Immunotherapy Toxicity

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KEYWORDS

- Immunotherapy • Toxicity • Immune checkpoint inhibitors
- Immune-related adverse events

KEY POINTS

- Advances in immunotherapy have improved treatment for patients with many types of malignancy.
- Immune checkpoint inhibitors are associated with unique side effects that can involve almost any organ system.
- Immune-related adverse events can limit further treatment options and can cause significant morbidity and mortality.

INTRODUCTION

Recent scientific advancements have led to substantial progress in the understanding of the immune system's ability to control cancer. With these advancements, novel therapies have been developed that manipulate the immune response against cancer. These approaches include innovative vaccines, modified immune cells, antibodies, and drugs that target immune cell signaling. In particular, immune checkpoint inhibitors (ICIs) have demonstrated activity in many malignancies and are currently approved for many cancer indications.

ICIs target T-cell interactions with antigen-presenting cells (APCs) through cytotoxic T-lymphocyte associated protein-4 (CTLA-4) or through T-cell interactions with normal tissue cells, APCs, and tumor cells through programmed death-1 (PD-1) or programmed death ligand-1 (PD-L1). Ipilimumab, which targets CTLA-4, was the first ICI that was approved by the Food and Drug Administration based on improved overall survival in metastatic melanoma patients in phase 3 trials.[1] Nivolumab and pembrolizumab, which target PD-1, have demonstrated benefit in melanoma, non–small cell

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lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, advanced gastric cancer, microsatellite instable or mismatch repair–deficient solid tumors, and hepatocellular carcinoma.[2–5] Atezolizumab, avelumab, and durvalumab, which target PD-L1, have been approved for use in bladder cancer, gastric cancer, Merkel cell cancer, and platinum-resistant urothelial carcinoma.[6] In addition, combination CTLA-4 blockade and PD-1 blockade are approved in the treatment of metastatic melanoma and renal cell carcinoma.[7]

The toxicity profile of ICI differs greatly from those observed with traditional chemotherapy or targeted therapy. Immune-related adverse events can require prolonged treatment with immunosuppression, which carries its own health risks and associated morbidity. Some of the immune reactions can lead to permanent organ damage or even death. These side effects frequently lead to treatment discontinuation and may limit subsequent treatment options.

THE PATHOPHYSIOLOGY OF IMMUNE CHECKPOINT INHIBITORS– RELATED TOXICITY

To function effectively, the immune system must be able to recognize self from nonself; there are several mechanisms that protect the host from developing autoimmune conditions. T cells that recognize the body's own proteins as foreign are deleted through negative selection in the thymus, a process termed central tolerance.[8] In the peripheral blood, spleen, and lymphatic organs T cells are exposed to professional APCs that may display self or foreign antigens. Peripheral tolerance mechanisms prevent T cells that recognize self-proteins from inflicting damage to self-tissues.[8,9]

ICIs act upon CTLA-4, PD-1, or other inhibitory pathways affecting peripheral immune tolerance. Notably, autoimmune toxicities can be induced by immunotherapies other than ICIs and can be triggered through various mechanisms. Antibody therapy may lead to innate immune damage due to complement activation or macrophage activity through antibody-dependent cell-mediated cytotoxicity. In patients treated with adoptive cell therapy, T cells may recognize antigens that are expressed on normal and tumor tissues. Immunotherapy may lead to the dysregulation of immune hemostasis by increasing immune cells not associated with the antitumor response that then attacks normal tissue. Cancer vaccines and immune adjuvants can lead to epitope spreading, thereby inducing a reaction against normal tissue.[10]

It has been postulated that immune-related adverse events are associated with antitumor response. Early studies suggested an association, but further analysis has been mixed to date.[11] One of the few side effects whereby numerous studies support an association with response is vitiligo in the case of melanoma.[12–14]

Immune-related toxicities often develop well after treatment initiation, following patterns that vary greatly from other cancer therapies.[15] The type, incidence, and severity of immune-related adverse events differ between CTLA-4 and PD-1/PD-L1 inhibitors.[15,16] Although there is minimal, if any, relation between dose and toxicity with PD-1/PD-L1 inhibition, the incidence and severity of immune-related adverse events have been shown to be dose related for the anti- CTLA-4 antibody ipilimumab.[17]

Immune-related toxicities can affect several organs. In the following, the epidemiology, diagnosis, and management of immune-related adverse event are reviewed by organ system.

SKIN TOXICITIES

Skin toxicity is the most common immune-related adverse event observed with ICI. Forty percent of patients treated with ipilimumab experience cutaneous adverse

effects. These toxicities are dose dependent with dermatologic toxicity occurring more frequently at the higher dose of 10 mg/kg compared with the lower dose of 3 mg/kg.[18] Cutaneous adverse events usually occur within 3 to 6 weeks after starting ipilimumab, but can arise at any time during the course of treatment or after treatment cessation.[19] The most common dermatologic toxicity is a morbilliform rash, which typically spares the head, palms, and soles.[19] Pruritus without a rash can also occur. Other less common side effects include lichenoid eruptions, prurigo nodularis, pyoderma gangrenosum, sweet syndrome, bullous dermatoses, and cutaneous sarcoidosis.[19]

Cutaneous adverse events are similar with PD-1 and PD-L1 inhibitors but typically arise later in the course of treatment compared with CTLA-4 inhibitors, ranging from 2 to 10 months.[19] A systematic review showed the incidence of pruritus ranged from 2.3% to 31.7% with nivolumab and 10% to 25.8% with pembrolizumab.[20] The rash from PD-1 and PD-L1 inhibitors is typically maculopapular, similar to that seen with CTLA-4 inhibition. Histologic examination of skin biopsies typically reveals a dermal hypersensitivity reaction with perivascular lymphocytic infiltrates and eosinophils.[18]

Management of mild, inflammatory rashes that do not affect quality of life involves topical corticosteroids with continuation of treatment. For grade 2 rashes, which affect quality of life, a treatment hold should be considered and oral corticosteroids can be used. Rashes are defined as grade 3 if they fail to respond to treatment. Treatment for grade 3 involves higher-dose corticosteroids. Grade 4 disease is defined as severe rashes that are intolerable and not improved with prior interventions. Treatment of grade 4 rashes includes inpatient admission with intravenous (IV) corticosteroids.[21]

Vitiligo, which is characterized by depigmented macules and patches, can occur with the use of ICIs to treat melanoma. In clinical trials of PD-1 and PD-L1 inhibitors in the treatment of melanoma, the incidence of vitiligo was 7.5% with nivolumab and 8.3% with pembrolizumab.[20] Vitiligo typically occurs several months after the initiation of treatment, which is later than other cutaneous side effects often observed.[21] It typically persists after discontinuation or completion of treatment and can become coalescent over time.[12] In a retrospective study of melanoma patients receiving nivolumab, vitiligo was observed in 9.6% of patients with metastatic disease and 24.2% of patients with resected disease. Development of vitiligo in patients with resected and metastatic melanoma is associated with a statistically significant improvement in overall survival (hazard ratio [HR], 0.22; 95% confidence interval [CI] 0.025–0.806; $P = .028$).[12] A meta-analysis of vitiligo in melanoma patients receiving various types of immunotherapy, including ICIs, vaccines, adoptive transfer, and immune stimulation, revealed a 4-fold improvement in overall survival (HR, 0.25; 95% CI, 0.10–0.61; $P<.003$) compared with patients who did not develop vitiligo.[14]

GASTROINTESTINAL TOXICITIES

Gastrointestinal toxicities are the second most common immune-related adverse event after dermatologic side effects. Patients can develop inflammation of any part of the gastrointestinal tract, with involvement of the colon (colitis) being the most common.

Colitis

Diarrhea is a frequent side effect of ICIs and has been reported in up to 44% of patients after treatment with the combination of CTLA-4 and PD-1 inhibition, 35% after CTLA-4 inhibition alone, and 20% after PD-1 inhibition alone.[22] Timely diagnosis of colitis in a patient who develops diarrhea after ICI is critical, but can be challenging. Typically, there are signs of colitis on computed tomographic (CT) scan, or endoscopy

shows characteristic inflammation with evidence of colitis on pathology.[23] In one study of ICI-induced diarrhea/colitis, 50% of patients had concurrent abdominal pain and 30% had hematochezia.[22] Although colitis is often mild, it can be severe and lead to intestinal perforation or death.[24] The incidence of colitis and timing of onset vary based on the type of ICI used. Colitis occurs more often with the use of ipilimumab and most frequently with the combination of ipilimumab/nivolumab treatment. In a recent meta-analysis of more than 8000 patients on prospective clinical trials of ICIs, the incidence of all-grade colitis was 13.6% with combination ipilimumab/nivolumab, 9.1% with ipilimumab, 1.4% with nivolumab, and 1.0% with atezolizumab.[25] Diarrhea develops at a median of 30 days with the use of combination ipilimumab/nivolumab therapy or ipilimumab alone and can manifest later with the use of PD-1 antibodies up to a median of 84 days after the initiation of treatment.[22] The incidence of grade 3 to 4 gastrointestinal side effects is dose related and reported to be 0%, 3%, and 15% in patients receiving 0.3, 3, and 10 mg/kg of ipilimumab, respectively.[24]

Endoscopic evaluation of patients with colitis often shows erythema, edema, loss of vascular patterns, erosions, or ulceration similar to that seen in inflammatory bowel disease.[26] The inflammation is usually continuous, but can be patchy.[24,26] Disease can occur in any part of the gastrointestinal tract, including the esophagus, stomach, small bowel, and colon.[26] If endoscopy shows ulceration, pancolitis, or a higher Mayo endoscopic score, which is used to monitor disease activity in ulcerative colitis, there is an increased risk of steroid-refractory colitis, which then requires second-line immunosuppressive treatments, such as infliximab.[22,24] For evaluation, a rectosigmoidoscopy is usually sufficient because disease most often affects the descending colon. However, if the left side does not show severe disease, a full colonoscopy is recommended because the ascending colon can be affected.

Biopsy often shows acute colitis, which is characterized by focal active colitis with patchy crypt abscess formation or diffuse mucosal inflammation[26] (**Fig. 1**). In one study of ipilimumab-induced colitis, biopsies showed infiltration of neutrophils in 46%, lymphocytes in 15%, and mixed neutrophil and lymphocyte in 38%. Granulomas are rarely seen.[26,27]

Although colonoscopy with biopsy is the gold standard for diagnosing colitis, CT scan has been shown to be a fast, noninvasive, diagnostic tool (**Fig. 2**). In a retrospective study of patients who developed diarrhea while receiving ipilimumab, CT scan had a positive predictive value of 96% when compared with biopsy-proven disease.[28] This study suggests that CT scan can be used to make a diagnosis of colitis but cannot rule out disease, and further workup should be obtained in the case of a negative CT scan.

In cases of suspected colitis, infection and hyperthyroidism should be ruled out and treatment should be initiated promptly. Grade 1 colitis, defined as an increase of fewer than 4 stools per day, can be monitored closely with continuation of treatment. For grade 2 through 4 disease, treatment should be held, corticosteroids initiated, and endoscopy pursued. If symptoms continue despite corticosteroids or symptoms improve and then recur, IV corticosteroids and infliximab therapy should be considered.[21]

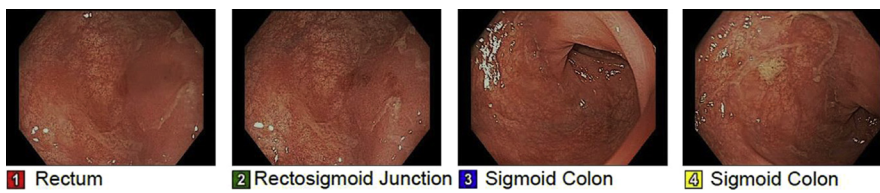

Fig. 1. Colonoscopy findings in a patient with colitis demonstrating erythema and erosions.

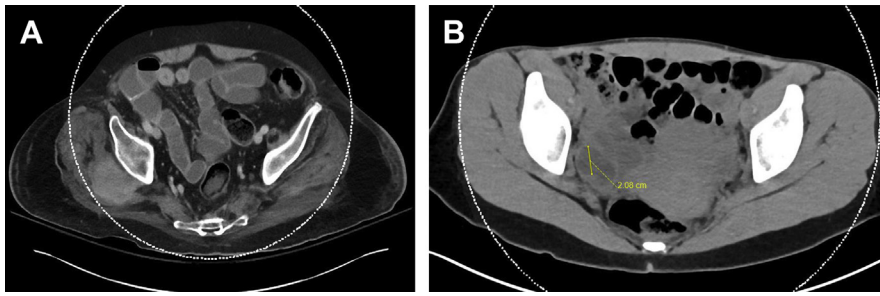

Fig. 2. (*A, B*) CT imaging from 2 patients with colitis demonstrating fluid-filled loops and stranding adjacent to bowel.

There have been efforts at trying to prevent colitis. Budesonide, which is a nonabsorbed oral steroid, has been evaluated in a prophylactic manner. A randomized, double-blind, placebo-controlled trial of prophylactic budesonide in melanoma patients receiving ipilimumab did not show any benefit to prophylaxis because there were similar rates of diarrhea and colitis in both arms.[29]

Hepatitis

Hepatic toxicity manifests as hepatitis with hepatocellular injury and elevation in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and (sometimes) bilirubin.[24] Hepatitis is often asymptomatic; however, patients can develop nausea, vomiting, or abdominal pain.[30] Hepatic toxicity can occur at any time but most commonly develops about 6 to 14 weeks after initiation of treatment.

Blood tests for autoimmune liver disease are usually negative.[24] The most common finding on liver biopsy is panlobular hepatitis followed by acinar zone 3 hepatitis.[30] An inflammatory infiltrate of lymphocytes and histiocytes in a mainly sinusoidal distribution is seen. Lymphocytic infiltrates are mainly composed of $CD8^+$ T cells with some $CD4^+$ T cells and scattered $CD20^+$ B cells.[30]

Hepatitis usually resolves with the use of corticosteroids alone, but occasionally requires additional immunosuppressive therapy.[24] Grade 1 disease with mild increase in serum aminotransferases and bilirubin can be monitored closely without intervention. For grade 2 disease, defined by an increase in AST or ALT 3 to 5 times the upper limit of normal (ULN) and/or an increase in total bilirubin of 1.5 to 3 times the ULN, treatment should be held and corticosteroids initiated if elevation persists. For grade 3 and 4 disease, treatment should be permanently discontinued and corticosteroids initiated promptly. If there is no improvement after 3 days of corticosteroids, use of mycophenolate mofetil or azathioprine should be considered.[21,24]

ENDOCRINE TOXICITIES

Thyroiditis

Alteration of thyroid function is one of the most common adverse events resulting from treatment with ICIs. Severe thyroid dysfunction is rare with a reported incidence of grade 3 hypothyroidism and hyperthyroidism of 0.2%.[31] Incidence of hypothyroidism and hyperthyroidism varies based on the type of ICI used.[31] Guidelines recommend thyroid studies (thyroid stimulating hormone [TSH] and free thyroxine [FT4]) before every treatment or at least once per month.[32] Most cases of thyroid dysfunction are diagnosed based on routine laboratory tests rather than clinical symptoms.[32] The

most common clinical scenario is development of thyroiditis sometimes associated with a transient thyrotoxic phase typically followed by persistent hypothyroidism.[33]

The pathophysiology of thyroid toxicity from ICI is not completely understood. PD-L1 and PD-L2 messenger RNA is known to be expressed in normal thyroid tissue.[33] In a meta-analysis of 38 prospective clinical trials of ICIs, the overall incidence of hypothyroidism was 3.8% with CTLA-4 inhibition, 7.0% with PD-1 inhibition, 3.9% with PD-L1 inhibition, and 13.2% with combination CTLA-4 and PD-1 inhibition.[31] Patients who received treatment with PD-1 or combination therapy were more likely to experience hypothyroidism than with ipilimumab alone (odds ratio [OR] 1.89; 95% CI, 1.17–3.05; adjusted $P = .03$).

Management of hypothyroidism involves thyroid hormone supplementation. For grade 1 disease with a TSH less than 10 and no symptoms, patients can continue to be monitored closely without thyroid hormone supplementation. For any symptoms of hypothyroidism, a TSH persistently greater than 10 and a low T4, thyroid hormone supplementation should be started and treatment can be held until symptoms resolve or continued if symptoms are mild. For severe cases with symptoms of myxedema, patients should be admitted for IV therapy and close monitoring.[21]

The incidence of hyperthyroidism is lower than that of hypothyroidism. A meta-analysis reported the overall incidence of hyperthyroidism to be 1.7% with CTLA-4 inhibition, 3.2% with PD-1 inhibition, 0.6% with PD-L1 inhibition, and 8.0% with combined CTLA-4 and PD-1 inhibition. Combination therapy with CTLA-4 and PD-1 inhibitors was more likely to result in hyperthyroidism compared with treatment with ipilimumab alone (OR, 4.27; 95% CI, 2.05–8.90; $P = .001$).[31] Treatment with PD-1 inhibitors also results in a higher incidence of hyperthyroidism than PD-L1 (OR, 5.36; 95% CI, 2.04–14.08; adjusted $P = .002$). Among PD-1 inhibitors, pembrolizumab is associated with a slightly higher incidence of hyperthyroidism compared with nivolumab (3.8% [95% CI, 2.1%-6.9%] vs 2.5% [95% CI, 1.3%-4.6%], $P = .04$).[31]

For asymptomatic or mildly symptomatic hyperthyroidism, treatment can be continued with close monitoring. For grade 2 disease with moderate symptoms, treatment can be continued and patients treated supportively with beta-blockers and hydration. If hyperthyroidism persists for longer than 6 weeks, testing for Graves disease should be done with initiation of thionamide treatment if positive. For grade 3 to 4 disease, which is characterized by severe symptoms limiting daily life, treatment should be held, beta-blocker started, and corticosteroids started. The patient may also require treatment with potassium iodide or thionamide. Patients with symptoms of thyroid storm need to be hospitalized for treatment and close monitoring.[21]

Hypophysitis

Hypophysitis consists of inflammation of the pituitary gland with alteration of hormone function. Patients who develop hypophysitis can present with headache or visual symptoms due to local effects of swelling of the pituitary gland or with nonspecific symptoms, such as fatigue, nausea, weakness, or loss of appetite from pituitary hormone dysfunction. Patients typically develop central adrenal insufficiency, and this can be accompanied by hypotension, hyponatremia, hypothyroidism, diabetes insipidus, or hypogonadism.[21] Endocrine adverse events such as hypophysitis typically occur around 9 weeks after treatment initiation but can manifest much later, over 1 year after treatment starts. Diagnostic workup should include brain MRI (**Fig. 3**) and hormonal workup, including ACTH, cortisol, TSH, FT4, T3, and others. In a meta-analysis of 6472 patients with advanced solid tumor malignancies who received ICI therapy, the incidence of any grade hypophysitis was 1.3%. Of the patients who developed hypophysitis, 89% were being treated for melanoma. Of these patients,

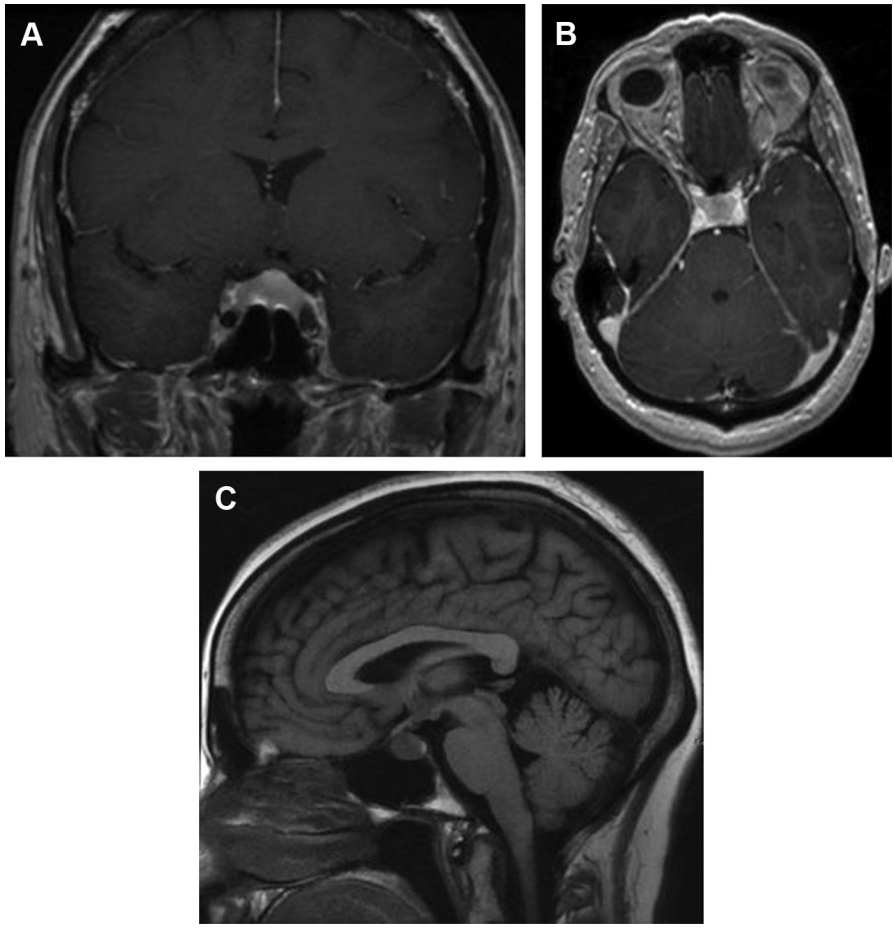

Fig. 3. (*A–C*) Brain imaging from a patient with hypophysitis demonstrating pituitary enlargement.

the incidence of hypophysitis was highest with combination CTLA-4 and PD-1 therapy at 6.4%, slightly lower with CTLA-4 treatment alone at 3.2%, and lowest with PD-1 inhibitors at 0.4% and PD-L1 inhibitors at less than 0.1%.[31]

Evaluation of the cause of hypophysitis has demonstrated CTLA-4 expression on a subset of adenohypophyseal endocrine cells. CTLA-4 expression occurs at different levels in different individuals and is thought to be responsible for the hypophysitis observed with ipilimumab.[34] Patients who develop hypophysitis typically require lifelong corticosteroid replacement. High doses of steroids during the development of hypophysitis have not been demonstrated to rescue endocrine function.

Patients need corticosteroid replacement as well as thyroid and hormonal replacement if indicated based on testing. Corticosteroids should always be given for several days before thyroid replacement to avoid adrenal crisis.[21]

Rare Endocrine Adverse Events

ICIs can rarely cause other endocrine toxicities, such as primary adrenal insufficiency and autoimmune diabetes mellitus. In a meta-analysis of 62 studies, primary adrenal

insufficiency was seen in 0.7% of patients and insulin-dependent diabetes developed in 0.2%.[31] Primary adrenal insufficiency warrants corticosteroid replacement therapy and may require fludrocortisone for mineralocorticoid replacement. Development of autoimmune diabetes should be treated with insulin as type 1 diabetes.[21]

PULMONARY TOXICITIES

Pneumonitis can occur with ICI, and its presentation can vary in severity; rarely, it can be a life-threatening adverse event. Time to onset of pneumonitis typically occurs several weeks after initiating treatment.[35]

Patients with pneumonitis can present with new respiratory symptoms, such as cough, dyspnea, or hypoxia. Imaging often shows bilateral, peripheral ground glass or consolidative opacities[35] (**Fig. 4**).

Pneumonitis is much more common in patients treated with PD-1 inhibitors compared with a CTLA-4 inhibitor. In a retrospective review of more than 4000 patients treated with a PD-1 inhibitor, the incidence of any grade pneumonitis was 2.7% and the incidence of severe grade 3 or higher disease was 0.8%,[36] while the incidence of pneumonitis after CTLA-4 inhibition was less than 1% in clinical trials.[17] More studies are needed to determine whether the rate of severe pneumonitis is higher in patients being treated for a diagnosis of lung cancer because the current studies show conflicting results.[35,36] There does appear to be a higher rate of mortality from pneumonitis in patients with lung cancer.[35]

In all cases of suspected pneumonitis, treatment should be held pending workup. For grade 1 pneumonitis, which is defined as asymptomatic disease and limited to one lobe of the lung or less than 25% of lung parenchyma, no steroids are indicated and treatment can be resumed if repeat testing in 3 to 4 weeks shows improvement or resolution. For grade 2 disease, in which 25% to 50% of lung is affected or the patient is symptomatic and limited in some activities of daily living, bronchoscopy with bronchoalveolar lavage (BAL) should be done and corticosteroids should be given. If disease improves to grade 1 or resolves, restarting treatment can be considered. For more severe disease classified as grade 3 or 4, patients should be treated with IV corticosteroids; bronchoscopy with BAL should be performed; transbronchial biopsy should be considered, and treatment should be permanently discontinued. If there

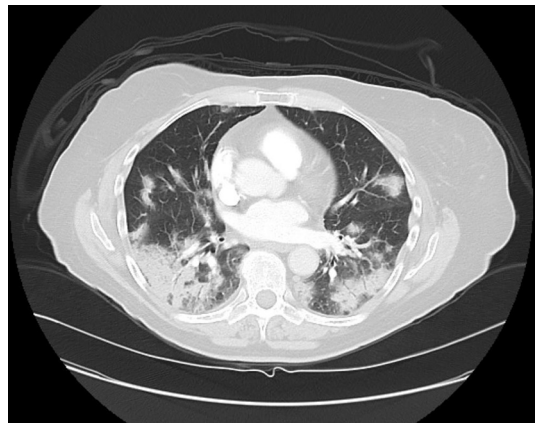

Fig. 4. Pulmonary imaging from a patient with pneumonitis demonstrating bilateral diffuse opacities.

is no clinical improvement after 48 hours, additional immunosuppressive therapy, such as infliximab, mycophenolate mofetil, IV immunoglobulin, or cyclophosphamide, should be considered.[21]

NEUROLOGIC TOXICITIES

Neurologic immune-related adverse events are uncommon but potentially serious. The most common neurologic side effects are mild, including headache or peripheral sensory neuropathy. Toxicities can vary depending on the immunotherapy agent used. In an analysis of 1500 patients with melanoma treated with ipilimumab, neurologic adverse events were seen in 0.1% of patients.[37] Treatment with ipilimumab has been rarely associated with peripheral neuropathy, Guillain-Barre syndrome, myasthenia gravis, aseptic meningitis, and chronic inflammatory demyelinating polyneuropathy.[37] Neurologic toxicity is less common with PD-1 inhibitors. Adverse events reported include peripheral neuropathy, Guillain-Barre syndrome, and myasthenia gravis. Treatment with nivolumab has also been associated with dizziness, nerve paresis, demyelination, and autoimmune neuropathy, whereas treatment with pembrolizumab has been associated with partial seizures. Immune-mediated encephalitis has also been reported and can be fatal.[37]

A review of serious neurologic immune-related adverse events in more than 3700 melanoma patients receiving nivolumab or combination of ipilimumab and nivolumab on a clinical trial from 2008 to 2016 was conducted. Serious events were defined as those considered medically significant, life threatening, requiring hospitalization, or resulting in disability or death. Of patients, 0.93% were reported to have developed a serious neurologic toxicity potentially related to their immunotherapy treatment. The most common neurologic adverse events were neuropathy (63%), encephalitis (17%), aseptic meningitis (14%), neuromuscular disorders (9%), and nonspecific events (20%) with some patients experiencing more than one event. Nonspecific events included headache, seizure, confusion, and syncope. Out of a total of 43 events, there was 1 case of fatal encephalitis. The time to onset of neurologic adverse events was a median of 45 days with a range of 1 to 170 days.[37]

Encephalitis

Patients with immune-related encephalitis can present with altered mental status characterized by confusion, aphasia, or agitation; ataxia; seizure; or fatigue. Treatment includes antiviral therapy and antibiotics to cover viral and bacterial encephalitis until an infectious cause is excluded. Management of immune-mediated encephalitis should include IV corticosteroids and treatment should be discontinued. Immunoglobulins or other immunosuppressive medications should be considered.

CARDIOVASCULAR TOXICITIES

Immune-related adverse events include cardiac toxicity in the form of myocarditis, pericarditis, or cardiomyopathy. Although cardiomyopathy is a rare side effect seen in less than 1% of patients, it can be serious or even fatal. Symptoms of cardiomyopathy are nonspecific and can include chest pain, shortness of breath, and fatigue. The pathophysiology is not clearly known. Studies have shown that human and murine hearts express PD-L1.[38] It has been demonstrated that mice lacking PD-1 develop dilated cardiomyopathy and congestive heart failure.[39] Affected mice have a high titer of circulating immunoglobulin G (IgG) autoantibodies against a protein on cardiomyocyte surface, and autopsies showed linear deposition of IgG on cardiomyocytes in PD-1–deficient mice but not in normal mice.[39]

Myocarditis is a rare but serious immune-related adverse event. In a review of more than 20,000 patients who were treated with ipilimumab, nivolumab, or the combination of both, 0.09% of patients experienced myocarditis. The average time to onset of myocarditis was 17 days, ranging from 13 to 64 days. Myocarditis was rare with any of the treatments; it occurred more frequently with the combination of ipilimumab and nivolumab compared with nivolumab alone, 0.27% versus 0.06%, respectively.[40] In 2 case reports of fatal myocarditis in clinical trials, the patients developed complete heart block and cardiac arrest. Autopsies of these patients showed immune cell infiltration of cardiac skeletal muscle, cardiac sinus, and the atrioventricular node.[40]

Management of myocarditis, pericarditis, or cardiomyopathy includes consideration of permanent treatment discontinuation at all grades. Patients should be treated promptly with high-dose glucocorticoids with further interventions guided by cardiology consultation.[21,40] If patients do not respond quickly to high-dose corticosteroids, pulse dose methylprednisolone at 1000 mg daily per cardiac transplant rejection treatment and consideration of mycophenolate mofetil, infliximab, or antithymocyte globulin should be considered. Infliximab should not be used at high doses in patients with moderate to severe heart failure given the drug's association with heart failure itself.[21]

RENAL TOXICITIES

ICIs can rarely cause renal toxicity. In a review of more than 3600 patients enrolled in phase 2 and 3 clinical trials of ICI, the incidence of acute kidney injury (AKI) was 2.2% overall with an incidence of grade III or IV renal disease of 0.6%.[41] The incidence of AKI varied between treatment regimens and was reported at 4.9% with combination ipilimumab-nivolumab, 2.0% with ipilimumab, 1.9% with nivolumab, and 1.4% with pembrolizumab.[41] Development of AKI ranged in onset from 21 to 245 days with a median of 91 days after the start of immunotherapy treatment.[41]

In a case series of 13 patients who developed renal toxicity after receiving an ICI and underwent a renal biopsy, the most common pathologic condition seen was acute tubulointerstitial nephritis (AIN). In the case of AIN, biopsies showed a lymphocytic infiltrate with a predominance of $CD3^+$ T lymphocytes. Granulomas were seen in 3 cases.[41]

The mechanism of AKI development after ICIs is not known, but it is thought to be separate from a typical drug-induced AIN. The delayed onset after drug initiation supports an immune-related cause. It is hypothesized that CTLA-4 and PD-1 inhibitors cause a loss of tolerance to endogenous antigens present in the kidney leading to an immune infiltrate and development of AIN.[41]

Patients who develop renal toxicity are commonly asymptomatic and present with an elevated creatinine detected on routine laboratory tests. In the above described case series of 13 patients who developed AKI after receiving an ICI, peak creatinine ranged from 2.5 to 13.3 with a median of 4.5.[41] Two patients presented with new onset hypertension; 2 patients developed oliguria, and pyuria was seen in 8 cases and hematuria in 3 cases. Mild proteinuria was seen with a urine protein:creatinine ratio ranging from 0.12 to 0.98 g/g. Seven of the 13 patients had a preceding diagnosis of an immune-related adverse event in another organ system.[41] Of 10 patients with biopsy-proven AIN who received corticosteroids for treatment, 2 patients recovered renal function to baseline and 7 patients partially recovered renal function. Two patients with biopsy-proven AIN were not treated with corticosteroids and did not recover renal function. Treatment was initially discontinued in all cases. However, treatment was resumed in 2 cases after improvement in renal function, and these

patients did not develop recurrent renal injury. Two of the 13 patients required temporary dialysis and another 2 patients required long-term dialysis.[41]

If nephritis is suspected, treatment should be held pending further evaluation. For a creatinine 2 to 3 times above baseline, corticosteroids should be initiated and high-dose corticosteroids used if there is no improvement. For a creatinine greater than 3 times baseline or requiring dialysis, treatment should be permanently discontinued.[21]

RHEUMATOLOGIC/MUSCULOSKELETAL TOXICITIES

Arthralgias and myalgias are relatively common musculoskeletal adverse events seen with ICIs.

Arthralgia/Arthritis

Arthralgias and arthritis are thought to be underestimated adverse events associated with ICIs. The incidence of arthralgias is reported to range from 5% to 16% in phase 3 trials of the PD-1 antibody, nivolumab.[42] A systematic review of 52 articles including musculoskeletal and rheumatic adverse events found that the prevalence of arthralgias in clinical trials ranged from 1% to 43%.[43] The incidence of inflammatory arthritis is not well known because it is often reported under arthralgia. In a meta-analysis of 5 clinical trials that reported on arthritis, the incidence ranged from 1% to 7%.[43] Arthritis is characterized by joint pain with associated swelling, stiffness after activity, or improvement in symptoms with nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids.[21] Patients typically experience bilateral pain of the large joints alone, such as shoulders and knees. Less frequently, symptoms also involve joints of the feet and wrists, whereas finger joints, spine, elbows, and hips are affected rarely. Patients do not typically have symptoms in small joints alone without involvement of large joints.[44] Most patients with arthritis test negative for rheumatoid factor and anticyclic citrullinated peptide.[42,44]

In a retrospective study of 195 patients receiving anti-PD-1 therapy, the incidence of arthralgia was 13.3% and the incidence of clinical arthritis was 0.5%. The median onset of arthralgia was 100 days (range 7–780 days) after initiating treatment. In some patients, synovitis could be seen on MRI or PET/CT, and several patients were found to have inflammation of joints with preexisting osteoarthritis.[44] Arthrocentesis done in the cases of synovitis showed inflammatory synovial fluid with 9000 to 30,000 white blood cells per milliliter with neutrophil predominance.[42] Most patients were adequately treated with NSAIDs, whereas 23% required low-dose corticosteroids and only 7.6% received additional immunosuppressive therapy.[44]

In most studies, arthritis is generally mild and grade 1 to 2. For grade 1 disease with mild symptoms, treatment can be continued and symptoms managed with NSAIDs or acetaminophen. For grade 2 disease with moderate symptoms limiting daily activities, treatment can be held and low-dose corticosteroids used if needed. For severe, grade 3 to 4 disease, corticosteroids should be used, and if unable to be tapered, then disease-modifying antirheumatic drugs should be considered.

Myalgia/Myositis

Myalgias have been reported in 2% to 20% of patients on clinical trials with ICI.[43] Myositis with muscle inflammation, weakness, and elevated creatine kinase (CK) is a rare, but potentially serious immune-related adverse event. The incidence is not known, and the most information comes from case reports and case series. Myositis can be life threatening when it involves muscles of the heart or diaphragm.

In a retrospective analysis of 10 patients treated with ICIs for treatment of melanoma, lung cancer, breast cancer, or renal cell carcinoma who were diagnosed with immune related myositis, average time to onset was 25 days after initiation of therapy (range 5–87).[45] The most common symptoms were acute to subacute myalgia, limb-girdle weakness, axial weakness, and oculomotor weakness. In most patients, pain preceded the development of weakness. Limb weakness was symmetric, whereas oculomotor weakness was asymmetric in most cases. Less common symptoms included dysphonia, dyspnea, and fatigue. Symptoms are typically progressive and do not fluctuate. Almost half of the patients had preceding immune-related adverse events of other organs before the development of myositis. Myositis was grade 3 to 4 in most patients diagnosed. One patient had involvement of the diaphragm causing respiratory failure requiring intubation. Four of the patients had concurrent myocarditis, and 3 of these patients had severe, disabling myositis.[45] ICI treatment was permanently discontinued in all 10 patients. Most patients received corticosteroids, whereas one patient required methotrexate and 3 patients required IV immunoglobulin or plasma exchange. All patients experienced an improvement in their symptoms with normalization of CK levels in a median of 44 days (range 6–96).[45]

Diagnosis of myositis can be based on objective muscle weakness, elevated CK level, electrodiagnostic studies showing a myopathic process without decrementing response during repetitive nerve stimulation, or muscle biopsy showing myositis. In the case series of 10 patients with myositis, all patients had elevated CK levels with a median of 2668 U/L (range 1059–16,620 U/L) and negative anti–acetylcholine receptor antibody and negative myositis-associated antibodies.[45] Electromyography shows abnormal spontaneous movement or myopathic motor units with normal or early recruitment, characteristic of a myopathic process. This myopathic process is mainly observed in the muscles of the proximal limbs, deltoids, and trapezius. Repetitive nerve stimulation should not show a decremental response, which would be seen in neuromuscular disorders such as myasthenia gravis.[45]

Muscle biopsies done in cases of myositis show multifocal necrotic myofibers with significant infiltration of macrophages and T cells. Major histocompatibility complex-I molecules in the sarcolemma of myofibers have been identified in areas of severe necrosis indicating an inflammatory myopathy. Focal inflammatory infiltrates in the endomysium consist of $CD68^+$ cells, $CD8^+$ cells, $CD4^+$ cells, and rare $CD20^+$ cells. PD-1 expression has been identified on T cells seen diffusely as well as surrounding myofiber necrosis but not invading the myofibers. PD-L1 has been observed on macrophages. Because of the focal nature of the infiltrates, site of muscle biopsy should be chosen based on location of clinical, electrophysiologic, or radiographic abnormalities.[45]

Guidelines for treatment of myositis classify mild muscle weakness with or without pain and no CK elevation as grade 1. Treatment can be continued and symptoms managed with NSAIDs or acetaminophen. For grade 2 disease with moderate symptoms limiting daily activity, treatment should be held and corticosteroids initiated for CK elevation. Permanent treatment discontinuation should be considered for patients with grade 2 disease, CK elevation, and testing consistent with myositis. For severe, grade 3 to 4 disease, high-dose corticosteroids should be used, and additional treatment such as plasmapheresis, IV immunoglobulin, methotrexate, azathioprine, mycophenolate mofetil, or rituximab should be considered.[21]

PREEXISTENT AUTOIMMUNE DISEASES

One of the concerns with immune-associated toxicity is that patients with baseline autoimmune disease may experience worse toxicity. Clinical trials previously

excluded these patients from enrollment. However, series of patients treated with immunotherapy have demonstrated that these agents can be administered relatively safely to most patients with preexistent autoimmune diseases, but patients need to be watched closely for toxicity.[46,47]

FUTURE DIRECTIONS

Work to better understand and limit the incidence of immune-related toxicities is ongoing. One study evaluating the efficacy of adding granulocyte-macrophage colony-stimulating factor (GM-CSF) to ipilimumab versus ipilimumab alone for treatment of melanoma showed an improvement in overall survival (17.5 vs 12.7 months, $P = .01$) as well as a lower occurrence of grade 3 to 5 serious adverse events (44.9% vs 58.3%, $P = .04$).[48] This study showed lower rates of serious gastrointestinal toxicity with GM-CSF (16.1% vs 26.7%), including fewer colonic perforations as well as less pulmonary toxicity (0% vs 7.5%).[48] Studies such as these may provide insight into agents that can be safely given to limit toxicity without affecting the anticancer immune effect.

As immunotherapy becomes more widely used, structured management approaches and national guidelines are being put in place to formally guide toxicity management. The American Society of Clinical Oncology, National Comprehensive Cancer Network, Society of Immunotherapy of Cancer, and European Society for Medical Oncology have published management guidelines.[21,32,49,50] In addition, close collaborations are being established between oncology providers and physicians with organ system expertise to establish management plans appropriate for the site of toxicity. Many centers have established institutional guidelines, toxicity algorithms, and multidisciplinary teams to assist with immunotoxicity management.

Further studies are ongoing to better understand immune-related adverse events with goals of reducing the incidence and improving the treatment of these side effects. This work will also contribute to a better understanding of autoimmune diseases and the immune system as a whole.

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