therefore, ICIs-P was diagnosed based on the aforementioned criteria, immunotherapy was immediately halted, and the patient was administered withmethylprednisolone (1.3 mg/kg, total 128 mg). The symptoms gradually improved, and glucocorticosteroid dose was reduced. When the dosage was reduced to 8 mg, clinical symptoms relapsed, and serum lipase levels increased again (>600 U/l). Therefore, the patient received long-term treatment (6.5 months) of high-dose systemic methylprednisolone with significant slow tapering until clinical symptoms were cleared and normal levels of serum pancreatic enzymes achieved. Therefore, management of ICIs-P requires a high initial dose and slow tapering of glucocorticosteroid dose (64).

Pathophysiological features underlying ICIs-P remain elusive. Similar to other irAEs, mechanisms can be through inflammatory responses in the pancreas after ICIs administration. A few studies report on functional T cell activation induced by ICIs treatment. Immuno-histochemical analysis shows that CD3+ T lymphocytes densely infiltrate pancreatic islets in “healthy” (nontumoral) areas, thereby increasing the ratio of CD8+/CD4+ T lymphocytes in peritumoral areas. These findings imply that immune T cell infiltrates might be the prevalent cytotoxic components of ICIs treatment (65). Furthermore, dense CD8+, TLA1+, and granzyne B+ lymphoid infiltration are present within a biopsied lesion as shown by immunohistochemical analysis (66).

NCCN guidelines for management of ICIs-P state that when potential symptoms of ICIs-P appear, laboratory tests and abdominal imaging should be performed. Once the diagnosis of ICIs-P is confirmed, hospital admission is recommended, however, other management approaches depend on grading.
For grade 2 pancreatitis (moderate), treatment with ICIs should be discontinued, and 0.5–1 mg/kg/day prednisone/methylprednisolone should be administered until symptoms improve to grade ≤1. After achieving grade ≤1, the dose should be tapered for 4–6 weeks, and IV hydration should be administered. For grade 3–4 of pancreatitis (severe and life-threatening), immunotherapy should be permanently discontinued, and treatment with a double daily dose of glucocorticosteroids rather than moderate grade and IV fluids should be started (73).

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