Managing Immunotherapy Related Organ Toxicities

A Practical Guide

Yinghong Wang
Editor

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Preface

During the past decade, immune checkpoint inhibitors (ICIs) have quickly become a paradigm-shifting treatment for a variety of advanced malignancies with a high efficacy. The Nobel Prize in Physiology or Medicine 2018 was awarded for the discovery of cancer therapy by inhibition of negative immune regulation. ICI-induced toxicities, however, pose significant morbidity on already vulnerable cancer patients and thus become a major barrier to this innovative cancer treatment.

I can never forget a scene approximately 5 years ago, when a desperate patient suffering from refractory GI toxicity wanted to give up her melanoma cancer treatment and choose hospice. That was a healthcare professional lady in low 40s that had an admirable career and a happy family with two lovely young kids. The initial ICI treatment showed encouraging response. Then quickly she developed severe colitis. The bleeding and uncontrollable diarrhea significantly deteriorated her physically and mentally. That pushed her to the edge of giving up the fight. We calmed her down and tried an aggressive non-traditional approach as the last resort. A surprising success was achieved with complete resolution of her colitis. She was able to resume the ICI treatment and miraculously conquered the cancer in the end. The patient was so grateful for what we offered to save her life. It was such a touching moment beyond words.

Stories like this are happening almost every day in our clinic and hospital services at The University of Texas MD Anderson Cancer Center MD Anderson, where more than 40% of over 5000 patients receiving ICI treatments each year experience different types and degrees of organ toxicities. Our management for ICI toxicities is especially challenging given the high patient volume, more complexity of disease presentations, wide diversity of cancer types, and large variation of providers' practice patterns.

To address this escalating demand and challenge, an institutional ICI toxicity initiative was launched aiming at an optimized strategy in clinical practice on both scientific and operational levels. Our multi-year cross-disciplinary endeavors dramatically improved the efficiency of our ICI toxicity clinical services, provided extensive collaborative and educational opportunities, and incubated various new research projects on clinical and quality improvement.

Given the preliminary successes at MD Anderson, we feel compelled and privileged to share what we have learned with the academic and community practices around the world. Totally 15 chapters covering all aspects of ICI toxicities management were contributed by our leading specialists at MD Anderson Cancer Center, which took nearly 10 months to complete this first-of-a-kind ICI toxicity book.

A unique feature about this book is the inclusion of perspectives from anesthesiology, infectious disease, and pathology besides specific organ toxicity management. To facilitate a quick overview by the readers, we also enclosed audio PowerPoint slide decks in the e-book version. It is a truly inspiring product from our esteemed group with strong passion, determination, and perseverance. Since this field is rapidly evolving, we plan to update it every 2–3 years after its debut. We truly hope the comprehensive topics reviewed here would add tremendous values to this important field and support our noble mission to make cancer history.

Houston, TX, USA Yinghong Wang

Introduction

Immune checkpoint inhibitors (ICI) have become a major component of immune oncology, which has revolutionized cancer therapy and joined surgery, radiation therapy, chemotherapy, and targeted therapy as the fifth pillar of cancer treatment. While already substantial, the full impact of ICI is far from being fully realized, as there has been an explosion in the number of clinical trials examining ICI combinations and ICI therapy combined with chemotherapy and targeted therapy. However, for the foreseeable future, the extent of the overall benefit of ICI will be limited by immune-related adverse events (irAE), a major subcategory of immune oncology toxicity (IOTox).

Immune-related AE were anticipated in the earliest descriptions of the cell surface receptor—ligand pairs designed by nature to control T-cells responses and their exploitation; not unexpectedly, irAE were observed in mouse models as strategies to block these receptor-ligand interactions first emerged to treat cancer [1]. Unfortunately, irAE also developed in patients who received the first ICI therapy directed against CTLA-4 for treatment of melanoma and ovarian cancer [2]. Similarly, irAE are commonly experienced in patients receiving ICI therapy targeting the PD-1/PD-L1 and other negative immunoregulatory ligand-receptor pairs, often with a frequency higher than anticipated based on pre-clinical cancer models.

Our understanding of the molecular and cellular pathogenesis of irAE is in its infancy and has become an area of intense investigation at our institution and around the world. Not surprisingly, management of irAE largely is empirical with algorithms carried over from those used to treat other inflammatory and autoimmune diseases. Because physicians within virtually every clinical subspecialty in the Division of Internal Medicine at The University of Texas MD Anderson Cancer Center are caring for patients with ICI-related irAE, these physicians, along with physician-scientists and scientists throughout MD Anderson, have partnered with colleagues in the Division of Cancer Medicine and Division of Pathology and

Laboratory Medicine to mount a robust and multi-faceted attack on this problem. This outstanding collection of chapters are tangible evidence of this superb effort.

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Chapter 1
Anesthesia

Peter H. Norman

Abstract This chapter is different than other chapters in that rather than focusing on specific organ toxicities related to immune checkpoint inhibitor (ICI) therapy, we are attempting to show how ICIs affect the care delivered by other professionals to the patients. Due to the limited anesthesiology training in medical schools, many oncologists may not have a good understanding of the scope of anesthesiologists' work. In addition to inducing unconsciousness for surgery and procedures, we also maintain the patients' physiologic homeostasis, protect them from pain and harmful reflexes, maintain and augment their ventilation and circulation, and provide cerebral protection. We also provide resuscitation when needed. Knowledge that a patient is receiving an ICI may significantly influence the anesthesiologist's decision-making, so it is essential for the patient's safety that oncologists provide good communication to all anesthesia, surgical, and procedural colleagues. This approach was suggested by our editor, Dr. Y Wang, and others in the ASCO Clinical Practice Guidelines who proposed using a wallet card [1]. We should advocate for a more complete communication - perhaps an electronic Best Practice Guideline - that could be attached to the patient electronic medical record to facilitate this. The most important information to include here would be details regarding ICI therapy. It may be well understood by the patient's primary oncology team, but the downstream anesthesiologists may not be as familiar with the patient's therapy, especially if the patient is treated at a different institution as is often the case in the event of emergency procedures. From the viewpoint of the anesthesiologist or surgeon, the incidence of significant side effects of ICI is sporadic as shown in the following examples: (1) a sudden cardiac death following trastuzumab cardiomyopathy which was asymptomatic prior to induction of anesthesia in a minor surgical procedure; (2) a persistent, severe hypotension in a patient undergoing cystectomy who had received pembrolizumab as neoadjuvant therapy; and (3) thoracic surgery patients

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on neoadjuvant ICI who may have their shrunken tumors tightly adherent to adjacent blood vessels leading to sudden and massive bleeding. Studies on the anesthetic management of patients treated with immune checkpoint inhibitors are very limited [2]. The discussion on the potential downstream consequences of specific organ toxicities and their management is described below by the ASCO Clinical Guidelines.

Keywords Anesthesia · Toxicity · Immune checkpoint inhibitors

1. Skin Toxicities. The most common side effect of ICIs became the inaugural sign of a change in our anesthetic practice though the cause was initially cryptic. Removal of tape holding endotracheal tubes would pull off strips of skin. In one case, the removal of eye tapes used to prevent drying and corneal abrasion when anesthetized torn off the skin from both eyelids of a patient (Fig. 1.1). Administration of a petrolatum cream to these patients is the appropriate management, while the detachment of the epidermis from the underlying dermis is a larger problem that may need additional therapy from the treating oncologist. Of interest, the official title for skin damage from tapes is MARSI (medical adhesive-related skin injury). We are currently trialing skin barrier wipes though their benefit remains to be seen.
2. Gastrointestinal (GI) Toxicities. Colitis and other GI toxicities will more likely affect medical management but might necessitate procedural or surgical intervention. The description of ICI-induced colitis with mesenteric vessel engorgement, bowel wall thickening, and fluid-filled colonic distention from the ASCO monograph certainly raises concern for the risk of hemorrhage and aspiration from an anesthesiologist's perspective.

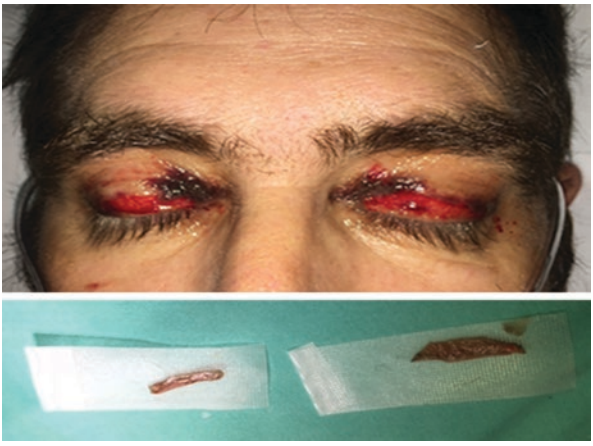

Fig. 1.1 Removal of eyelid skin seen on tape. This patient shown had amyloidosis, but there have been an increasing number of similar incidents since ICIs were introduced. (Courtesy images provided by Dr. Acsa Zavala [3])

3. Hepatic Toxicity. This directly impacts anesthetic management. Anesthetics have been investigated for hepatic dysfunction since the National Halothane Study in 1966 [3, 4]. Hepatic dysfunction significantly increases the risk for further hepatotoxicity as most anesthetics are metabolized or detoxified in the liver. Hepatic dysfunction as manifested by enzyme elevations may result in treatment delay as a search for viral hepatitis is undertaken. Steroid therapy may also be delayed in the setting of preparation for a procedure or surgery unless the history of ICI therapy is known and its significance understood.
4. Lung Toxicity. Anesthesiologists are very experienced in dealing with lung dysfunction of all kinds. Preprocedural or presurgical evaluation will elucidate the degree of dysfunction and guide management as is done in every case. ICI-related lung toxicity may increase the necessity for post-anesthetic ventilatory support. There has been no mention so far of accelerated oxygen toxicity with ICIs such as is seen with bleomycin and others.
5. Endocrine Organ Toxicities. Hyperthyroidism is easily managed under anesthesia with beta-blockers. Although the differential of a hypermetabolic patient includes malignant hyperthermia, the two conditions are clinically distinct. Hypothyroidism on the other hand will potentiate intravenous agents and particularly narcotics resulting in a patient difficult to rouse. Adrenocortical insufficiency may be a major problem as the causes of hypotension during a surgical procedure are numerous, and without some hint that cortisol depletion might be the cause, appropriate therapy may be dangerously delayed. Diabetes or hyperglycemia/hypoglycemia, on the other hand, is easier to manage.
6. Musculoskeletal Toxicities. Arthritis is self-explanatory and can be easily dealt with for anesthetic management of procedures and surgeries. Myositis may be more problematic especially if it affects cardiac muscle and function. Muscle relaxants are used in anesthesia and act at the neuromuscular junction where they block transmission of nerve impulses. Muscle relaxation and concomitant lung ventilation allow for safe surgery. At the end of surgery, however, the muscle relaxant needs to be reversed or neutralized. A preexisting myositis may make this difficult. Myositis may predispose to dangerous hyperkalemia with the depolarizing agent succinylcholine though this is theoretical. Another concern to anesthesiologists dealing with patients with muscle diseases is the development of malignant hyperthermia with inhalational anesthetics and succinylcholine. There are no case reports of this as yet theoretical risk.
7. Renal Toxicity. Renal dysfunction is well understood by anesthesiologists. Many drugs require renal excretion, but there are alternative methods that work. Substitution of the renally excreted rocuronium for muscle relaxation with cisatracurium is one such change. Maintaining adequate perfusion pressure and hydration to prevent worsening of an already compromised renal function is another. Ensuring electrolyte normality preoperatively is critical.

8. Nervous System Toxicities. This is where the anesthetic management becomes particularly intricate. Relaxants interfere with neuromuscular transmission, and anesthetic agents may interfere with nerve function and recovery.

    8.1. Myasthenia Gravis. If recognized and treated, there are anesthetic methods to manage these patients. If subclinical and unrecognized, the usual dose of a depolarizing muscle relaxant may last 24 hours rather than half an hour. So, diagnosis is key. These patients are relatively resistant to depolarizing muscle relaxants in contrast to those with myositis who are sensitive to both depolarizing and nondepolarizing relaxants.
    8.2. Guillain-Barré Syndrome. Well understood by anesthesiologists but patients may require ventilation.
    8.3. Peripheral Neuropathy. May cause hyperkalemia with depolarizing relaxants (succinylcholine). Also, may be more susceptible to exacerbation with prolonged procedures and surgery due to positioning.
    8.4. Autonomic Neuropathy. May predispose to lability of blood pressure and heart rate during procedures. If diagnosed, must be communicated to your anesthesiologists. If undiagnosed and unappreciated, the blood pressure and heart rate dips may cause morbidity, and overcorrection may be as deleterious. Vagal blocking with an anticholinergic like sodium glycopyrrolate prior to any procedure could potentially be helpful. Traditional antivagal treatment with an intramuscular atropine injection 1 hour preoperatively is a remnant from a bygone era, but equally helpful for prevention of sudden bradycardias.

9. Hematologic Toxicities. Easily diagnosed and managed during procedures and surgeries only if appropriate laboratory work is ordered. To note, this appropriate laboratory investigation may be omitted in an otherwise normal-appearing individual to prevent unnecessary expense either by the institution or insurer. Warning of ICI therapy should permit and suggest a more thorough laboratory examination despite a relatively benign appearance.
10. Cardiovascular Toxicities

    10.1. Myocarditis, Pericarditis, Arrhythmias, Impaired Ventricular Function with Heart Failure, and Vasculitis. If suspected and investigated, then they will be well handled by anesthesiologists though preference should be given to those who are well trained in the field of cardiovascular disease. The problem for anesthesiologists is unsuspected cardiovascular compromise or well-compensated failure that becomes uncompensated when stressed by anesthetic agents or the demands of surgery. Laparoscopy, the mainstay of minimally invasive abdominal surgery, decreases venous return and significantly increases afterload. What was adequate circulation may suddenly become life-threatening. Importantly, pembrolizumab-related hypotension requires an inotropic cocktail commonly used in cardiopulmonary bypass procedures.

10.2. Venous Thromboembolism. Most procedures and surgeries now include prophylaxis for venous thromboembolism. If ICI therapy significantly increases the risk of thromboembolism, more directed measures may be needed during procedures and surgery.

11. Ocular Toxicities. Most of these unless detected beforehand will be assumed to be a result of the anesthetic management rather than a late effect of prior therapy.

General Recommendations

The management of these patients is critically dependent on awareness of their ICI therapy and the risks associated with specific ICI agents. In the absence of this or with inattention to the patient's oncologic history, how can management be improved? History and physical examination remain paramount. Complaints of change in activity level, dyspnea, lethargy, low energy, or weight gain or loss may predispose to diagnosing some long-term effect before they become a life-threatening problem. Similarly, signs and symptoms of hypothyroidism may help avoid a prolonged postoperative period of ICU ventilation. Significant ecchymosis may prompt an investigation of coagulation parameters. Patients may however seem normal considering their other diagnoses. Standard laboratory tests should be reviewed for evidence of anemia, thrombocytopenia, hyperglycemia, and renal failure. Thyroid function in these patients should always be suspected and most eventually become hypothyroid. While an EKG is a relatively poor screening tool except for rhythm or obvious myocardial infarction/ischemia, an EKG is rarely completely normal in the presence of significant left ventricular dyssynergy. Echocardiograms are helpful to elucidate cardiomyopathy and the regional wall motion abnormalities of coronary artery disease. Brain natriuretic peptide test may help diagnose congestive heart failure. Addisonian symptoms may be missed on simple or quick evaluation.

Organ-Specific Treatment Strategies

1. Careful titration of induction drugs with invasive monitoring if cardiac issues are suspected. Or planned transesophageal echo monitoring of cardiovascular function.
2. Availability of more potent vasopressors than the ubiquitous ephedrine.
3. Local analgesia or regional anesthesia where appropriate, although mortality and morbidity are basically the same between careful competent local, regional, or general anesthesia.

4. Dobutamine and norepinephrine infusions to maintain perfusion pressure in the context of hypotension after ICI. A low threshold for steroid supplementation in the presence of refractory hypotension may be lifesaving.
5. Consideration of fibrinolysis inhibitors during surgery to decrease blood loss and perhaps improve operative conditions.
6. Delay of elective surgery to normalize thyroid function after replacement.
7. Careful titration of neuromuscular blocking drugs with appropriate reversal.
8. The long-term effects of anesthesia and surgery or other procedures in patients who have had ICI toxicities should be comparable to otherwise similar patients.
9. There is a possibility of poor healing and wound dehiscence.

The message for the readers of this book is to ensure that downstream physicians are aware of the ICI therapy and its potential side effects. The electronic medical record alone may not be adequate to provide sufficient information for safe management in all specialties. Effective communication between treating oncologists and downstream physicians plays a critical role to ensure the high quality of clinical care and best outcome.

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Chapter 2
Cardiology (Heart)

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Abstract Immune checkpoint inhibitors (ICIs) represent one of the most exciting therapeutic advancements in the field of oncology. While myocarditis is one of the rarest side effects of immune checkpoint inhibitor (ICI) therapies with an incidence of 1%, it ranks as one of the deadliest with a mortality rate approaching 25–50% [1]. The nuances involved in diagnosing ICI-associated myocarditis and a wide range of symptoms characterizing the clinical presentation create a challenge in identifying with great specificity the disease in clinical trials, in clinical case series, and, ultimately, in patients [2]. The keys to diagnosis and treatment of ICI-associated myocarditis lie with a circumspect understanding of the various cardiac biomarkers, noninvasive imaging modalities, and invasive methods that are combined in conjunction with the patient's clinical presentation to establish the diagnosis and treatment plan. While ICI-associated myocarditis is a clinically distinct entity, the emerging diagnosis and treatment strategies for this disease are founded on the diagnostic and treatment principles established for cardiotoxic chemotherapy agents, viral myocarditis, and cardiac allograft rejection. However, ICI-associated myocarditis remains unique in that there remains much work in not only seeking a uniform definition for the disease process but also in discovering increasingly specific biomarkers and novel imaging techniques to further aid in diagnosis. Furthermore, while high-dose steroids are acknowledged as a mainstay treatment

Chapter debriefing: Power point video presentation is provided at the end of the chapter.

Supplementary Information The online version contains supplementary material available at [https://doi.org/10.1007/978-3-031-00241-0_2].

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for the disease, the discovery of second-line agents that may successfully control disease progression is still underway, in addition to identifying the patient characteristics for those at highest risk of failing frontline therapies.

Keywords Immune checkpoint inhibitors · Immunotherapy · Immune-related adverse events · Myocarditis · Cardiotoxicity · Cardio-oncology

Abbreviations

ASCO	American Society of Clinical Oncology
CMR	Cardiac magnetic resonance
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ICIs	Immune checkpoint inhibitors
irAE	Immune-related adverse event
MACE	Major adverse cardiac events

Available Immune Checkpoint Inhibitors

As of 2021, the immune checkpoint inhibitor (ICI) therapies available in the United States are cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitor (ipilimumab), three PD-1 inhibitors (pembrolizumab, nivolumab, and cemiplimab), and three PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab) [3]. In cases of untreated or metastatic melanoma, ipilimumab and nivolumab monotherapy have individually improved survival in these patients [4, 5]. Later studies showed improved survival and antitumor activity using combination ICI therapy (nivolumab and ipilimumab) for untreated melanoma [6]. Since then, the use of ICI has been expanded to several malignancies including many genitourinary cancers and lung cancers [7, 8]. With the increased use of ICI as both first-line cancer therapy and combination therapy, clinicians must be aware of the potential for myocarditis and be vigilant to diagnose and treat the potentially fatal cardiotoxicity.

Cardiac Side Effect Profile of Immune Checkpoint Inhibitors

The side effects of ICI are called immune-related adverse events (irAEs) for which several grading scales exist. In oncology clinical trials, the Common Terminology Criteria for Adverse Events (CTCAE) are often used; however, due to limitations in these criteria for irAEs, the American Society of Clinical Oncology (ASCO) released clinical practice guidelines in 2018 for grading the severity of irAEs specifically [9].

Table 2.1 Comparison of CTCAE and ASCO clinical practice guideline grading of cardiovascular irAE

CTCAE myocarditis grading	ASCO irAE myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure, and vasculitis
Definition: a disorder characterized by inflammation of the muscle tissue of the heart	Definition: signs and symptoms may include chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, and fatigue
Grade 1: not applicable	Grade 1: abnormal cardiac biomarker testing, including abnormal ECG
Grade 2: symptoms with moderate activity or exertion	Grade 2: abnormal screening tests with mild symptoms
Grade 3: severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms	Grade 3: moderately abnormal testing or symptoms with mild activity
Grade 4: life-threatening consequences; urgent intervention indication (e.g., continuous IV therapy or mechanical hemodynamic support)	Grade 4: moderate to severe decompensation, IV medication or intervention required, life-threatening conditions

CTCAE Common Terminology Criteria for Adverse Events, *ASCO* American Society of Clinical Oncology, *irAE* immune-related adverse event, *ECG* electrocardiogram

Differences between the CTCAE grading of myocarditis and the ASCO guidelines can be seen in Table 2.1. In addition, the ASCO guidelines provide expert consensus recommendations for treatment of different grades of myocarditis. It should also be noted that myocarditis is not the only potential cardiac irAE from ICI therapy. The ASCO guidelines group the grading of irAE to include all cardiac irAEs which include myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure, and vasculitis. In addition to pericarditis, recurrent pericardial effusion requiring pericardiocentesis has been recognized with ICI therapy [10]. Also, a recent study by Drobni et al. showed that patients on ICI had increased risk of atherosclerotic events (HR 3.3, 95% CI 2.0–5.5, $p < 0.001$) compared to controls [11]. The role of inflammation in atherosclerosis is well established, and more studies are needed to see if ICIs lead to increased atherosclerotic events. Due to the limited literature regarding other cardiac adverse events and the high mortality of myocarditis, this chapter will focus only on diagnosing and treating ICI-associated myocarditis.

Mechanisms of Myocardial Toxicity

While the precise mechanism of ICI-associated myocarditis is unknown, work has been done to elucidate it. Researchers at the Vanderbilt-Ingram Cancer Center performed histopathological analyses of the hearts of two patients with metastatic melanoma who had fatal reactions to one infusion of the ipilimumab-nivolumab

combination [12]. The histopathology in one patient demonstrated patches of highly concentrated lymphocytic infiltrate within the myocardium, sinus node, and atrioventricular node. Isolated myocytes within the skeletal muscle were targeted for destruction by lymphocytes [12]. The histopathology of the second patient similarly showed evidence of lymphocytic myocarditis and myositis. To further characterize the nature of the destructive lymphocytes, the researchers performed next-generation sequencing of the CDR3 region and the antigen-binding portion of the T-cell receptor beta chain [12]. They found specific T-cell receptor sequences in infiltrates from the cardiac muscle, skeletal muscle, and tumors, suggesting that epitopes from each of these three tissues were recognized by the same T-cell clones [12]. Given that only striated muscle (cardiac and skeletal) was affected by the lymphocytes, it is also possible that the same T-cell receptor may be targeting a tumor antigen and a different but homologous muscle antigen. Finally, a third mechanism is that different T-cell receptors are targeting different antigens [12]. Further molecular studies with larger cohorts would be required to elucidate the exact mechanism of action.

ICI-Associated Myocarditis

The diagnosis of ICI-associated myocarditis can be problematic in the clinical setting because of the lack of a uniform definition and lack of specificity of many noninvasive imaging modalities. When studies report ICI-associated myocarditis, the incidence varies greatly and is likely due to lack of a widely accepted uniform approach to concretely establishing the diagnosis [1]. Decades before immune checkpoint inhibitors were in clinical use, the 1986 Dallas Criteria attempted to provide a histopathological designation for defining viral *myocarditis*, which requires an inflammatory infiltrate of the myocardial tissue and associated myocyte necrosis or damage that cannot be attributed to an ischemic event [13]. Endomyocardial biopsy for a tissue diagnosis is still considered the gold standard for myocarditis diagnosis [14, 15]; however, due to the invasive nature of this procedure and the need for a specialized center with pathologists experienced in interpreting cardiac pathology, its use is limited in the general clinical setting. For this reason, many reports of ICI-associated myocarditis rely on a combination of the clinical presentation, cardiac biomarker analysis, and noninvasive cardiac imaging (electrocardiogram, echocardiogram, cardiac magnetic resonance imaging) to diagnose myocarditis [2].

Overall, ICI-associated myocarditis is among the rarest but most fatal irAEs [16]. Surveying the literature, ICI-associated myocarditis has a reported incidence ranging from 0.04% to 1.14% with an associated mortality of 25–50% [3, 17]. For relative comparison with the incidence of other irAEs, Wang et al. conducted a query of the World Health Organization (WHO) pharmacovigilance database

(VigiBase-VigiLyze) and performed a meta-analysis of published trials to establish the incidence of ICI-associated toxic effects [16]. For example, in anti-CTLA-4 deaths, 70% were usually from colitis [16]. Anti-PD-1/PD-L1-related fatalities were often from pneumonitis (35%), hepatitis (22%), and neurotoxic effects (15%) [16]. Combination PD-1/CTLA-4 deaths were frequently from colitis (37%) and myocarditis (25%) [16]. In a fatality rate analysis of the irAEs, myocarditis composed 39.7% of cases, whereas endocrine had 2%, colitis had 5% reported fatalities, and other organ system toxic effects ranged from 10% to 17% of reported fatal outcomes [16]. Additionally, in a retrospective review of 3545 patients treated with ICIs from 7 academic centers, the overall fatality rate from ICI-related events was 0.6%, and cardiac and neurologic events together composed 43% of those [16]. Initial pharmacovigilance studies published early in the acknowledgment of ICI-associated myocarditis showed that myocarditis only occurred in 0.27% of patients treated with a combination of ipilimumab and nivolumab [12]. However, as awareness of recognition of myocarditis has improved, more contemporary studies report a prevalence of myocarditis around 1% that is generally accepted [16, 17]. Other ICI-associated cardiotoxicities including pericardial tamponade, myocardial infarction, stroke, cardiac failure, and cardiorespiratory arrest approach a similar individual incidence rates ranging from 0.7% to 2.0%, according to a meta-analysis of 22 clinical trials of PD-1 and PD-L1 inhibitors for lung cancer [18].

The clinical presentation of ICI-associated myocarditis can range from the asymptomatic patient with slightly elevated troponin to the patient in cardiogenic shock on multiple pressors with advanced atrioventricular block and ventricular arrhythmias (Table 2.2) [1, 3]. Few diagnoses in medicine carry such a heterogeneous repertoire of presentations. The clinical presentation of myocarditis often mimics other common acute cardiac disorders such as acute coronary syndrome or heart failure with common symptoms of chest pain/pressure, dyspnea, orthopnea, and lower extremity edema [3] (Table 2.2).

Table 2.2 Range of signs and symptoms in ICI-associated myocarditis

Symptoms	Signs
Fatigue	Asymptomatic troponin elevation
Heart failure symptoms (dyspnea, orthopnea, paroxysmal nocturnal dyspnea, lower extremity edema)	Change in mental status
Palpitations	Cardiogenic shock
Chest pain	Complete heart block
Lightheadedness	Intractable ventricular arrhythmias
Syncope	Cardiac arrest

Timing Onset of Myocarditis

Based on small patient cohorts, the first 2–3 months are high risk for onset of myocarditis, and patients need only one to two ICI doses before being at risk for myocarditis [3, 17]. This timing of onset is comparable to the overall onset of fatal toxic effects seen for all irAEs, which typically occurred within the first 1–3 months of therapy initiation for combination therapy, anti-PD-1, and ipilimumab monotherapy (median 14.5, 40, and 40 days, respectively) [16]. A breakdown of the timing of onset of irAEs per organ system seen with combination therapy shows that the renal, hepatic, endocrine, pulmonary, gastrointestinal, and dermatologic organ systems are affected at 3.75, 2.62, 2.16, 1.93, 1.63, and 0.71 months, respectively [19]. The median time to onset of myocarditis after ICI therapy is initiated is 34 days (range 21–75 days as recorded in 35 patients described by Mahmood et al. [17]). In another cohort of 30 patients analyzed by Escudier et al., patients were diagnosed with myocarditis at a median of 65 days (range 2–454 days) after an average of 3 infusions of the medicine [20]. In an analysis of 33 patients with ICI-associated myocarditis from VigiBase, the World Health Organization (WHO) database of individual safety case reports, the median onset to diagnosis was 27 days (range 5–155 days), with 76% occurring in the first 6 weeks. Of these patients, 64% had only received one or two doses of ICI [21]. In a Bristol-Myers Squibb corporate safety database of 20,594 patients, 18 drug-related severe adverse events of myocarditis were reported (0.09%). In patients receiving ipilimumab and nivolumab combination therapy, myocarditis occurred at a median of 17 days (range 13–64 days) after one dose of treatment [12]. Another observation worth noting is that combination ICI therapy tends to lead to increased observance of severe myocarditis events in association with severe myositis (grades 3–4) compared with single-agent use only (0.24% vs. 0.15%) [12]. Patients can present with multiple irAEs or overlap syndromes, and myocarditis most commonly overlaps with myositis and myasthenia gravis irAEs [16].

Diagnostic Testing Considerations in ICI-Associated Myocarditis

Given that the presenting symptoms of myocarditis have such a wide range of differential diagnoses including the spectrum of acute coronary syndrome, heart failure, pericardial effusion, and side effects of other irAEs, the diagnostic schema to begin an investigation into myocarditis should necessarily include testing for these other disease processes as well (Fig. 2.1) [1–2].

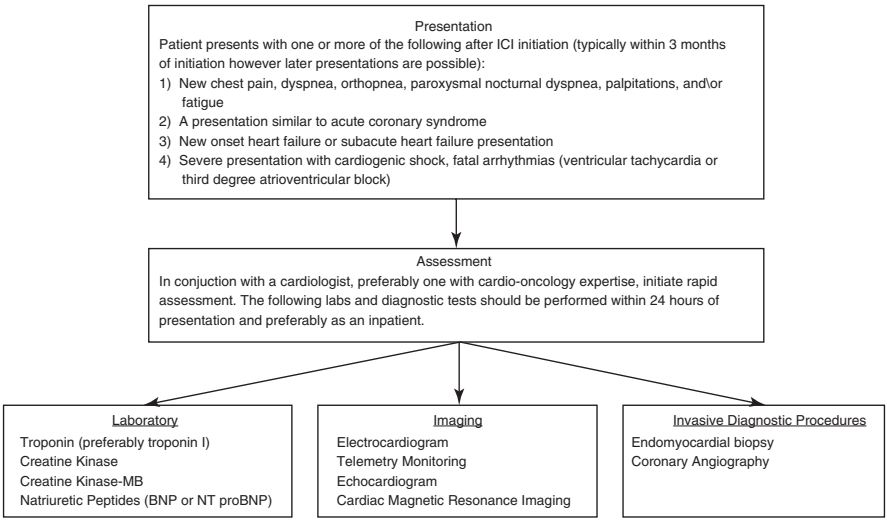

Fig. 2.1 Presentation and diagnostic workup for immune checkpoint inhibitor-associated myocarditis

Troponin

Prior to patients receiving monotherapy or combination immunotherapy agents, there is general agreement among several authors in the cardio-oncology field; their proposed treatment algorithm is that these patients have a documented baseline troponin and electrocardiogram (ECG) [1, 2]. In particular, troponin I is preferred over troponin T due to its better specificity for myocardial injury, though it still can be elevated in other non-myocardial situations including chronic kidney disease and pulmonary embolus. Troponin T is additionally not preferred as a marker for ICI-associated myocarditis because in cases where the patient also has myositis, there are already elevated levels of creatine kinase and its isoforms as well as troponin T, which is a protein integral to the contraction of both skeletal and heart muscles [2]. Troponin I has a greater specificity for myocyte injury in patients with clinically suspected myocarditis than creatine kinase levels, and while superior to other markers, they are still non-specific and when normal do not exclude myocarditis [15]. The other value of troponin is it has both diagnostic and prognostic values with some studies showing a fourfold increase in major adverse cardiac events with higher troponin levels [17]. Some literatures based on expert opinion have recommended consideration of troponin surveillance early after ICI initiation; however, two small prospective single-arm studies have been limited by the low incidence of myocarditis with the majority of troponin elevations not being related to myocarditis but rather other etiologies [22, 23]. Early assessment to rule out myocarditis is essential to limit interruptions in ICI therapy if a surveillance strategy is used.

Natriuretic Peptide

The natriuretic peptides (B-type natriuretic peptide and NT-proBNP [N-terminal pro-B-type natriuretic peptide]) have been considered for the diagnosis of myocarditis, but they are not specific enough for this purpose. They generally indicate the degree of stress on the ventricles and thus are elevated in patients with heart failure exacerbations or severe left ventricular dysfunction. They may also be elevated in the setting of inflammation [2]. Since not all patients with myocarditis present in heart failure, normal natriuretic peptides should not exclude the diagnosis. A recent study evaluating the association between NT-proBNP levels and grade of myocarditis showed an association with troponin T levels but not with proBNP [24].

Electrocardiogram (ECG)

Electrocardiographic changes frequently accompany ICI-associated myocarditis. However, a patient may have a completely normal ECG and still have the diagnosis [25, 26]. While there is no specific sign on an ECG that determines whether a patient has ICI-associated myocarditis, there are some non-specific changes that can suggest myocarditis in the right clinical setting [3]. Patients admitted to the hospital with suspected myocarditis should be monitored on telemetry for early detection of arrhythmias and other electrical changes [3].

Complete atrioventricular block is the most common electrical complication of ICI-associated myocarditis (Fig. 2.2) [27]. ICI-associated myocarditis can present with conduction disturbances ranging from bundle branch block to complete heart block. Other inflammation-associated arrhythmias include sinus tachycardia, atrial fibrillation, ventricular tachycardia and fibrillation, and frequent supraventricular and ventricular premature beats and non-specific ECG changes such as Q wave formation, ST depression, and diffuse T wave inversions [3, 20, 25]. While some patients may have PR interval prolongation induced by ICI-associated myocarditis that resolves with treatment of the inflammation [3], one registry showed that overall patients with myocarditis did not have a prolonged PR interval [28].

In an international registry comparing QRS duration and QTc interval between 140 myocarditis cases and 179 controls across multiple time points, it was found that the QRS duration (representing ventricular depolarization) prolonged with myocarditis, but the QTc interval (corrected using the Fridericia formula) remained unchanged [28]. The sensitivity for myocarditis with a QRS duration of >110 ms was determined to be 48.6% with a specificity of 87%, and a QRS duration of >130 ms yielded a sensitivity of 16.4% and a specificity of 92.6% [28]. In fact, an increase in the QRS duration of 10 milliseconds at the time of diagnosis of myocarditis conferred a 1.30-fold increase in the odds of major adverse cardiac events (MACE) including cardiovascular death, cardiac arrest, cardiogenic shock, and hemodynamically significant complete heart block [28].

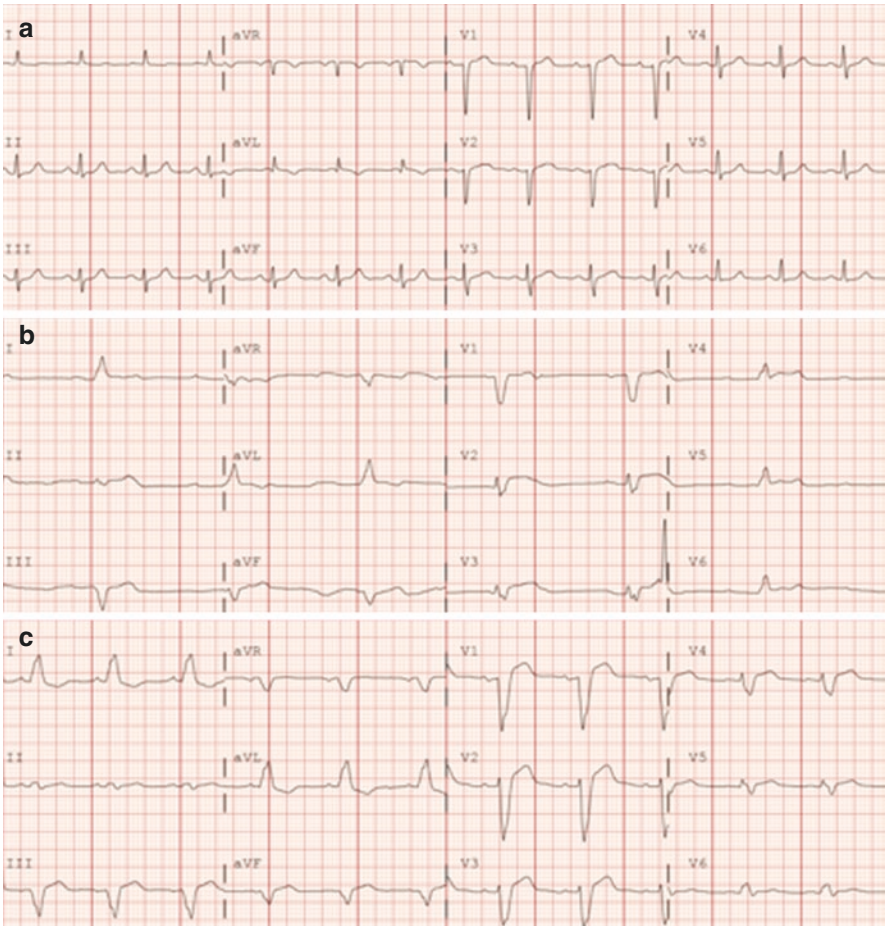

Fig. 2.2 Electrocardiograms of a patient who developed immune checkpoint inhibitor-associated myocarditis. (**a**) Baseline electrocardiogram 3 months prior to presentation with myocarditis. The electrocardiogram shows normal sinus rhythm with Q waves in V1 and V2 consistent with the patient's history of a previous anteroseptal myocardial infarction. (**b**) Initial electrocardiogram upon presentation to the emergency room with dyspnea and fatigue after which patient was diagnosed with myocarditis by endomyocardial biopsy. The electrocardiogram shows complete heart block with a ventricular escape rhythm. (**c**) Electrocardiogram after one dose of 1000 mg methylprednisolone showing sinus rhythm with recovery of atrioventricular conduction; however, a left bundle branch block persisted

Echocardiography

The echocardiogram is another noninvasive imaging modality to aid the clinician in the diagnosis of ICI-associated myocarditis [3, 29]. Echocardiography is fast, readily available, and relatively lower cost when compared to other imaging modalities, such as cardiac magnetic resonance (CMR) imaging. The ease of use of

echocardiography makes it ideal for serial evaluations of the heart to investigate changes in clinical condition [30]. With increased use of point-of-care ultrasound, also known as bedside echocardiograms, patients presenting in the emergency room can be quickly examined to look for the presence of a new pericardial effusion, which would raise suspicion for myocarditis [3]. Escudier et al. reported that three-fourth of patients diagnosed with ICI-associated myocarditis developed left ventricular dysfunction on echocardiography [20]. However, Mahmood et al. reported that ejection fraction was within normal limits in more than half of the patients who suffered ICI-associated myocarditis [17]. A normal ejection fraction in ICI-associated myocarditis is not necessarily a sign of a benign course, which is why it is important especially in these persons to proceed to tests such as cardiac magnetic resonance imaging (MRI) to find evidence of myocardial inflammation and fibrosis [26].

Overall, the clinical guidelines are not unanimous regarding obtaining baseline echocardiograms prior to initiating ICI therapy. ASCO guidelines regarding managing irAEs in patients on ICI therapy are neither in favor of nor against obtaining one prior to therapy initiation [9], likely reflecting the aforementioned results of studies showing that a normal ejection fraction will not necessarily identify nor predict course in a patient with ICI-associated myocarditis. In contrast, ASCO guidelines regarding general cardiotoxicity of any cancer therapeutic recommend obtaining an echocardiogram prior to starting any of the potentially cardiotoxic standard chemotherapies such as anthracyclines [31]. With how uncommon myocarditis is, there may not be a benefit for performing echocardiogram at baseline in all patients, and once better risk factors for myocarditis are found, it may be useful in a higher risk subset.

Much work is being made in the field of echocardiography to utilize more sensitive methods in detecting ICI-associated myocarditis before symptoms manifest [32]. In fact, one methodology, two-dimensional speckle tracking echocardiography (2D-STE)-derived strain and strain rate, can detect changes in myocardial mechanics before changes in LVEF occur, so it aims to find preclinical signs of ventricular dysfunction [30]. To do this, 2D-STE uses software to assemble a global assessment of LV myocardial mechanics using three spatial dimensions of cardiac deformation – longitudinal, circumferential, and radial strain and strain rate [30]. In studies of patients treated with anthracyclines, taxanes, and trastuzumab, 2D-STE has shown early decreases in global longitudinal, circumferential, and radial strain or systolic or early diastolic strain rate [33–37]. Hypothesizing that global longitudinal strain (GLS) will be decreased in patients receiving ICIs just like those receiving standard cardiotoxic chemotherapy, Awadalla et al. retrospectively compared echocardiographic GLS by speckle tracking in cases of ICI-associated myocarditis ($n = 101$) from a large international multicenter registry with controls ($n = 99$) [38]. The summary of findings was that GLS decreases in patients with ICI-associated myocarditis and, furthermore, lower GLS was strongly associated with major adverse cardiac events (MACE) [38].

Cardiac Magnetic Resonance (CMR) Imaging

Cardiac magnetic resonance (CMR) imaging is the gold standard diagnostic imaging tool for myocarditis in the noninvasive arsenal of available tests [25]. CMR is not often used as a frontline screening tool due to its expense, lack of availability in certain hospital settings, incompatibility with other patient-worn devices including implantable cardioverter-defibrillators and pacemaker leads, longer test completion length, and intra-hospital transportation considerations in patients who are critically ill requiring intensive care unit stays and multiple complex life support machines [32].

The 2018 Lake Louise criteria, as put forth by the *Journal of the American College of Cardiology* Scientific Expert Panel, detail the different parametric mapping techniques that may be used to diagnose myocardial inflammation in patients in whom myocardial inflammation is likely active [39]. The original Lake Louise criteria were published in 2009, centering on three diagnostic characteristics of myocardial tissue which are (1) edema, (2) hyperemia, and (3) necrosis/scar, as seen on validated CMR imaging techniques such as T2-weighted imaging, early gadolinium enhancement (EGE), and late gadolinium enhancement (LGE) [39]. Using the 2009 criteria, if two out of three of the criteria were met, then there was a high likelihood of the presence of acute myocarditis (inflammation) [40].

The updated 2018 Lake Louise criteria have been validated by multiple studies as having a high diagnostic accuracy, with one meta-analysis reporting both a high sensitivity and high specificity at 80% and 87%, respectively [41]. The criteria are founded on the following principle: evidence of inflammatory myocardial injury is seen based on at least one T2-based criterion (global or regional increase of myocardial T2 relaxation time or an increased signal intensity in T2-weighted CMR images) *and* at least one T1-based criterion (increased myocardial T1, extracellular volume, or LGE). Thus, the current Lake Louise criteria are as follows:

1. *Main criteria (2 of 2)*: CMR highly suggests myocarditis with great specificity if both *myocardial edema* and *nonischemic myocardial injury* are identified. However, if only one of these two is identified, myocarditis may still be identified under the appropriate clinical circumstances.
   (a) Myocardial edema identified with abnormal findings on T2 mapping or T2-weighted images
   (b) Nonischemic myocardial injury identified with abnormal findings on T1 mapping, LGE, or extracellular volume fraction
2. *Supportive criteria (suggestive, but not diagnostic)*: These criteria support a diagnosis of myocarditis in a clinical setting that lacks the 2 of 2 main criteria.
   (a) Pericarditis
      (i) Evidence of pericardial effusion or abnormal LGE/T2 or T1 findings in pericardium

(b) Left ventricular systolic dysfunction

(i) Regional or global wall motion abnormalities

While CMR is less sensitive than endomyocardial biopsy at diagnosing myocarditis [9], it can provide more certainty in the clinician's diagnosis of a patient with suspect ICI-associated myocarditis and obviate the need for invasive procedures [42].

When it comes to applying the CMR utility in the population of patients with ICI-associated myocarditis, there are some notable downfalls. In one series, 26% (8/31) patients diagnosed with ICI-associated myocarditis did not have LGE on CMR [17]. In another study, 77% (10/13) patients with the diagnosis of ICI-associated myocarditis who underwent CMR did not have LGE on CMR [20]. Using an international registry, Zhang et al. analyzed 103 ICI-associated myocarditis patients who also had a CMR and found that LGE on CMR was present in 48% overall, and elevated T2-weighted short tau inversion recovery (STIR) was present in 28% overall [43]. Delayed CMR imaging was noted to increase in sensitivity for detecting ICI-associated myocarditis as the presence of LGE was 21.6% when CMR was performed within 4 days of admission and increased to 72.0% when CMR was performed on day 4 of admission or later [43]. This data supports a possible explanation for patients with a negative LGE myocarditis, which is the scans were performed too early in the disease process to detect nonischemic myocardial injury. Fifty-six patients of the 103 registry patients in the Zhang et al. study had cardiac histopathology obtained, and LGE was present in 35% of patients with pathological fibrosis, and elevated T2-weighted STIR signal was present in 26% with a lymphocytic infiltration [43].

Endomyocardial Biopsy (EMB)

While CMR is the noninvasive diagnostic gold standard, endomyocardial biopsy (EMB) is the de facto gold standard test for the diagnosis of ICI-associated myocarditis [15, 32]. Historically, the histopathological diagnosis of myocarditis is based on the Dallas Classification System, devised in 1987 by eight cardiac pathologists known as the Dallas panel [13, 14]. The histopathological diagnosis of myocarditis is defined by myocyte necrosis and/or degeneration with adjacent inflammatory infiltrates [14, 44]. In ICI-associated myocarditis, immunohistochemical staining typically shows CD8+ T-cell infiltration intermixed with subsets of CD4+ T cells and CD68+ monocyte/macrophage lineages [24]. In addition, prominent expression of programmed death ligand 1 on immunohistochemical staining has been observed in areas of inflammatory infiltrate as displayed in Fig. 2.3 [24].

Biopsy comes with several technical considerations. Myocarditis often affects the myocardium focally with patchy immune cell infiltration, and thus sampling error can occur if biopsies are not obtained from areas of myocarditis [14]. Obtaining samples from the affected areas is critical, or there is a risk of false negatives [14, 24]. At least five different samples help increase the yield [45]. However, despite

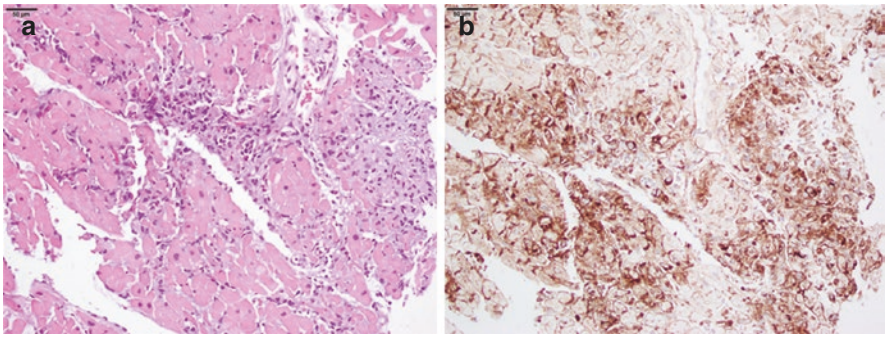

Fig. 2.3 Endomyocardial biopsy of a patient with immune checkpoint inhibitor-associated myocarditis. (**a**) Hematoxylin and eosin stain at 20× power lens showing inflammatory infiltrate and myocyte loss consistent with myocarditis. (**b**) Programmed cell death ligand 1 immunohistochemistry stain showing diffuse uptake in corresponding areas of inflammatory infiltrate

current practice to optimize yield with 4–6 biopsies and attempts at targeting biopsy location via triangulation with CMR, one postmortem analysis of myocarditis cases determined that more than 17 samples were actually needed in order to accurately diagnose myocarditis in >80% of cases [46]. This highlights the limitations in the sensitivity of the EMB, which is overall 70% in pure myocarditis cases [46]. Furthermore, 17 biopsies are neither feasible nor safe in clinical practice, and the number of biopsies obtained to achieve diagnostic answers must be balanced with the risks of EMB. The most concerning of risks is perforation, which is reported in <1% by experienced operators. Overall, an endomyocardial biopsy is typically performed in less than 15% of myocarditis cases due to the above limitations and effectiveness of studies earlier in the diagnostic algorithm at providing reasonable evidence of ICI-associated myocarditis [28, 47].

Management

Currently there are no studies or randomized controlled trials evaluating treatment options for ICI-associated myocarditis [1, 3]. Treatments will vary by institution and local expertise. Current recommendations borrow from treatment of other irAEs and cardiac allograft rejection treatment strategies. Treatment of ICI-associated myocarditis consists of a dual-pronged approach including cessation of the culprit immunotherapy agent and early initiation of immunosuppression consisting of glucocorticoids in the form of oral prednisone and intravenous methylprednisolone [3, 17, 48]. There are data to suggest that patients receiving higher doses of corticosteroids (1–2 mg/kg/day) early in their disease onset exhibit recovery of left ventricular function and experience less MACE [17, 20, 49]. In clinical practice, the average time from admission to administration of steroids in the retrospective series by Mahmood et al. was 21.4 ± 16 hours (range 1–60 hours) [17]. From this retrospective series, the suggested treatment is 1000 mg of methylprednisolone daily for 3

days as a standard starting dose, with 1 mg/kg daily of either oral or intravenous steroids thereafter and a rapid taper over 4–6 weeks or until symptoms improve to grade 1 [17, 50]. ASCO clinical practice guidelines support this regimen for treatment of irAEs, suggesting initiation of methylprednisolone 1–2 mg/kg with tapering over also at least 4–6 weeks, with allowance for re-escalation as clinically needed [9]. In patients receiving glucocorticoid doses equivalent to greater than or equal to 20 mg of prednisone daily for 1 month or longer, it is important to remember to prescribe concomitant pneumocystis pneumonia prophylaxis [1]. Trimethoprim sulfamethoxazole can be given as one double-strength tablet daily (or three times per week) or as one single-strength tablet daily in patients with normal kidney function [51].

There is no consensus on the standard duration of treatment length [9]. Downtrending levels of troponin, improvements in LVEF, and resolution of conduction abnormalities are markers that can indicate that the treatment is effective, but these goals can take more than 6–12 weeks to accomplish [1]. In fact, trials for viral myocarditis treatment include steroid durations of at least 12 weeks and up to a year [3]. For ICI-associated myocarditis, isolated case reports track troponin levels to assess steroid response and increase the taper doses and extend the treatment duration if the levels increase [3]. If this strategy is not effective, immunomodulators are the next medications in the treatment arsenal for ICI-associated myocarditis (Fig. 2.4) [3].

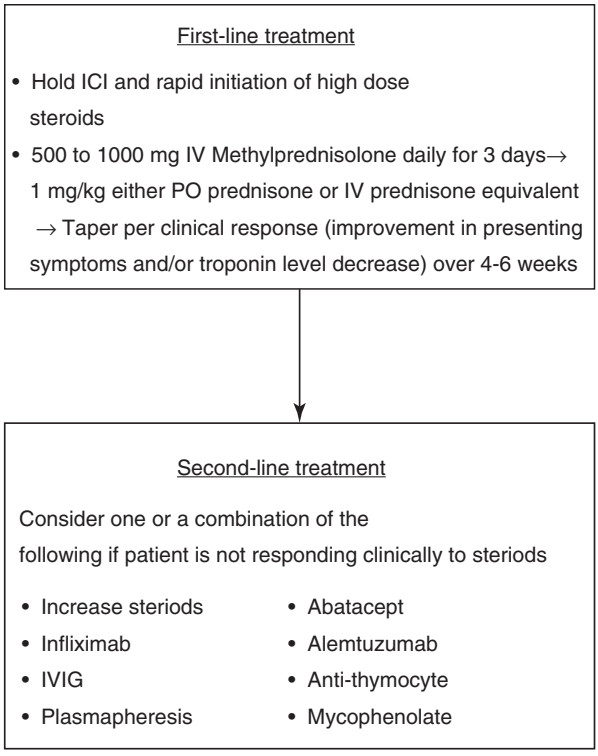

Fig. 2.4 Treatment options for immune checkpoint inhibitor-associated myocarditis

In patients who do not improve on high-dose steroids, there are second-line options as detailed in various case reports or case series [3]. Various institutions have used different immunologic medications in these cases including intravenous immunoglobulin (pleiotropic immunomodulating actions) [52–54], anti-thymocyte globulin (depletes T lymphocytes) [55], mycophenolate (powerful inhibitor of lymphocyte proliferation) [53], infliximab (monoclonal antitumor necrosis factor alpha antibody) [24], plasmapheresis [24, 56], alemtuzumab (CD52 monoclonal antibody) [57], abatacept (a CTLA-4 agonist which blocks CD86/CD80-CD28 interaction) [58], and belatacept (a second-generation form of abatacept with higher binding affinity to CD86/CD80) [1, 3]. The overall effectiveness of these agents is unclear, as their use has been documented in a limited number of cases. Additionally, patients whose disease course progresses on high-dose steroids are typically very ill, requiring intensive care unit level of care [53]. Infliximab should be used with caution in these critically ill patients as it can worsen heart failure in patients with acute decompensated heart failure, though this risk appears dose-dependent [59]. Given that preclinical studies have shown that serum levels of tumor necrosis factor alpha are elevated in patients with heart failure and that severity of disease corresponds with higher levels, Chung et al. did a preliminary investigation asking the question of whether infliximab, the antibody to this inflammatory cytokine, would be helpful in patients with moderate to severe heart failure [59]. The authors found that neither low-dose (5 mg/kg) nor high-dose (10 mg/kg) infliximab improved the patient's clinical heart failure symptoms despite effective suppression of cytokine levels, though the 5 mg/kg dose did confer a modest increase in ejection fraction [59]. Patients receiving 10 mg/kg infliximab had increased risk of death from any cause or increased hospitalization from heart failure that persisted for up to 5 months after the cessation of therapy, suggesting the dose-dependent nature of this therapy [59]. However, in diametric opposition to the infliximab data just presented and in spite of the black box warning of infliximab on its use in heart failure, Zhang et al. showed that in four of their patients with ICI-associated myocarditis who failed high-dose steroids and were in intensive care unit settings for acute decompensated heart failure or high-risk arrhythmia sequelae of their disease, a single dose of infliximab 5 mg/kg has been effective and safe [60]. All four patients survived their initial infliximab dosing without worsening heart failure [60]. Given the low numbers of patients involved in these cohorts or case reports secondary to low incidence of ICI-associated myocarditis, it is expected for future studies to often contradict each other, and once again, meta-analyses of more of these studies could help determine more definitive standards with regard to this second-line therapeutic.

Abatacept and belatacept, both classes of CTLA-4 agonists, work by inhibiting CD28-B7-mediated T-cell co-stimulation thus leading to rapid global T-cell deactivation, enacting a specific targeted reversal of the pathways that are activated by immune checkpoint inhibition [58]. Salem et al. used abatacept in a patient with metastatic lung cancer who had received three doses of nivolumab and subsequently developed myocarditis, with disease progression including troponin rise and high-burden ventricular ectopy even on high-dose intravenous methylprednisolone and plasmapheresis [58]. The introduction of abatacept reduced the troponin levels,

premature ventricular contractions, and myositis, allowing her to be discharged 2 months later [58]. Alemtuzumab is an antibody to CD52, which is present on the surface of mature immune cells and leads to complement-mediated destruction of these peripheral immune cells [57]. Esfahani et al. reported a woman with stage IV melanoma who developed ICI-associated myocarditis after receiving pembrolizumab with disease progression in the form of life-threatening arrhythmias despite high-dose steroids, mycophenolate mofetil, plasmapheresis, and rituximab [57]. Initiation of a single cycle of alemtuzumab rapidly depleted T cells and resulted in termination of the arrhythmia, normalization of inflammatory markers, and recovery from the intensive care unit setting [57]. While these single cases show signs of promise in these immunosuppressive agents, larger randomized controlled trials would be needed to determine efficacy and dosing of these second-line therapies for ICI-associated myocarditis [3].

In cases of ICI-associated myocarditis, the ICI should be held during any signs of toxicity, even mild ones, because of the high mortality tied with ICI-associated myocarditis [3]. This is in contrast with management of other organ system irAEs, in which the ICI can be continued in cases of grade 1 toxicity [9]. Based on very limited data, restarting an ICI is not recommended after occurrence of ICI-associated myocarditis [9], but this view is controversial, and there are studies that indicate that the risk of recurrence is not as high as first thought [1]. One case report supporting holding ICI therapy indefinitely due to the risks details a man with metastatic melanoma who developed nivolumab-induced myocarditis after ten infusions and recovered on high-dose steroids opted to proceed again despite risks of fatality with single-agent pembrolizumab and subsequently died from recurrence of ICI-associated myocarditis and its complications after only one infusion [61]. In defense of attempting a second round of ICIs, re-trial of an ICI was conducted in 4 out of 30 patients in the Escudier et al. cohort without incidence of repeat ICI-associated myocarditis [20]. With limited data to guide decisions on restarting an ICI after ICI-associated myocarditis, the decision is typically made on an individualized basis in a multidisciplinary discussion taking into account cancer status and prognosis, prior responses and cardiotoxicity to immunotherapy, availability of alternatives, and patient preference after an informed discussion [68 Ganatra]. In patients experiencing severe (grade 3) or life-threatening (grade 4) toxicities, permanent discontinuation of ICI therapy is recommended as risks far outweigh benefits [9].

Advanced Management

Patients with critical acute decompensated heart failure requiring advanced support due to ICI-associated myocarditis should be under care in the intensive care unit and managed according to the American College of Cardiology/American Heart Failure guidelines [62]. In addition to diuretic drips, pressors, inotropes, mechanical circulatory support, and life-threatening arrhythmia management such as pacemakers (temporary or permanent), patients like these should be considered for second-line

immunosuppressive therapies as described earlier on an individualized basis [3]. The general treatment principle for institutions regarding ICI-associated myocarditis is to treat as aggressively as possible as there are several cases of reversibility [60]. Goals of care discussions and palliative measures may also be appropriate depending on the clinical situation and multidisciplinary discussions with heart failure and cardiothoracic surgery and oncology [60].

Conclusion

With cancer surpassing cardiovascular disease as the major cause of mortality in some countries, treating cancer patients with immune checkpoint inhibitors is going to become more common [63]. ICI-associated myocarditis will become increasingly more relevant in the future as currently approximately 50% of the cancer population is eligible for immune checkpoint inhibitors [64]. The low frequency of ICI-associated myocarditis would almost be negligible in the consideration of giving ICI therapy were it not for its potential lethality [64]. Existing study outcomes vacillate with regard to positive or negative findings of certain treatments of ICI-associated myocarditis, as should be expected given the overall relatively low incidence of this irAE compared with others, making randomized controlled trials difficult to conduct. Future directions include gathering more extensive clinical data to guide standardization of diagnostic and therapeutic protocols versus institution- or experience-based protocols [64]. Benchwork and clinical translational laboratories involving biological samples from patients will play a large role in driving further illumination of the pathogenesis of ICI-associated myocarditis at the molecular and cellular levels, which will help guide the clinician's methodology of diagnosis and treatment of this important disease [64].

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Chapter 3
Dermatology (Skin)

Alexandria M. Brown, Wylie M. Masterson, and Anisha B. Patel

Abstract Immune checkpoint inhibitors (ICIs) are increasingly used in cancer therapy and can have unintended side effects affecting several organ systems. Immune-related cutaneous adverse events (irCAEs) are the most frequent and earliest toxicities to arise. The most common irCAEs include maculopapular/morbilliform rash, pruritus, eczematous dermatoses, urticaria, lichenoid reactions, psoriasiform eruptions, and vitiligo. Interestingly, irCAEs are associated with an improved tumor response rate and positive prognosis in melanoma patients. Most irCAEs are mild and reversible, but when severe, they can drastically affect quality of life and cancer treatment course. Treatment is still an active area of research and depends on the rash severity. Management options include observation, topical and systemic corticosteroids, and various biologic and immunomodulatory therapies. This chapter outlines the epidemiology, clinical characteristics, evaluation, and management of irCAEs following ICI treatment.

Chapter debriefing: Power point video presentation is provided at the end of the chapter.

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Abbreviations

AGEP	Acute generalized exanthematous pustulosis
BP	Bullous pemphigoid
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
DH	Dermatitis herpetiformis
DIF	Direct immunofluorescence
DRESS	Drug reaction with eosinophilia and systemic symptoms
EM	Erythema multiforme
ICI	Immune checkpoint inhibitor
irCAEs	Immune-related cutaneous adverse events
HLA	Human leukocyte antigen
MPR	Morbilliform/maculopapular rash
PD-1	Programmed cell death receptor-1
PD-L1	Programmed cell death ligand-1
PG	Pyoderma gangrenosum
PV	Pemphigus vulgaris
SCARs	Severe cutaneous adverse reactions
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis

Epidemiology

Immune checkpoint inhibitors (ICIs) were first approved by the Food and Drug Administration in 2011 for the use of ipilimumab in metastatic melanoma. This cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitor has since been used in various solid organ malignancies including, but not limited to, melanoma, non-small cell lung cancer, gastrointestinal cancer, and renal cell carcinoma. Its development was followed by programmed cell death-1 (PD-1) inhibitors and programmed cell death ligand-1 (PD-L1) inhibitors. More than 40% of melanoma patients treated with anti-PD-1 therapy are faced with immune-related cutaneous adverse events (irCAEs) [1]. ICI immune-related adverse events occur the earliest and most frequently on the skin [2]. They occur in up to 45% of patients on CTLA-4 inhibitors and up to 34% on PD-1/PD-L1 inhibitors [3]. Additionally, while dual ICI therapy with CTLA-4 and PD-1 combination blockade works synergistically to increase objective response rate and progression-free survival in advanced

melanoma patients, there is also an increased rate of all-grade dermatologic toxicities (59–71% with combination therapy vs. 42% and 55% with nivolumab and ipilimumab monotherapy, respectively) [1].

While the majority of dermatologic complications from ICI therapy are mild, reversible, and manageable with supportive care, severe-grade toxicities can result in significant morbidity and impact quality of life. Based on current data, less than 5% of toxicities are reported as grade 3 or 4 events and may require permanent discontinuation of ICI therapy [1]. The incidence of severe irCAEs is similar for CTLA-4 and PD-1 inhibitors (2.4% and 2.6%, respectively) [4]. One study suggested roughly 25% of patients on ICIs with irCAEs require temporary or permanent discontinuation of immunotherapy [5]. Therefore, it has been shown that early recognition and intervention reduce irCAE severity and duration and are essential to maintaining patients on their life-saving cancer therapy [6]. Due to the novelty of ICIs, data supporting best practices is still an active area of research.

Interestingly, the development of dermatologic toxicities in melanoma patients is associated with improved tumor response rates and can indicate a favorable prognosis [7–9]. Current evidence does not support a correlation between the different ICI dose regimens and irCAE development [1].

Clinical Characteristics

As ICIs continue to become a mainstay of cancer treatment, standardized reporting of irCAE type and severity will be imperative to ensuring proper clinical management and patient safety. Most clinicians delineate rash severity based on the Common Terminology Criteria for Adverse Events (CTCAE) (Table 3.1). Establishing risk factors associated with the development of irCAEs is still an active area of research. One study found an association between human leukocyte antigen (HLA) DRB1*11:01 and pruritus [10].

Clinical characteristics, average time to onset, and histopathology of common irCAEs are summarized in Table 3.2. The most common irCAEs include maculopapular/morbilliform rash (MPR), pruritus, eczematous dermatoses, urticaria, lichenoid reactions, psoriasiform eruptions, and vitiligo [11, 12].

Morbilliform/Maculopapular Rash (MPR)

A morbilliform eruption or maculopapular rash is the most commonly reported irCAE and can be seen with any of the ICI drugs (Fig. 3.1). While MPR is usually self-limiting (grades 1–2), in 4% of patients, it can progress to severe-grade (3–4) erythema multiforme (EM) or Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) [13].

Table 3.1 Common Terminology Criteria for Adverse Events – skin and subcutaneous tissue disorders – chart copied from the NIH CTCAE chart [100]

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10–30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self-care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Eczema	Asymptomatic or mild symptoms; additional medical intervention over baseline not indicated	Moderate; topical or oral intervention indicated; additional medical intervention over baseline indicated	Severe or medically significant but not immediately life-threatening; IV intervention indicated	–	–
Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10–30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital lesions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self-care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	-	-
Maculopapular rash	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10–30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL; rash covering >30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL	–	–

Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	–	–	–
Steven-Johnson syndrome	–	–	Skin sloughing covering <10% BSA with associated symptoms (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	Skin sloughing covering 10–30% BSA with associated symptoms (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	Death
Toxic epidermal necrosis	–	–	–	Skin sloughing covering >30% BSA with associated symptoms (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	Death
Urticaria	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10–30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	–	–
Other skin disorders	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Abbreviations: *BSA* body surface area, *ADL* activities of daily living

Table 3.2 Clinical and histopathologic characteristics of common immune-related cutaneous adverse events

Rash type	Clinical presentation (morphology and distribution)	Histopathology	Onset (weeks)	ICI association	Incidence (?)	TR (Y/N/NA)
Morbilliform/maculopapular	Erythematous macules and papules coalescing into blanchable patches and plaques. Variable pruritus Distribution: trunk and extensor surfaces of extremities [15] Face is usually spared [1, 101]	Superficial, perivascular CD4-predominant T-cell infiltrate with minimal epidermal change, papillary dermal edema, variable eosinophils, and dyskeratosis	3–6 [15]	Anti-PD-(L)1 Anti-CTLA-4	20% 49–68% [2, 13]	NA
Eczematous	Pruritic, erythematous, scaly, or crusted papules coalescing into plaques. Distribution: variable; typically, trunk and extremities with flexural preference	Prominent spongiosis with variable eosinophils [102]	3–6	Anti-PD-(L)1 Anti-CTLA-4	NA	NA
Urticaria	Pruritic, erythematous wheals. Distribution: variable	Lymphocytic, eosinophilic, and variable neutrophilic infiltrate with minimal epidermal change and an edematous dermis	Days	Anti-PD-(L)1 Anti-CTLA-4	Look at trials	NA
Lichenoid	Multiple, pruritic, discrete, erythematous, or violaceous colored papules and plaques. Distribution: normally chest and back, but may involve the extremities, palmoplantar surfaces, genitals, and oral mucosa with characteristic Wickham striae [15, 103]	Dense superficial band-like lymphocytic infiltrates in the upper dermis with vacuolar degeneration and scattered apoptotic keratinocytes. Eosinophils, parakeratosis, and spongiosis may also be present [103, 104]	6–12 [15]	Anti-PD-(L)1 Anti-CTLA-4	20% [2, 17] Less common [14, 105]	Y – Improved [106]
Psoriasiform	Well-demarcated, erythematous, papules and plaques with adherent scale. Distribution: trunk and extremities, scalp predilection	Acanthosis with elongation of rete ridges, parakeratosis, hypogranulosis, and a perivascular lymphocytic infiltration [26, 107]	3	Anti-PD-(L)1 Anti-CTLA-4	More Less [24]	Y [15]

Vitiligo	Multiple flecked macules of depigmentation that coalesce into larger patches. May have a preceding inflammatory phase [108]. Scalp hair, eyelashes, and eyebrow depigmentation can occur concomitantly or by itself [40]. Distribution: bilateral, symmetric, and photo-distributed [108]	Loss of melanocytes at the dermal-epidermal junction. CD4+ and CD8+ T lymphocytes can be seen in the perivascular areas and perifollicular areas and at the margins of vitiligo lesions [109]	Months	Anti-PD-(L)1 Anti-CTLA-4	11% 25% [15, 92]	Y – Improved mortality [8, 92, 110, 111]
Granulomatous dermatitis	Erythematous to apple-jelly-colored subcutaneous nodules. Other cutaneous findings include papules, coalescing plaques, annular lesions, isolated facial lesions, or tattoo sarcoidosis [98, 112–116]	Nodular to diffuse histiocytic infiltrate without evidence of organisms or foreign bodies [117, 118]	3–277 [117]	Anti-PD-(L)1 Anti-CTLA-4 [119, 120]	NA	NA
Bullous pemphigoid	Prodromal phase of pruritus followed by generalized or localized tense vesicles/bullae filled with serous or hemorrhagic fluid. Distribution: trunk and extremities [2]. Oral mucosa may be involved in 10–30% of cases [121, 122]	Subepidermal cleft with eosinophilic infiltrate. A characteristic linear deposit of IgG and C3 at the dermal-epidermal junction on DIF; however, this is not entirely specific for BP [116]	14 [2]	Anti-PD-(L)1	1% [31, 105, 122]	NA
Pemphigus vulgaris-like	Flaccid bullae and crusting	Suprabasal acantholysis, dyskeratosis, inflammatory infiltrate and eosinophils	NA	Anti- PD-1 [32]	NA	NA
Dermatitis herpetiformis[33]	Erythematous papules and vesicles. Distribution: usually extensor surfaces of the elbows, knees, and buttocks [123]	Neutrophilic infiltrate in the papillary dermal tips with variable subepidermal clefting and IgA deposition in the papillary dermis seen on immunofluorescence [76]	NA	Anti-CTLA-4 [33]	NA	NA

(continued)

Table 3.2 (continued)

Rash type	Clinical presentation (morphology and distribution)	Histopathology	Onset (weeks)	ICI association	Incidence (?)	TR (Y/N/NA)
SCARs (SJS/TEN) [34]	Fever, widespread rash, edema, vesicles/bullae/pustules, skin sloughing, and end-organ dysfunction	Full-thickness epidermal necrosis with minimal inflammatory infiltrate	1–20 [35]	Anti-PD-(L)1 Anti-CTLA-4	NA	NA
Erythema multiforme (EM) [29]	Targetoid lesions on the skin and mucous membranes, which may progress to EM major and other SCARs such as SJS [124]	Lymphohistiocytic infiltration along the dermal-epidermal junction with spongiosis and keratinocyte necrosis. Edema in the papillary dermis with potential subepidermal separation [125]		Anti-PD-(L)1 Anti-CTLA-4	NA	NA

Note: Treatment with immunomodulatory therapy should take cancer status into consideration with the oncology team

Abbreviations: *TR* tumor response in melanoma patients, *BID* two times a day, *GABA* gamma aminobutyric acid, *HCQ* hydroxychloroquine, *ICI* immune checkpoint inhibitor, *IL* interleukin, *IVIG* intravenous immune globulin, *JAK* janus kinase, *mg* milligrams, *MPR* maculopapular rash, *MTX* methotrexate, *NB-UVB* narrowband ultraviolet B phototherapy, *PO* by mouth, *SCARs* severe cutaneous adverse events, *TCS* topical corticosteroid, *TNF* tumor necrosis factor, *tx* treatment

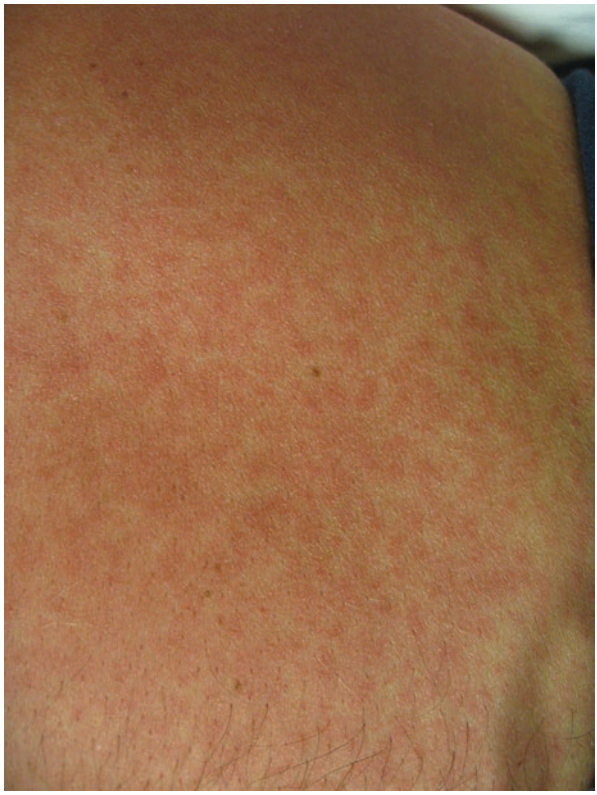

Fig. 3.1 Morbilliform eruption of the back

Pruritus

The second most common irCAE is pruritus, which often coexists with other irCAEs but can also be associated with normal-appearing skin [14]. Distribution commonly involves the scalp, with sparing of the face. Pruritus affects 11–21% of patients treated with anti-PD-1/PD-L1 therapy and up to 30% of patients treated with anti-CTLA-4 or dual ICIs and can severely impact quality of life [1, 15–17]. Symptoms are usually limited to grade 1–2 severity, with high-grade pruritus occurring in <3% of cases [14, 18].

Eczematous Dermatitis

Eczematous lesions are vulnerable to superinfection due to secondary micro-fissures and excoriations (Fig. 3.2).

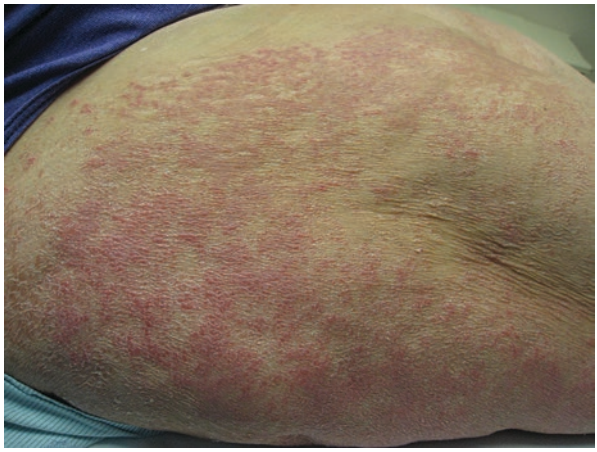

Fig. 3.2 Eczematous dermatitis of the abdomen

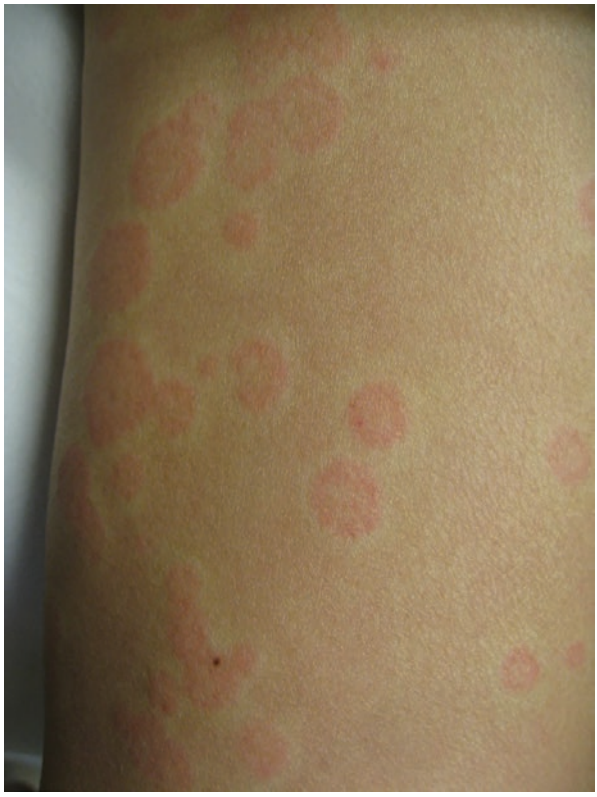

Fig. 3.3 Urticaria of the leg

Urticaria

Urticaria is the most common type 1 hypersensitivity reaction seen with ICIs (Fig. 3.3).

Lichenoid/Lichen Planus-Like Eruption

Lichenoid eruptions can have varied presentations including bullous or hypertrophic morphologies and oro-genital/mucosal or diffuse distributions (Fig. 3.4) [15].

Psoriasiform Dermatitis

Psoriasiform dermatitis most commonly presents as a reactivation in patients with a history of psoriasis, though it can also occur de novo [19–21]. Inverse, guttate, and palmar psoriasiform lesions as well as presentations of psoriatic arthritis have also been observed (Fig. 3.5) [19, 22, 23]. It is most frequently seen in patients being treated with PD-1/PD-L1 inhibitors, though it can also be seen with anti-CTLA-4 agents [24].

Fig. 3.4 Lichenoid dermatitis of the back

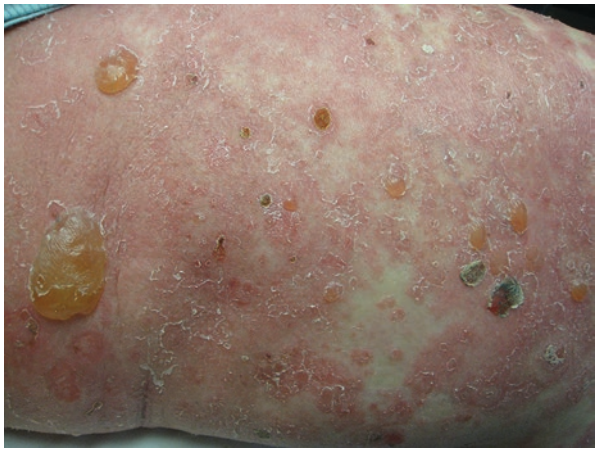

Fig. 3.5 Psoriasiform eruption of the leg with bullous pemphigoid

A psoriasiform eruption is strongly correlated with tumor response [15]. It is important to note that T-helper (Th) 17 lymphocytes have been shown to play an important role in the pathogenesis of psoriasis and are, in part, downregulated by the PD-1 pathway. Therefore, anti-PD-1 checkpoint inhibitors may increase Th17 activation, inducing psoriasis [25, 26].

Vitiligo

This irCAE is seen in up to 25% of patients being treated for melanoma and is uncommonly reported with other malignancies (Fig. 3.6) [14, 15, 27]. It does not appear to be dose related, and lesions often persist after treatment discontinuation [27].

Granulomatous Dermatitis

Granulomatous dermatitis may present as cutaneous disease only or part of drug-induced sarcoidosis. Systemic disease must be ruled out [28].

Xerosis

Xerosis occurs in 2–9% of patients with anti-PD-1/PD-L1 agents and usually does not progress past grades 1–2 [1]. This condition is characterized by dry skin and hyperkeratosis.

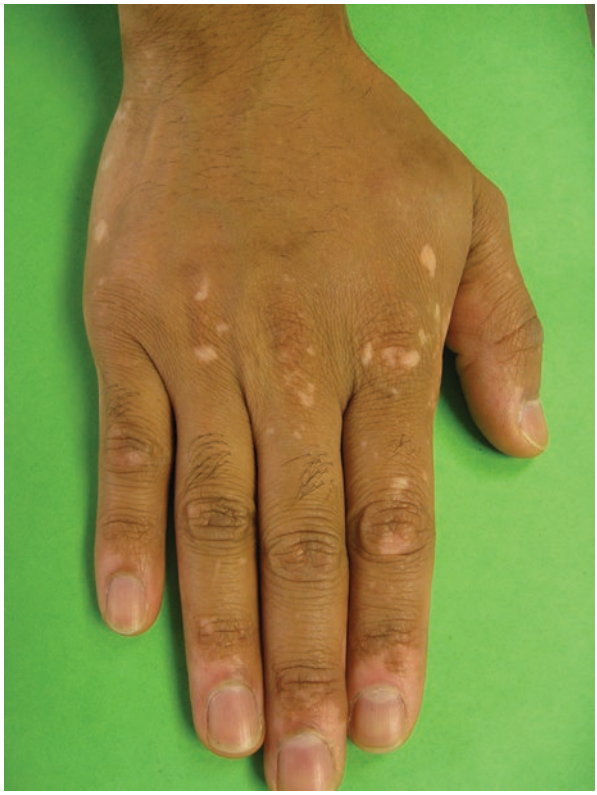

Fig. 3.6 Vitiligo of the hand

Autoimmune Bullous Disorders

They have been reported with PD-1/PD-L1 inhibitors [29].

Despite the lower incidence of bullous pemphigoid (BP) compared to other irCAEs, it is associated with a prolonged course with significant morbidity, often requiring permanent ICI discontinuation. A high degree of clinical suspicion should be maintained for BP eruptions in patients with pruritus or rash refractory to topical corticosteroids [30]. Persistent BP lesions have been reported to last several months after ICI discontinuation [31].

Pemphigus vulgaris-like lesions and dermatitis herpetiformis (DH) have also been noted [32, 33]. Development of DH is strongly associated with celiac disease. Gastrointestinal work-up should follow diagnosis of DH.

Severe Cutaneous Adverse Reactions

While severe cutaneous adverse reactions (SCARs) are rare (incidence estimated to be less than 1%), they can be life-threatening without proper intervention. SCARs include Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), erythema multiforme (EM), and drug reaction with eosinophilia and systemic symptoms (DRESS). In general, clinical presentation usually includes fever, widespread rash, edema, vesicles/bullae/pustules, skin sloughing, and end-organ dysfunction.

SJS/TEN has been most closely associated with ipilimumab and nivolumab combination therapy [34]. The mortality rate is 10% for SJS, 30% for overlapping SJS-TEN, and 50% for TEN [35].

Erythema Multiforme (EM)

Although more commonly associated with herpes simplex virus and mycoplasma pneumonia, EM can be seen after treatment with immunomodulators [29, 36].

Neutrophilic Dermatoses

Although less common, there have been several case reports of neutrophilic dermatoses with ICIs.

Sweet's Syndrome (Acute Febrile Neutrophilic Dermatosis)

Ipilimumab-induced Sweet's syndrome has been reported [37–39] with at least one additional case related to nivolumab [40]. This rash presents with erythematous edematous papules coalescing into plaques with variable pseudovesicles and is best diagnosed with skin biopsy showing a diffuse neutrophilic infiltrate and papillary dermal edema [37].

Pyoderma Gangrenosum

There have been two reported cases of ipilimumab-induced pyoderma gangrenosum (PG) [41, 42] and one case of a pyoderma gangrenosum exacerbation due to anti-PD-1 therapy [43]. Classic findings of PG include an ulceration with rolled

violaceous borders that may be preceded by pustules. Biopsy shows a diffuse neutrophilic infiltrate and infection must be ruled out.

Follicular Eruptions

Acneiform eruptions (or papulopustular folliculitis) can be induced or exacerbated by ICIs. Distribution normally involves the trunk. At least 12 cases have been reported for patients on anti-CTLA-4 therapy [44], and a few others have been reported with anti-PD-1/anti-PD-L1 therapy [2, 17, 45]. In addition, immune-related facial papulopustular rosacea can present as an exacerbation of preexisting rosacea [46–48]. Historically, acneiform eruptions are associated with EGFR inhibition and confer a clinical benefit. However, more data is required for ICI-related manifestations.

Rheumatologic Disease

Patients receiving ICIs may also present with new-onset rheumatologic diseases such as dermatomyositis, large-vessel vasculitis, Sjogren's disease, and cutaneous lupus erythematosus [49, 50]. It is unclear whether these manifestations are being unmasked or induced by the drug. It is, however, important to try to delineate whether a manifestation, such as dermatomyositis, is a result of a paraneoplastic disease or is a direct result of the ICI.

Dermatomyositis and polymyositis

Immune checkpoint inhibitor-related dermatomyositis presents with characteristic cutaneous lesions including violaceous lichenoid papules of the dorsal hands, upper back, upper chest, and photo-distributed areas. Skin findings can appear within the first cycle of ICI treatment and may or may not be associated with myositis. Several cases have been reported in patients on ipilimumab [51, 52]. Cases of polymyositis also have been described in all ICI drugs [23, 53–55].

Mucosal Toxicities

Mucosal toxicities include aphthous ulcers, stomatitis, mucositis, isolated salivary gland dysfunction (sicca syndrome), periodontal disease, and lichenoid reactions [56]. They can have a significant impact on quality of life and have mostly been

described with anti-PD-1/PD-L1 therapy [15]. Xerostomia has been reported at an incidence of 3–7% in patients on anti-PD-1/anti-PD-L1 therapy [14, 57]. Histology displays a salivary lymphocytic infiltrate with negative anti-SSA/SSB antibodies.

Mucosal lichenoid eruptions commonly present with characteristic reticulated white streaks (Wickham striae) with occasional plaque-like, atrophic, and/or erythematous lesions [17, 58, 59]. Differential diagnosis should always include candidiasis for patients receiving corticosteroids for other immune-related adverse events. Histologic analysis demonstrates a lichenoid interface dermatitis with lymphocytic infiltrate.

Periodontal disease usually manifests as periodontal pocket formation, alveolar bone resorption, and tooth loss [60].

Hair Toxicities

The most common ICI-related hair toxicity is alopecia areata, which can present as a partial (scalp and facial hair) or a diffuse universalis type [61]. It is seen at an incidence of 1–2% [3, 15, 62]. Onset typically occurs within 3–6 months of ICI initiation. The development of alopecia areata has been reported with a favorable ICI response and may represent another positive prognostic predictor, independent of vitiligo [63].

Clinically there are round alopecic patches of the scalp or the body. Histopathology generally displays a non-scarring alopecia with peribulbar lymphocytic inflammation [61]. Regrown hair commonly exhibits poliosis [61].

Other hair toxicities may include telogen effluvium or a change in hair texture (persistent curly hair) [64]. Additionally, a series of 14 lung cancer patients treated with anti-PD-1/PD-L1 therapies were reported to develop diffuse progressive hair re-pigmentation [65].

Nail irCAEs

While rare, nail toxicities include onycholysis, onychoschizia, paronychia, nail psoriasis, and nail lichen planus [14, 61].

Less Common irCAEs

Grover's Disease

Grover's disease (also known as transient acantholytic dermatoses) presents as diffuse, pruritic papulokeratotic, or vesicular eruption of the trunk. Lesions will appear fairly soon after treatment initiation and can last for several months after

discontinuation. Though rare, it has been reported with ipilimumab as well as anti-PD-1 therapy [66–69].

Keratoacanthoma/Cutaneous Squamous Cell Carcinoma

To date, there have been at least six patients with reported eruptive keratoacanthoma, a type of squamous cell carcinoma, while on anti-PD1 therapy [70–74]. Lesions improved with topical or intralesional corticosteroids with or without cryosurgery and did not require treatment interruption.

Evaluation

Many irCAEs represent or mimic common cutaneous diseases familiar to dermatologists. They are typically diagnosed by visual inspection of clinical morphology and biopsy with histopathologic examination, if needed. Wound and tissue cultures may be used to rule out infectious causes.

Diagnostic Tests for Specific irCAEs

Bullous Pemphigoid

The standard diagnostic work-up for BP includes performing serologic testing for BP antigens 180 and 230 and obtaining a biopsy that includes both the lesion and surrounding normal tissue for histopathologic evaluation and direct immunofluorescence (DIF). DIF findings demonstrate linear IgG and C3 deposition at the dermal-epidermal junction. Serologic testing by ELISA for circulating autoantibodies against the basement membrane components BP180 and BP230 has been shown to correlate with disease severity and can be used to monitor treatment response [75].

Dermatitis Herpetiformis

The standard work-up for dermatitis herpetiformis includes serology, biopsy, and direct immunofluorescence. ICI-induced DH may represent a dermatologic manifestation of celiac disease and should be kept into consideration. Transglutaminase 2 antibodies are useful in the diagnosis of celiac disease and can therefore aid in the diagnosis of DH. DIF will show granular IgA deposition in the papillary dermis [76].

Pemphigus Vulgaris-Like Lesions

In addition to clinical and histopathologic examination, pemphigus vulgaris (PV) can be diagnosed with immunofluorescence tests. DIF will show intercellular IgG and C3 deposition throughout the epidermis [77].

Urticaria

Urticaria is most often evaluated clinically. Current guidelines do not recommend further work-up; however, skin prick testing and IgE levels can be used for diagnosis when symptoms are severe [78].

Hair Toxicities

Diagnostic work-up typically includes clinical and histopathologic evaluation of the scalp, a hair pull test, and laboratory testing for secondary metabolic or vitamin deficiencies (i.e., thyroid-stimulating hormone, iron, ferritin, vitamin D, folate).

Rheumatologic Diseases

As discussed above, it may be hard to delineate when a new-onset rheumatologic disease is being caused or unmasked by the immune checkpoint inhibitor or if it is a manifestation of a paraneoplastic syndrome. Therefore, a thorough rheumatologic evaluation should be performed. Several laboratory tests can help narrow down a diagnosis including ANA, anti-dsDNA, anti-Smith, anti-histone, anti-RNP, ANCA, anti-SSA, and/or anti-SSB antibodies. Other laboratory tests may include creatine kinase, aldolase, ESR, CRP, and TSH.

Treatment

While the management of irCAEs is still an active area of research, the vast majority of rashes can be managed with observation and topical corticosteroids, if needed. Immune checkpoint inhibitor dosing can usually be maintained, and interruption is rarely needed [3, 79]. The American Society of Clinical Oncology (ASCO) and several other organizations/studies have proposed modified versions of the CTCAE to guide management of skin toxicities based on severity grading. Summary of treatment recommendations is presented in Table 3.3.

For severe-grade rashes, the current literature focuses on topical or systemic corticosteroid administration with potential reduction or cessation of ICI dosing. There

Table 3.3 Treatments for common immune-related cutaneous adverse events [14, 100]

Rash type	Grade 1	Grade 2	Grade 3+
MPR, eczematous	Face/axilla/groin: bland emollient, low-potency TCS BID Trunk/extremities: bland emollient, mid-potency or high-potency TCS[a] BID Continue ICI	1st line: high-potency TCS[a] BID 2nd line: low-dose oral steroids[b] +/- NB-UVB Continue ICI (consider dose delay until return to grade 1)	TCS + low- to high-dose oral steroids[b] for 4 weeks (with taper) Withhold ICI until rash is grade 1 or less Dupilumab
Pruritus	1st line: oral antihistamines +/- mid-potency TCS[a] BID Other topical options: camphor-menthol lotion, emollients, capsaicin lotion 2nd line: GABA analogs (pregabalin, gabapentin) Continue ICI		Aprepitant (80 mg/day × 5 days) If elevated IgE, then omalizumab
Urticaria	1st line: oral antihistamines + mid-potency TCS[a] BID 2nd line: oral steroids[b], dapsone, colchicine Continue ICI		Omalizumab Withhold ICI until rash is grade 1 or less
Lichenoid	See MPR	See MPR +/- acitretin (10–25 mg PO daily)	Consider phototherapy, acitretin, HCQ, MTX, apremilast, IL-17 inhibitor, and/or aprepitant Withhold ICI until rash is grade 1 or less
Psoriasiform	High-potency TCS[a] BID +/- oral antihistamines Continue ICI	Grade 1 tx +/- calcipotriene, acitretin, apremilast, NB-UVB Low-dose oral steroids, if needed Continue ICI (consider dose delay until return to grade 1)	Oral retinoids or biologics: IL-17, IL-23, IL-12/23, and TNF inhibitors (IL-23 first line) Withhold ICI until rash is grade 1 or less
Vitiligo	Recommend photoprotective practices (sunscreen, clothing/hats) Other options: high-potency TCS, NB-UVB, topical JAK inhibitors		
Bullous pemphigoid	High-potency TCS[a] Continue ICI	High-potency TCS[a] + oral antihistamine (1st line) or doxycycline +/- niacinamide (2nd line) or low-dose oral steroids (3rd line) Dose delay until rash is grade 1 or less	Grade 2 tx + high-dose oral steroids Other options: rituximab, omalizumab, IVIG, dupilumab, MTX, mycophenolate mofetil[c] Withhold ICI until rash is grade 1 or less
SCARs			Options: oral or IV steroids[b], IVIG, cyclosporine, TNF-alpha inhibitors Discontinue ICI

(continued)

Table 3.3 (continued)

Note: Treatment with immunomodulatory therapy should take cancer status into consideration with the oncology team

Abbreviations: *TR* tumor response in melanoma patients, *BID* two times a day, *GABA* gamma aminobutyric acid, *HCQ* hydroxychloroquine, *ICI* immune checkpoint inhibitor, *IL* interleukin, *IVIG* intravenous immune globulin, *JAK* janus kinase, *mg* milligrams, *MPR* maculopapular rash, *MTX* methotrexate, *NB-UVB* narrowband ultraviolet B phototherapy, *PO* by mouth, *SCARs* severe cutaneous adverse events, *TCS* topical corticosteroid, *TNF* tumor necrosis factor, *tx* treatment

[a] Mild-/low-potency topical corticosteroids include hydrocortisone 2.5% or desonide 0.05%
Mid-potency topical corticosteroids include triamcinolone 0.1%
High-potency topical corticosteroids include betamethasone dipropionate 0.05% and clobetasol dipropionate 0.05%

[b] Starting/low dose for oral systemic corticosteroids: prednisone 0.5–1 mg/kg/day; may increase to 2 mg/kg/day in grade 3 if needed. Grade 4 rashes should be treated with methylprednisolone 2 mg/kg/day

[c] These treatment options have only shown clinical benefit in anecdotal reports; prospective research on safety and efficacy still required

is consensus that most irCAEs resolve within 6–12 weeks of corticosteroid therapy. However, systemic steroids are not always a viable option if the patient has a prolonged or steroid-refractory dermatologic toxicity.

Additionally, there is concern that the early use of corticosteroids during ICI therapy may impair immunotherapy efficacy, negatively affecting the rate or quality of tumor response and reducing survival [80–85]. This, however, is an area of debate as other studies report no such effects for those receiving corticosteroids or other immunosuppressive therapies [3, 63, 84].

Alternatively, there is a growing body of clinical evidence that supports the use of targeted biologic immunomodulatory therapies for certain steroid-refractory irCAEs [86]. As ICI use continues to expand, it is important for clinicians to be able to recognize and offer nuanced treatment options for patients with steroid-refractory irCAEs. Since much of this evidence has been anecdotal and there is little data on the safety and efficacy of using these agents in ICI-treated patients, recommendations suggested in this chapter will be noted as such. More prospective data is required to support these alternative options.

Treatment Pearls

Pruritus

Management of pruritus includes oral antihistamines with or without the addition of medium-potency topical corticosteroids [15]. Other topical therapies include camphor-menthol lotion, moisturizing emollients, and capsaicin lotion. Second-line oral therapies with demonstrated efficacy include GABA analogs (i.e., pregabalin and gabapentin) [86]. Third-line oral treatment options include doxepin, selective

serotonin reuptake inhibitors (SSRIs), aprepitant, naloxone, marinol, oral steroids, dupilumab, and omalizumab. Aprepitant (80 mg/day for 5 days) has been efficacious in patients with refractory pruritus during nivolumab treatment [87].

Eczematous

For long-lasting severe-grade irCAEs, biologic therapy targeting interleukin-4 receptor alpha subunit (IL-4Ra) may be used [4].

Urticaria

Can usually be controlled with oral antihistamines and medium-potency topical steroids. Biologic therapies, such as anti-IgE monoclonal antibodies, can also be considered [4]. Second-line options include oral steroids, dapsone, and colchicine.

Lichenoid

Grade 2 rashes may be supplemented with acitretin 10–25 mg PO daily. High-grade toxicity management may include phototherapy, acitretin, methotrexate, apremilast, or hydroxychloroquine [14, 88].

Psoriasiform

Immunotherapy is typically able to be maintained with high-potency topical steroids and oral antihistamines [1]. Treatment may be escalated to involve vitamin D3 analogs, oral acitretin, oral apremilast, narrowband ultraviolet B (NB-UVB) phototherapy, or oral steroids. Refractory lesions may require oral retinoids or biologics [15]. Successful treatment with interleukin-7 (IL-17), interleukin- 23 (IL-23), IL-12/23, and TNF inhibitors has been reported in several cases [89]. Several patients who developed psoriatic arthritis with anti-PD-1 therapy were successfully managed with methotrexate in addition to oral corticosteroids and did not require treatment discontinuation [90, 91].

Vitiligo

Specific treatment is patient-dependent based on the impact of the disease; however, photoprotective practices are recommended. Treatment options include high-potency topical steroids, NB-UVB, and topical JAK inhibitors. The lesions typically do not resolve after cessation of immunotherapy [92, 93].

Bullous Pemphigoid

Grade 1 eruptions may be treated with twice daily high-potency topical steroids. Grade 2 and higher presentations may require the addition of an oral antihistamine (first line) or doxycycline +/− niacinamide (second line). Due to rash severity and impact on quality of life, most cases require treatment interruption and initiation of systemic steroids [33]. Refractory or severe-grade (3–4) bullous pemphigoid eruptions may benefit from the addition of rituximab [86, 94]. Early data suggests that it may not interfere with the antitumor activity of ICIs [88]. Other options which have shown anecdotal clinical benefit in several cases include omalizumab, IVIG, dupilumab, methotrexate, and mycophenolate mofetil [95].

Alopecia

Recommended treatment for alopecia includes high-potency topical steroids. Intralesional steroids (triamcinolone 0.1% 2.5–5 mg/cc) may be considered as well.

Mucosal Toxicities (Including Lichenoid Eruptions)

These lesions can be treated with topical corticosteroids and lidocaine in order to maintain immunotherapy dose intensity [96]. ICI interruption may be required.

Nail Toxicities

Good nail hygiene is recommended with clean and clipped nails, no lacquer, and minimal cuticle manipulation. Avoiding trauma to the fingers can also help decrease potential toxicities.

Neutrophilic Dermatoses

Neutrophilic dermatoses respond quickly to oral corticosteroids, although dapsone and colchicine are better long-term options [14].

Granulomatous

Grade 2 reactions may be treated with hydroxychloroquine 200 mg PO BID. Severe (grade 3–4) reactions may require doxycycline 100 mg PO BID, hydroxychloroquine 200 mg PO BID, and/or a TNF inhibitor.

SCARs

ICI discontinuation is mandatory. Treatment to reduce morbidity and mortality may include systemic corticosteroids, IVIG, cyclosporine, and biologic TNF-alpha inhibitors [15, 97].

Erythema Multiforme

Depending on the severity, EM can be treated with oral or IV steroids with drug cessation [4].

Sarcoidosis

The initiation of systemic corticosteroids will allow for exacerbations to regress. Isolated cutaneous eruptions can be treated with the addition of topical corticosteroids [98], intralesional steroids, and hydroxychloroquine.

Treatment Recommendations

No prospective studies have been done to support immunomodulatory therapies in the treatment of irCAEs. All recommendations are based on anecdotal data from the literature including case reports and case series. Ample tumor response data is not available at this time.

Although there are no prospective studies on immunomodulatory therapies for irCAEs, retrospective studies show that the use of these drugs does not blunt the tumor response. In fact, one study demonstrated a potential benefit to patients treated with immunomodulatory therapy [99]. Another study investigated tumor necrosis factor alpha inhibitors and concluded there was no negative impact on overall survival or time to treatment failure [84].

Long-Term Complication and Follow-Up

The large majority of patients on ICI therapy present with low-grade irCAEs that are easily managed until ICI completion. Fortunately, most irCAEs resolve and have no long-term sequelae. However, a small percentage of patients may present with severe-grade rashes requiring early cessation of ICI treatment [99]. This early cessation is problematic as it could result in malignancy progression. These severe

presentations may be successfully treated with immunosuppressive/immunomodulating agents (+/- ICI cessation), but the impact on malignancy progression is still an active area of research.

Some patients may experience rash recurrence upon restarting the ICI. This is variable in severity and timing and warrants close dermatologic follow-up. Most patients with severe-grade rashes follow up with their provider every 1–2 weeks until the rash is stable.

As discussed earlier, new research on tumor response data shows improved melanoma response rates associated with the development of dermatologic toxicities following ICI treatment [7–9, 99]. Additional evidence suggests that patients with grade 3 or higher rashes show an improved melanoma response rate compared to those with grade 1–2 rashes [99]. This topic is an active area of research.

Treatment Algorithm See Table 3.3.

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Chapter 4
Endocrine

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Abstract Immune checkpoint inhibitors have been approved for treatment of various malignancies. Endocrine dysfunction is one of the most common adverse effects and includes hypophysitis, thyroid dysfunction, insulin-deficient diabetes, and adrenal insufficiency. Diagnosis can be challenging as onset is variable and patients can have damage to more than one organ. However, if diagnosed appropriately and treated in a timely manner, the patients can continue immunotherapy. In this chapter, we present an overview of clinical presentation, diagnosis, management, and long-term follow-up of the more common endocrine adverse effects.

Keywords Hypophysitis · Thyrotoxicosis · Hypothyroidism · Adrenal insufficiency · Checkpoint inhibitor-induced diabetes

Abbreviation

^{18}FDG PET	2-(Fluorine-18)-fluoro-2-deoxy-D-glucose positron emission tomography
ACTH	Adrenocorticotropic hormone
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Anti-T-cell antigen-4
FSH	Follicle-stimulating hormone

Chapter debriefing: Power point video presentation is provided at the end of the chapter.

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IGF-1	Insulin-like growth factor 1
irAEs	Immune-related adverse events
LH	Luteinizing hormone
MRI	Magnetic resonance imaging
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid-stimulating hormone

Introduction

An increase in immune response induced by checkpoint inhibitor such as CTLA-4 antibodies (ipilimumab), anti-PD-1 antibodies (nivolumab, pembrolizumab), and anti-PD-L1 antibodies (avelumab, atezolizumab, and durvalumab) can lead to immune-related adverse events (irAEs) that can affect any organ system at varying severity. Endocrine adverse events include hypophysitis, thyroid dysfunction, adrenal insufficiency, and type 1 diabetes. Hypophysitis is most seen with CTLA-4 inhibitors, whereas thyroid dysfunction is commonly seen in patients receiving anti-PD-1 and anti-PD-L1 inhibitors. Type 1 diabetes is extremely rare and is also seen in patients receiving anti-PD-1 and anti-PD-L1 inhibitors. Combination therapies with different immune checkpoint inhibitors are associated with higher incidence of irAEs. Endocrine-related irAE can sometimes be reversible. Recovery of the gonadal and thyroid axis has been seen over time. However, adrenal axis and beta cell damage tend to be permanent resulting in lifelong adrenal insufficiency and type 1 diabetes.

Checkpoint Inhibitor-Induced Hypophysitis

Epidemiology

Hypophysitis is the inflammation of the pituitary gland caused by overactive lymphocytes. This ultimately leads to pathological damage to the gland causing hormonal dysfunction [1]. These patients present with one or more pituitary hormone deficiency and which may be accompanied by MRI abnormalities. Hypophysitis in the setting of immune checkpoint inhibitor therapy with CTLA-4 inhibitor was initially reported in 2003 and occurs in 0.4–17% of patients and can be related to the dose of the medication [2, 3]. The incidence increases from 0.5% with a dose of 3 mg/kg of ipilimumab to 18% when the dose is administered at 10 mg/kg. Incidence is also higher in patients receiving combination therapy with anti-CTLA-4 with anti-PD-1 therapy. It is quite rare in patients receiving single-agent anti-PD-1 or anti-PD-L1 therapy [4, 5].

The onset of symptoms of hypophysitis usually occurs around 10 weeks in patients treated with anti-CTLA-4 and variable with anti-PD-1 therapy with an average of 27 weeks. It can occur as early as 4 weeks when these agents are used in combination [6–8].

The pathophysiology causing hypophysitis in the setting of immune checkpoint inhibitor therapy is not well understood. Patients treated with CTLA-4 inhibitors were more likely to develop hypophysitis than patients treated with anti-PD-1 therapy alone [9]. Research in mice indicates the presence of circulating anti-pituitary antibodies and lymphocytic infiltration when treated with CTLA-4 inhibitors. Similarly, anti-pituitary antibodies were also observed in patients who developed hypophysitis [1, 10]. Variable levels of CTLA-4 expression were observed in the adenohypophysis. This variability could explain why some patients develop irAE while others do not and offer therapeutic options in some patients as shown by the report of an aggressive hyper-mutated ACTH-secreting pituitary carcinoma treated with immune checkpoint inhibitors [11].

Clinical Characteristics

Clinical symptoms tend to be nonspecific with fatigue and headache being the most reported symptoms. Visual defects can very rarely be seen when there is enlargement of the pituitary compressing the optic chiasm. Multiple hormonal deficiencies can occur simultaneously. The most common deficiencies are seen in TSH, ACTH, and gonadotropins. Diabetes insipidus is a very rare finding in immunotherapy-induced hypophysitis as the anterior hypophysis is mostly affected [9, 12].

Secondary adrenal insufficiency is the most common hormonal abnormality and is often permanent. Patients present with fatigue that is severe which is often accompanied by loss of appetite, GI symptoms (nausea, vomiting, abdominal cramps), and cognitive dysfunction. Secondary or central hypothyroidism and hypogonadism can be present at diagnosis, but these are often self-limiting with potential for recovery in the future. Other than hormonal abnormality, patients may present with hyponatremia as a result of hypothyroidism or cortisol deficiency.

Evaluation

Given the variation in onset and clinical symptoms, a high degree of clinical suspicion is needed to establish the diagnosis with appropriate biochemical testing and imaging with MRI of the pituitary (Table 4.1).

Adrenal insufficiency – ACTH and cortisol are best tested in the morning hours as ACTH is normally highest in the early morning (between 6 a.m. and 8 a.m.) and lowest in the evening (between 6 p.m. and 11 p.m.). It is also very important to remember that exogenous corticosteroids which are often used in cancer patients can impair the evaluation of the pituitary-adrenal axis. In such situation, tests should be undertaken only when the steroids are safely discontinued.

Patients with hypophysitis often have low or inappropriately normal ACTH in the setting of low cortisol. A cosyntropin or ACTH stimulation test can be useful in diagnosing adrenal insufficiency. Baseline cortisol is measured prior to administration of 250 mcg of cosyntropin intravenously. Cortisol is again measured in 30 minutes and at 60 minutes. A peak cortisol of less than 18 mcg/dl is suggestive of adrenal insufficiency. However, timing is important in interpretation of this test particularly in patients with new-onset central adrenal insufficiency as seen in immunotherapy-induced hypophysitis. They may have normal response to cosyntropin as it takes time for the adrenal glands to atrophy after hypophysitis [13].

Central hypothyroidism – patients with central hypothyroidism present with low or inappropriately normal TSH in the setting of low to undetectable free T4. A declining TSH usually precedes the diagnosis of hypothyroidism [9].

Central hypogonadism – it is often seen with low LH, FSH, and testosterone in men and low estrogen in premenopausal women. In postmenopausal women, LH and FSH will be inappropriately low as we would expect them to be elevated in the setting of estrogen deficiency. Patients may present with laboratory findings of central hypogonadism in the setting of acute and severe illness. Hence, a low testosterone in a hospitalized patient may not be indicative of central hypogonadism. When appropriate, testosterone levels will have to be checked at 8 a.m. as the levels peak in the morning hours and decline during the day [14]. Other pituitary hormone levels such as growth hormone and IGF-1 tend to be low in patients who are ill [9].

Imaging – pituitary enlargement can be seen in patients with immunotherapy-induced hypophysitis. Pituitary enlargement may precede the onset of symptoms of hypophysitis. Enlargement is mild and often resolves in weeks [9]. As radiology findings resolve relatively quickly, imaging of the pituitary may be normal by the time testing is undertaken. Hence, diagnosis is often based on clinical and biochemical findings.

Treatment

Central adrenal insufficiency should be promptly treated with steroid replacement at physiological doses such as hydrocortisone at 10–12 mg/m^2/day in two to three divided doses. High-dose glucocorticoids are not often necessary unless patients are critically ill or have severe symptoms of headache or visual compromise caused by the enlarging pituitary abutting against the optic chiasm. Since thyroid hormone can increase the clearance of cortisol, steroid therapy must be initiated before thyroid hormone replacement to prevent adrenal crisis. Steroid should be tapered off to a physiological dose upon clinical improvement [13].

Secondary/central hypothyroidism is diagnosed by the presence of normal or low TSH with low free FT4 levels. Full replacement with levothyroxine at 1.6 mcg/kg/day can be started in patients without underlying cardiac issues. In elderly patients

and in patients with severe cardiac issues, consider starting at partial replacement dose. Dose titration needs to be done by monitoring thyroid levels every 4–6 weeks. Caution must be used while interpreting TFTs as TSH is unreliable in these patients, and hence, T4 must be used to titrate the dose of levothyroxine [13].

Testosterone replacement in men and estradiol replacement in selected premenopausal women should be considered. Growth hormone therapy is contraindicated in patients receiving treatment for cancer. Recovery of the gonadal axis and thyroid axis have been observed. While down-titrating the dose of thyroid hormone can be easily done, it may be prudent to wait for recovery of the gonadal axis before committing to treatment.

Immunotherapy can be continued if patients are clinically stable and asymptomatic. Patients should also be on physiological doses of steroids: no more than 7.5 mg of prednisone or its equivalent daily (hydrocortisone 15–25 mg). There was no difference in outcome of hypophysitis in patients who were continued on treatment compared to those who discontinued immunotherapy. It is to be also noted that patients who developed hypophysitis may have better survival [9, 15].

Long-Term Complications and Follow-Up

Hypophysitis secondary to immunotherapy can lead to lifelong hormonal deficiencies. Central adrenal insufficiency seems to be permanent while there is recovery of central hypothyroidism and hypogonadism. Resolution of the central hypogonadism appears to be the most common finding [7].

As recovery of the adrenal axis is rare, all patients diagnosed with adrenal insufficiency will need to be counseled on sick day rules and stress dosing, which entails increasing the dose during illness and physiological stress. Patient should also be provided with an injectable high-dose steroid kit and instructed on how to administer the intramuscular injection during emergencies when they are unable to take oral hydrocortisone. Wearing a medical alert bracelet or necklace noting the diagnosis of adrenal insufficiency is recommended in all patients with adrenal insufficiency [13].

Thyroid Dysfunction

Epidemiology

Thyroid dysfunction is the most common endocrine adverse effect of immunotherapy and includes subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism, and overt hyperthyroidism or thyrotoxicosis. Thyroid dysfunction was

noted in approximately 7% of the patients receiving ipilimumab, 19% receiving anti-PD-1 and anti-PD-L1 inhibitors, and 28% receiving combination therapy [16, 17].

Hypothyroidism is a more common thyroid dysfunction. Patients treated with anti-PD-1 and anti-PD-L1 had more incidence of hypothyroidism as compared with anti-CTLA-4 therapy. Combination therapy was associated with the highest incidence. Similar differences were seen in thyrotoxicosis. It is to be noted that thyrotoxicosis was significantly greater in patients treated with anti-PD-1 as compared to anti-PD-L1 therapy. Among the anti-PD-1 drugs, incidence of thyrotoxicosis was higher for pembrolizumab as compared to nivolumab [16, 17].

The underlying mechanism of thyroid dysfunction is not well established and is typically due to a destructive thyroiditis. Histological evaluation showed chronic thyroid lymphocytic inflammation and formation of granulomas with destruction of follicles [18].

Thyroid antibodies including thyroid peroxidase (TPO) antibody and thyroglobulin (Tg) antibody have been found in several cases of immunotherapy-induced thyroid dysfunction. However, at the same time, several patients who develop thyroid dysfunction did not have elevated titers of thyroid antibodies. Some studies have shown that patients with preexisting thyroid antibodies are more likely to develop thyroid dysfunction [19, 20].

Clinical Characteristics

The symptoms of thyroid dysfunction are generally nonspecific with onset as early as 3 weeks after treatment to up to 10 months following therapy. Symptoms of hypothyroidism are fatigue, weight gain, and constipation. Patients may also complain of cold intolerance and edema. Severe hypothyroidism such as myxedema coma is very rarely seen but has been reported [21, 22].

Fatigue, palpitations, and weight loss are the most common symptoms of thyrotoxicosis. Occasionally patients may have other symptoms of hyperthyroidism such as heat intolerance, tremors, anxiety, and hyperdefecation. Elderly patients may present with new-onset atrial fibrillation. Severe thyrotoxicosis or hyperthyroidism resulting in thyroid storm is extremely rare [23, 24]. Thyrotoxicosis caused by immunotherapy-induced thyroiditis is self-limiting with rapid resolution and often resulting in hypothyroidism. Hyperthyroidism in these patients occurs due to release of preformed thyroid hormone during the thyroiditis phase. Occasionally thyrotoxicosis may be a result of Graves' disease where there is endogenous thyroid hormone production. In these patients, hyperthyroidism will be prolonged and persistent. Graves' disease including Graves' ophthalmopathy is extremely rare in patients treated with immunotherapy but has been reported [25, 26].

Evaluation

TSH and free T4 should be assessed simultaneously to distinguish between various types of thyroid disorders. Elevated TSH with low free T4 is the typical laboratory finding in patients with primary hypothyroidism. However, in patients with secondary hypothyroidism, both TSH and free T4 are low. This should raise the concern of hypophysitis and prompt an evaluation of the pituitary hormones particularly the pituitary-adrenal axis (Table 4.1).

Suppressed TSH with elevated free T4 and T3 is seen in thyrotoxicosis. Laboratory assay to look for thyroid-stimulating immunoglobulin, TPO, and thyroglobulin antibodies can be helpful in patients suspected to have Graves' disease [27].

Thyroid uptake and scan can help distinguish between thyroiditis and Graves' disease. However, it may be challenging in cancer patients as they often have imaging with iodine contrast resulting in a false-negative test. Other imaging modalities such as ultrasonography with color flow can be useful. In thyroiditis, there will be an enlargement of the gland - which may appear hypoechoic - and decreased glandular blood flow. Increased uptake on ^{18}FDG PET can be seen in destructive thyroiditis. It has also been noted that increased ^{18}FDG PET uptake in the thyroid before initiation of immunotherapy could be a marker for increased risk of developing thyroid dysfunction [28].

Treatment

Thyroiditis usually presents with self-limiting thyrotoxicosis and can be managed symptomatically with β-blockers. In severe cases of thyrotoxicosis secondary to thyroiditis, treatment with high-dose steroids may be indicated. After resolution of thyrotoxicosis, most of the patients develop hypothyroidism and hence will need thyroid hormone therapy when T4 levels dip below the normal range. Anti-thyroid drugs are not indicated unless Graves' disease is suspected [29].

Asymptomatic patients with primary hypothyroidism with mildly elevated TSH (<10 U/L) can be observed. When treatment is indicated, thyroid hormone therapy should be initiated at full daily replacement dose calculated as 1.6 mcg per kg body weight, and the patients should be monitored by checking TSH and free T4 every 4–6 weeks. Dose adjustments should be made to keep TSH and T4 in the normal range. In elderly patients or patients with underlying cardiac disease, consider initiating therapy at a partial replacement dose. In patients with secondary (central) hypothyroidism, TSH is often unreliable, and free T4 should be used as a guide for titrating thyroid replacement. Adrenal insufficiency should be ruled out prior to

initiating thyroid hormone therapy esp. in patients suspected to have hypophysitis [27, 30].

Baseline thyroid function tests along with regular monitoring of TSH and free T4 is recommended before each treatment cycle and should be considered when patients present with symptoms suggestive of thyroid dysfunction. Immunotherapy can be continued in patients with thyroid dysfunction. It can be briefly held if the patients have severe symptomatic thyroid dysfunction [31].

Long-Term Complications and Follow-Up

Hypothyroidism is the most common thyroid dysfunction and is often permanent requiring lifelong thyroid medications and follow-up. Therapy with levothyroxine is generally well tolerated and efficacious in resolving the symptoms of hypothyroidism and has an excellent safety profile. Levothyroxine is easily absorbed from the intestine, and patients can maintain stable levels if taken appropriately and regularly. The levels need to be adjusted to keep thyroid functions in the normal range. Increasing the dose based on symptoms alone can lead to overtreatment causing iatrogenic thyrotoxicosis which can result in adverse effects such as atrial fibrillation and osteoporosis [32].

Primary Adrenal Insufficiency

Epidemiology

Primary adrenal insufficiency or autoimmune adrenalitis is extremely uncommon with reported incidence of 0.9–4.2%. As with other endocrine irAEs, the incidence is higher with combination therapy. Primary adrenal insufficiency arises due to destruction of the adrenal cortex by immune cells [16].

Clinical Presentation

Patients are usually acutely ill and present with hypotension as a result of volume depletion, fever, and abdominal pain with nausea and vomiting. Laboratory studies show hyponatremia, hypokalemia, and hypoglycemia. Unlike adrenal insufficiency in patient with hypophysitis, these patients have high ACTH with low cortisol levels. These patients fail the cosyntropin stimulation test as the adrenal glands have been destroyed by immune cells. Other than cortisol deficiency, these patients also have aldosterone deficiency which is not seen in hypophysitis [33]. Caution must be

exercised in interpreting results as patients can have co-existing hypophysitis with primary adrenal insufficiency.

Treatment

Patients with primary adrenal insufficiency need replacement with glucocorticoids such as hydrocortisone (10–12 mg/m^2 of body surface area) and mineralocorticoids such as fludrocortisone (0.05–0.20 mg daily). During acute illness and stress, the steroids will need to be doubled or tripled based on the severity. Patients will need counseling on stress dosing, medical alert ID, and use of hydrocortisone injection [34].

Checkpoint Inhibitor-Induced Diabetes

Epidemiology

Diabetes was first formally described as a complication of checkpoint inhibitor therapy in 2015 when nivolumab and pembrolizumab entered clinical use [35, 36]. These patients developed a clinical condition analogous to type 1 diabetes, but with onset far more rapid than is traditionally seen in that condition, with many developing acute diabetic ketoacidosis (DKA) as their first sign of hyperglycemia. All patients developed evidence of insulin deficiency suggestive of immune destruction of beta cells requiring insulin therapy. Notably, there were only exceedingly rare reports of new-onset diabetes in patients treated with CTLA-4 inhibitors such as ipilimumab as monotherapy prior to the introduction of the PD-1 inhibitors [37].

New-onset type 1 diabetes was noted in some of the phase 3 trials for both pembrolizumab and nivolumab [38, 39]. However, the full clinical description and how hyperglycemia alone was distinguished from formal new-onset diabetes are unclear. Early cases in clinical trials may have been missed in part due to the lack of "diabetes" as a distinct reportable adverse effect of cancer therapy at the time. Initial trials typically reported hyperglycemia which has defined grades in CTCAE, but whether this hyperglycemia was associated with true insulin deficiency was not consistently reported.

Since that time, onset of diabetes was also reported in patients on the PD-L1 inhibitors avelumab, durvalumab, and atezolizumab. While the condition has been widely recognized, due to its rarity, a unified, formal description as well as how to formally diagnose, best treat, and prevent it remains unclear.

Checkpoint inhibitor-induced diabetes appears to be rare, and reported incidence varies depending on the methods of analysis. Estimates of incidence from single-institution studies range from 0.37% to 1.8%, although between studies the diagnostic criteria used, presence of preexisting type 2 diabetes, and whether all patients

who received any checkpoint inhibitor therapy, including monotherapy with CTLA-4 inhibitors, were included or just those who received PD-1 or PD-L1 therapy were variable [40–42].

A meta-analysis of 38 clinical trials of checkpoint inhibitors found sparse reporting of diabetes with only 13 cases giving an incidence of 0.2% [16], although this may be reduced in comparison to the case series studies due to inclusion of CTLA-4 monotherapy trials. An analysis of the FDA Adverse Event Reporting System between 2015 and 2019 found 735 patients with new-onset diabetes or development of diabetic ketoacidosis not thought due to type 2 diabetes, giving an incidence of 1.2% [43].

The patient populations appear to be typical of the populations receiving CPI therapy with incidence too low to confidently make broader conclusions regarding demographics. Generally, there is a slight predominance of males and significant predominance of Caucasians, although this likely reflects the high percentage of patients treated for melanoma. In cases reported to the FDA, the median age was 66 years, with a wide range from 15 to 95 years [43].

The timing of onset of checkpoint inhibitor-induced diabetes, in comparison to other irAEs, appears to be more variable. The reported range varies widely with onset after 1–78 cycles of treatment in one case series [40]. From a larger meta-analysis of studies, most cases, 71%, onset within the first 3 months of therapy with median time to onset of 49 days, although cases after more than a year of treatment were also noted in this analysis [44]. The presence of type 1 diabetes-associated autoantibodies is also associated with more rapid onset of hyperglycemia [42, 44].

Some of this heterogeneity may be because hyperglycemia is a late finding in patients with beta cell damage. A small portion of beta cells can produce enough insulin to maintain euglycemia in an otherwise insulin-sensitive person, and the vast majority (80–95%) of beta cells are lost by the time clinically significant hyperglycemia is present. Thus, the underlying rate of beta cell loss may be a larger determinant of time to symptom onset than the timing of the onset of the inflammatory attack itself. At present, there is not a proven measure of early beta cell damage in this patient population.

HLA typing was performed on a subset of patients in one case series which showed a predominance of HLA-DR4, a haplotype associated with type 1 diabetes, in 76% of those tested. Other haplotypes associated with diabetes such as HLA-A2 and HLA-DR3 were present, but not at rates higher than what has been reported in Caucasian populations in the United States [40]. This may represent the most consistent method to identify patients at risk of development of checkpoint inhibitor-induced diabetes and could guide future prospective studies. Concurrent irAEs are common with additional adverse effects reported in up to 62% of patients [41].

Clinical Characteristics

The result of most cases of checkpoint inhibitor-induced diabetes is like type 1 diabetes: absolute (or near absolute) insulin deficiency. However, whether this represents the same clinical entity is debated. Immune-mediated diabetes itself is likely a spectrum of diseases, and where checkpoint inhibitor-induced diabetes falls on that spectrum remains unclear.

The pathophysiology of immune-mediated diabetes has been studied extensively in efforts to delay or prevent this life-altering condition. It can be helpful to understand this underlying pathophysiology to better understand checkpoint inhibitor-induced diabetes.

Links between the PD-1/PD-L1 pathway and type 1 diabetes were recognized prior to any clinical use of checkpoint inhibitors for cancer therapy. Knockout of PD-1 in the nonobese diabetes mouse model of type 1 diabetes showed rapid onset of diabetes before the timeframe typical of the model [45]. Antibody-mediated inhibition of the pathway also accelerated diabetes development which was independent of the presence of antibodies [46]. In the same study, blockade of CTLA-4 induced diabetes only in neonate mice. This is consistent with clinical observations that checkpoint inhibitor-induced diabetes is primarily seen with PD-1 and PD-L1 inhibitors and not consistently with CLTA-4 monotherapy.

Immune-mediated diabetes not related to checkpoint inhibitors is typically broken down into several subcategories. Type 1 diabetes affects primarily children and young adults. There is a well-described pre-symptomatic phase of beta cell autoimmunity with gradual development of asymptomatic dysglycemia prior to development of symptomatic diabetes which can take years to decades [47].

Several antibodies are associated with type 1 diabetes and target antigens in islet cells. Antibodies to glutamic acid decarboxylase (GAD-65), insulinoma-associated protein 2 (IA-2), zinc transporter 8 (ZnT8), and insulin itself are typically screened and identified in up to 85% of patients with type 1 diabetes [48]. Of note, insulin antibodies rapidly become positive in people taking insulin injections and are only useful in patients who have never taken insulin. A subset of people with type 1 diabetes do not have measurable antibodies or a clear autoimmune response and are sometimes termed type 1B or idiopathic type 1 diabetes.

Latent autoimmune diabetes in adults (LADA) is a similar condition to type 1 diabetes but has a more gradual course in older adults and is often mistakenly diagnosed and treated as type 2 diabetes. Characteristics of the group are heterogeneous, but the presence of anti-GAD-65 antibodies has been associated with more rapid progression and lower c-peptide levels [49]. Fulminant diabetes, or fulminant type 1 diabetes, is a relatively recently recognized condition of extremely rapid onset of insulin deficiency which has been best described in Japanese populations [50]. Fulminant diabetes is typically not associated with antibodies, and due to its rapid

onset, hemoglobin A1c levels are typically normal, and amylase and lipase levels are elevated, suggestive of an acute inflammatory process in the pancreas beyond the islets.

Onset of hyperglycemia in checkpoint inhibitor-associated diabetes is very rapid in most cases with little warning before onset of hyperglycemia. The rate of beta cell loss appears to be far more rapid than type 1 diabetes with consistent progression to absolute insulin deficiency. While type 1 diabetes traditionally has a "honeymoon period" after diagnosis where no or little insulin is required due to residual beta cell function, this is not typically seen in checkpoint inhibitor-induced diabetes, suggestive of advanced beta cell destruction at diagnosis.

Diabetes-associated antibodies are present in around half of cases: 40–71% of patients in two case series and 43% of patients in one meta-analysis, with GAD-65 detected most consistently [40, 41, 51]. In clinical trials where pre-treatment serum samples were available for analysis, both preexisting autoantibodies and new development of antibodies have been detected [40]. Diabetic ketoacidosis (DKA) on presentation is common, around half of patients in most studies and up to 67.5% in one review [51]. DKA occurs when severe insulin deficiency leads to metabolic deterioration and can be life-threatening if not urgently addressed. Onset of hyperglycemia can be so rapid that DKA can develop between cycles of therapy without significant preceding hyperglycemia.

Evidence of pancreatitis such as elevated amylase and lipase levels has been reported in a subset of patients (51% in one review) although notably pancreatitis itself as an irAE was only diagnosed in 4% of patients [51]. Reporting of amylase/lipase level is also variable in the literature. However, acute DKA can also cause transient mild amylase/lipase elevation, and some of these patients may not have clear clinical pancreatitis [52]. A separate analysis of patients referred to gastroenterology for checkpoint inhibitor-associated pancreatitis with persistent amylase and lipase elevation noted new-onset diabetes in 7% of patients [53] suggesting that there is only slight overlap between the two conditions.

Hemoglobin A1c values on presentation are used to give an estimate of chronicity of the patient's hyperglycemia. As glucose is non-enzymatically bound to proteins such as hemoglobin at a concentration-dependent rate, the percentage of glycosylated hemoglobin estimates overall glucose over the lifespan of erythrocytes, typically 3 months. Reported A1c values on presentation also have a wide range (5.8–13.1%, median 7.8%) suggesting heterogeneity to the rate of onset of hyperglycemia [51].

Given the rapid onset, clinical presentation of CPIDM is like fulminant diabetes in many respects and is classified as such in many reports [21]. Others have proposed that it represents a new clinical entity, distinct from our current classification schemes [54]. Others argue that the relatively high frequency of HLA types and antibodies associated with type 1 diabetes suggests that at least a subset of patients have some underlying risk factors for traditional type 1 diabetes and may have a similar, albeit accelerated, pathophysiology [40, 41]. It is certainly possible that these patients represent a mixture of these various conditions with acute acceleration of the underlying process by the more aggressive autoimmune response

stimulated by PD-1 or PD-L1 inhibitors, including other rare occurrences such as immune-mediated lipodystrophy or insulin resistance [51, 55]. Further research and classification of these patients will aid in better defining and describing this condition in the future.

Evaluation

Patients will typically present with typical symptoms of hyperglycemia such as polyuria, polydipsia, weight loss, and blurred vision. Patients with diabetic ketoacidosis may also have vomiting, weakness, shortness of breath, signs of dehydration, abdominal pain, and classic fruity breath odor. Mild hyperglycemia may be present on routine testing at each cycle of therapy, and any new onset or acute worsening of hyperglycemia should be investigated as early intervention with insulin can prevent development of DKA.

Currently, there is no clearly defined diagnostic criteria for checkpoint inhibitor-induced diabetes, and much is left up to clinical judgment. Most studies use a general presentation of new-onset or worsening hyperglycemia requiring insulin therapy and evidence of insulin deficiency as suggested by low or inappropriately normal insulin or c-peptide levels. Presentation with evidence of diabetic ketoacidosis without an alternative cause is essentially diagnostic of the condition. Presence of autoantibodies is also highly suggestive. Given the clinical difficulty in interpreting this diagnosis and initial dosing of insulin, early consultation with an endocrinologist should be considered if possible.

Initial assessment with serum glucose level, metabolic panel, and serum or urine ketones can determine presence of DKA (Table 4.1). C-peptide and diabetes-associated autoantibody levels (insulin, GAD-65, IA-2, and ZnT8) should be sent, but these tests are often sent to reference labs and may not be available for immediate decision-making. Insulin levels can be used at the time of initial diagnosis but are unreliable for patients already taking insulin due to variable cross reactivity of clinically used insulin formulations with most insulin assays. C-peptide is co-secreted with insulin by pancreatic beta cells and is a more reliable long-term method of monitoring endogenous insulin production.

Preexisting type 2 diabetes, or undiagnosed LADA, represents a difficult clinical scenario as changes in diet, missed medications, or natural progression of diabetes may worsen hyperglycemia without an acute change in endogenous insulin production. Thus, the rate of change in overall glycemic control can be informative, and a good diabetes history is essential. Large postprandial hyperglycemic excursions may suggest insulin deficiency due to insufficient functional beta cells to produce insulin bursts in response to glucose. While development of CPI-induced diabetes in patients with preexisting diabetes has been described, inclusion of these patients in descriptive studies is variable as it can be difficult to distinguish normal progression of type 2 diabetes, particularly in patients treated with high doses of steroids. Although new-onset diabetes is more common, patients with preexisting type 2

diabetes accounted for 12.5% of patients in one review, and close monitoring of these patients' glycemic control is warranted [51].

Treatment

Given the risk of ketoacidosis and the rate at which hyperglycemia can progress, early therapy with insulin should be considered for any patient with otherwise unexplained hyperglycemia. Often, gathering the necessary data to determine the presence and persistence of insulin deficiency takes time, and a definitive diagnosis may not be clear immediately. Reassessment of glycemic control on insulin therapy with simultaneous serum glucose and c-peptide levels over time can guide if progressive beta cell loss has occurred.

DKA requires aggressive therapy including IV hydration, IV insulin, and correction of electrolyte imbalances, typically treated in an intensive care unit according to the institution's protocol. After resolution of DKA, patients with suspected CPI-induced diabetes should be maintained on a full insulin regimen due to the high likelihood of permanent insulin deficiency. Although DKA in this scenario may be due to insulin deficiency alone, patients should be assessed for an underlying trigger for the episode such as infection.

Patients with suspected or confirmed CPI-induced diabetes should be treated with a full basal/bolus insulin regimen for safety. This includes both a long-acting insulin analog such as glargine, detemir, or degludec and a rapid-acting insulin analog such as lispro, aspart, or glulisine. Older human insulins can be used if cost is prohibitive but are not preferred due to higher risk of hypoglycemia. Rapid-acting insulin should be given both to compensate for the carbohydrate content of food and to correct hyperglycemia. If CPI-induced diabetes is ruled out, treatment can be adjusted for progressive type 2 diabetes or steroid-induced hyperglycemia as indicated. Insulin doses should be individualized to each patient, but in studies, typical doses required are consistent with insulin deficiency rather than resistance with median dose follow-up at 0.49 units/kg/day reported with range of 0.2–1.03 [42]. It is possible that patients with preexisting type 2 diabetes may have underlying insulin resistance and require higher doses.

Diabetes education is required at the time of initial treatment with insulin, either after admission for DKA or as an outpatient, to ensure safe blood glucose monitoring and insulin injection technique. Teaching on avoidance and treatment of hypoglycemia should also be performed for any patient on insulin. Glucagon, either as an injection or a nasal spray, can be a lifesaving rescue treatment for severe hyperglycemia, and family members should be educated on its use.

There are no current consensus recommendations on holding or discontinuing checkpoint inhibitors after development of diabetes. The American Society of Clinical Oncology suggests consideration of a hold on treatment for grade 2 (fasting blood glucose >160–250 mg/dL) hyperglycemia and holding therapy for grades 3–4 (fasting glucose >250–500 mg/dL and >500 mg/dL, respectively) [27]. However, no

clear guidance on distinguishing type 1 from type 2 diabetes is given. They suggest resuming treatment when hyperglycemia is controlled at grade 1 (fasting glucose >160 mg/dL) or less.

The National Comprehensive Cancer Network, in comparison, recommends holding therapy after development of DKA but continuing in all other situations with treatment of diabetes as indicated [56].

There is currently no evidence to suggest that holding checkpoint inhibitors increases rates of recovery from insulin deficiency. Given the near-universal lifelong dependence on insulin therapy in reported cases other than rare reports of recovery, there does not appear to be a significant impact.

In type 1 diabetes, beta cell loss is quite advanced at the time of hyperglycemia as only a small proportion of beta cells are required to maintain euglycemia. Thus, unlike many irAEs, treatment focuses on replacing the lost hormone rather than directly reducing the causative immune response. High-dose corticosteroids, the mainstay of initial therapy for irAEs, acutely worsen hyperglycemia and could worsen or induce DKA in newly diagnosed patients.

In published case series, a subset of patients developed hyperglycemia while on steroids which persisted with evidence of insulin deficiency after steroids were withdrawn suggesting that the condition can onset or worsen while on steroid therapy [40, 42]. Other groups have attempted high doses of steroids without any other irAEs without recovery of beta cell function [57].

Therapies to eliminate or delay the autoimmune attack in people with early stage type 1 diabetes have been widely researched, but few have proven successful. These studies are typically performed in patients who have known antibody positivity and high risk for type 1 or very recently diagnosed diabetes through the Type 1 Diabetes TrialNet group. However, the timeframe to clinically significant beta cell loss in these patients is often on the order of years. Whether these therapies would be successful in the setting of the more rapid beta cell loss in checkpoint inhibitor-induced diabetes is unclear at this time.

Despite this, there have been some published reports of recovery, either spontaneous or induced by medication. Notably, in two cases of spontaneous recovery, the patients did not develop DKA, and c-peptide levels remained normal despite development of hyperglycemia [55, 58]. Given these findings, holding CPI therapy could be considered in patients without DKA and with normal c-peptide levels to evaluate for resolution, but a permanent hold on therapy should be weighed against possible benefit in cancer response. Another group reported resolution of hyperglycemia in a patient after he was treated for checkpoint inhibitor-induced seronegative arthritis with infliximab [59]. However, prior use of systemic and intraarticular steroids in this patient clouds his presentation somewhat.

Some of our knowledge may be limited by an overly narrow diagnostic criteria, and there may be forms of checkpoint inhibitor-induced diabetes which have not been fully recognized including more gradually progressive beta cell loss or potentially transient injury which resolves with time. In these cases, holding checkpoint inhibitors or anti-inflammatory therapy may prove more effective. Further research on risk factors, detection of early beta cell damage, and effective

anti-inflammatory therapy could provide therapeutic options for a subset of these patients in the future.

Long-Term Complications and Follow-Up

For most patients who develop permanent beta cell loss, lifelong insulin therapy will be required to prevent DKA and the long-term complications of uncontrolled hyperglycemia. As with patient with insulin deficiency due to type 1 diabetes, insulin doses must be adjusted both to account for the patient's requirement due to weight and degree of insulin resistance and per meal to account for variable carbohydrate intake. Extensive long-term diabetes education including carbohydrate counting is required to achieve good glycemic control. Modern diabetes technology such as continuous glucose monitors and insulin pumps can also aid in glucose control and assist in the prevention of hypoglycemia.

It can be difficult, but possible, for these patients to achieve good glycemic control. Less data is available on long-term management of these patients, but in one case series, average A1c values after follow-up ranged from 6.1% to 9.2% [42]. Doses of insulin require adjustment with changes in weight and oral intake and particularly if high-dose steroids are required for treatment of other irAEs or as part of subsequent cancer therapies.

Patients who have extended remission of their underlying malignancy should start preventative care for complications of diabetes including lipid testing and possible high-intensity statin therapy, annual dilated eye exams, foot examinations and monofilament testing, and urine microalbumin screens for early nephropathy. Target A1c levels in these patients should be determined individually depending on age, prognosis, comorbidities, and risk of hypoglycemia.

A subset of patients may have damage to exocrine pancreatic cells and could be at risk of long-term exocrine deficiency and issues with malabsorption. In one study, atrophy of pancreatic volume was noted in all patients on serial CT scan with median loss of 16% immediately following diagnosis of diabetes and 31% at long-term follow-up [42]. Although this is also seen in type 1 diabetes, beta cells are known to make up a small proportion of total pancreatic mass, suggesting that there is some loss of exocrine pancreatic tissue. Assessment for exocrine pancreatic insufficiency should be considered for patients with suggestive symptoms or weight loss despite insulin therapy.

Like other irAEs, patients who develop diabetes appear to have a higher rate of response to therapy with a meta-analysis showing 22.7% of patients with progressive disease, 19.3% stable disease, and 58% partial or complete responses to therapy [51]. However, numbers are currently too small to differentiate between different cancer types and forms of checkpoint inhibitors (Table 4.1).

Table 4.1 Summary of immunotherapy-associated endocrine dysfunction

Disease condition	Clinical presentation	Evaluation	Treatment
Hypophysitis	Patients may be asymptomatic Headache and fatigue Hypotension and hyponatremia in the setting of adrenal insufficiency	Labs a.m. ACTH, cortisol TSH with free T4 LH, FSH, estrogen in women, and testosterone in men Prolactin Growth hormone and IGF-1 Imaging MRI of the pituitary	Central adrenal insufficiency Hydrocortisone at 10–12 mg/m^2/day in 2–3 divided doses Central hypothyroidism LT4 at 1.6 mcg/kg daily Start at 50% of dose in older patients and those with cardiovascular comorbidities Hypogonadism Most patients recover their gonadal axis, and hence it's advisable to wait and watch for recovery When there is no recovery, consider estrogen in premenopausal women and testosterone in men if there are no contraindications Growth hormone therapy is not an indication in patients with malignancy
Thyrotoxicosis	Patients may be asymptomatic Headache and fatigue Hypotension and hyponatremia in the setting of adrenal insufficiency	Labs TSH, free T4, and T3 TPO, TSI, and TRAb in patients suspected to have Graves' disease Imaging Ultrasound. Thyroid appears hypoechoic and with decreased vascularity Radioiodine uptake scan (very rarely used when hyperthyroidism such as Graves' disease)	Symptomatic management with beta-blockers Anti-thyroid medication is not useful except in the setting of hyperthyroidism Patients tend to develop hypothyroidism and hence need to be monitored and treated accordingly

(continued)

Table 4.1 (continued)

Disease condition	Clinical presentation	Evaluation	Treatment
Hypothyroidism	Asymptomatic in mild cases Fatigue, weight gain, and constipation Myxedema coma is extremely rare	Labs TSH and free T4	Mild asymptomatic cases can be monitored (TSH <10 with normal free T4) Levothyroxine 1.6 mcg/kg daily Start at 50% of dose overall in elderly patients or patients with underlying cardiac comorbidities Adrenal insufficiency must be ruled out and patient suspected to have hypophysitis or primary adrenal insufficiency. Steroid therapy must be initiated before starting thyroid replacement
Primary adrenal insufficiency	Hypotension, fever, abdominal pain with nausea and vomiting, weight loss Electrolyte abnormalities such as hyponatremia and hyperkalemia	Labs a.m. ACTH and cortisol Electrolyte panel Dynamic testing – -cosyntropin stimulation test (patients will not have adequate rise in cortisol)	Hydrocortisone at 10–12 mg/m^2/day divided into 2–3 doses Fludrocortisone 0.05 to 0.2 mg daily
Insulin-deficient diabetes	Polyuria, polydipsia, weight loss, blurred vision, fatigue Diabetic ketoacidosis (DKA) presenting with vomiting, weakness, shortness of breath, signs of dehydration, and classic fruity breath odor	Labs Glucose, CMP, serum and urine ketones C-peptide and diabetes-associated autoantibody (insulin, GAD-65, IA-2, ZnT8)	DKA should be treated in the ICU with aggressive IV hydration, IV insulin, and correction of electrolyte imbalances Basal/bolus insulin regimen which includes both a long-acting insulin analog (glargine, detemir, degludec) and a rapid-acting insulin analog (lispro, aspart, glulisine)

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Chapter 5
Gastroenterology (GI)

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Abstract Immune checkpoint inhibitor (ICI) blockade has revolutionized the management, outcomes, and survival rates in advanced malignancies. However, the use of these immunotherapeutic agents comes with the risk of toxicities, namely, immune-related adverse events (irAEs). Toxicities involving the gastrointestinal (GI) tract are frequent and vary in severity from mild disease to aggressive life-threatening clinical presentations. Timely clinical, biochemical, imaging, endoscopic, and histologic evaluation is key to ensure efficacious management and favorable outcomes. The severity of these toxicities drives management which comprises supportive care in mild disease and selective immunosuppressive therapy (SIT, infliximab or vedolizumab) in aggressive cases.

Keywords Immune checkpoint inhibitors · Immunotherapy · Colitis · Diarrhea · Enterocolitis · Gastrointestinal adverse events

Chapter debriefing: Power point video presentation is provided at the end of the chapter

Supplementary Information The online version contains supplementary material available at [https://doi.org/10.1007/978-3-031-00241-0_5].

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Abbreviations

CDI	*Clostridioides difficile* infection
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
FCal	Fecal calprotectin
FMT	Fecal microbiota transplantation
IBD	Inflammatory bowel disease
ICI	Immune checkpoint inhibitor
IMC	Immune-mediated colitis
IMM	Immune checkpoint inhibitor-mediated mucositis
IrAEs	Immune-related adverse events
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
SIT	Selective immunosuppressive therapy (infliximab and vedolizumab)

Epidemiology and Risk Factors

The overall incidence of immune checkpoint inhibitor mediated colitis (IMC) ranges from 10% to 30% [1–5] and varies heavily based on the type of ICI agents, the cancer type, and the patient.

Type of ICI Agent

Programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) blockade is notable to pose a lower risk of incidence and grade of IMC compared to cytotoxic T-lymphocyte-associated protein 4 (CTLA4) blockade as well as combination therapy [6]. Toxicity secondary to the latter presents earlier as opposed to the former presumably secondary to the shorter half-life [7]. However, in exceptional cases, reports of toxicities occurring up to 2 years after the first infusion is highly suggestive of a persistence of the biological impact of the drug long after its clearance [7]. Studies also report that higher doses of ICI therapy predispose to a greater risk of developing IMC [8, 9].

Type of Cancer

Patients with advanced-stage malignancies bear a significant risk of developing IMC. In particular, malignant melanoma poses an increased risk of developing the same [10] which has caused some to speculate the role of tumor biology in irAEs.

The Patient

Patient characteristics, namely, gender and baseline microbiome, may play a crucial contributory role in determining the risk of developing IMC. While conclusive data is lacking, it has been hypothesized that given the significantly varied immune response pattern and tumor biology among men and women [11], this might translate similarly in terms of irAEs. Anecdotal case reports and series propose a role of the baseline gut microbiome unique to the patient to predict both the therapeutic response to ICI and the risk of developing IMC [12]. Large-scale controlled clinical trials are necessary to confirm the same. Lastly, preexisting IBD with active disease may confer a higher risk of IMC [13].

Clinical Presentation and Evaluation

Clinical Presentation

Patients often present with clinical symptoms of diarrhea (increased stool frequency) or colitis (abdominal pain, rectal bleeding, or the presence of mucus in stools) and occasionally along with radiologic evidence of colonic inflammation as defined by the American Society of Clinical Oncology (ASCO) [14]. Infrequently, these patients may also present with complications of enterocolitis such as ileus, colonic distension, toxic megacolon, intestinal perforation, or even death [15].

Clinical Evaluation

The Common Terminology Criteria for Adverse Events *version 5.0* [16] that relies heavily on clinical signs and symptoms alone has been employed in numerous clinical trials and is routinely used to grade the severity of clinical presentation of IMC. However, it is important to note the poor correlation between the grading of diarrhea and colitis symptoms and grading of inflammation measured endoscopically using this tool [17].

Biochemical and Stool Evaluation

Infectious work-up is imperative to rule out bacterial (e.g., *Clostridium difficile*), viral (e.g., CMV), parasitic, or fungal infections in an immunocompromised patient population which may present in a similar fashion [18]. Additionally, a comprehensive evaluation of various etiologies for diarrhea is recommended with celiac disease panel, fecal elastase for pancreatic insufficiency, and TSH for thyroid

dysfunction. Fecal lactoferrin and calprotectin (FCal) may serve as useful biomarkers of inflammation. While data suggests that the former can be highly sensitive in detecting endoscopic and histologic inflammation, stool calprotectin testing can be applied as an alternative to endoscopic surveillance to assess treatment response [19, 20]. A retrospective analysis of 77 cancer patients with IMC showed a significant decrease in FCal concentrations from the onset of disease to the end of therapy ($p < 0.001$). Furthermore, patients who achieved endoscopic remission after treatment demonstrated a significantly lower FCal concentration ($p < 0.001$) compared to those without endoscopic remission. Cutoff levels of FCal were defined with high specificity for endoscopic and histologic remission [20].

IMC, Infections, and Its Management

IMC is often complicated by GI superinfection, and differentiating the two may be clinically challenging. Our prior study [21] shows that patients with concurrent GI infection (i.e., *E. coli* and non-CMV viruses) and IMC have a longer duration of symptoms, higher grade of colitis, frequent hospitalization, and a higher rate of IMC recurrence if treated with antimicrobials. This analysis also demonstrated that antimicrobial use did not circumvent the need for immunosuppressant or improve the clinical outcomes. Concurrent infectious diarrhea was not associated with worse overall survival.

Clostridioides difficile infectious (CDI) diarrhea is common in patients on ICI therapy (9.7%) especially with IMC diagnosis requiring SIT and often requires concurrent antibiotic therapy which does not alter the need for immunosuppression. These patients have a significantly longer duration of symptoms (20 vs. 5 days, $P = 0.003$) and a higher grade of diarrhea. Preceding antibiotic ($P = 0.050$) and PPI ($P = 0.038$) use is associated with an increased risk of CDI [22] before steroid administration.

Our group has also explored the incidence of CMV infections in patients with ICI exposure and found the incidence to be lower in comparison to non-ICI-exposed cancer patients. Our analysis also was suggestive of both higher treatment success rates and recurrence rates in patients with hematological malignancies compared to solid tumor cancer patients [23]. Albeit a small sample size, among the eight patients with GI CMV, the only one patient that died secondary to CMV infection had advanced pulmonary CMV infection and pulmonary irAE.

The coronavirus disease 2019 (COVID-19) pandemic posed an increased risk of severe illness and mortality from infection in immunocompromised cancer patients [24]. It is a big concern if gut inflammation and therapeutic immunosuppression for IMC could increase the risk of COVID-19 infection and its related complications. Our questionnaire-based study [25] demonstrated a low infection rate presumably due to high levels of compliance with effective preventive measures of social distancing and wearing masks. The other speculation for this finding is that immunosuppression may mitigate the cytokine release syndrome associated with severe COVID-19 infection [26]. Therefore, the concern for COVID-19 should not negatively affect optimal management of IMC with SIT as long as protective efficacious measures are practiced [27]. Furthermore, similar to IBD, all the COVID-19

vaccines are routinely recommended to patients with IMC as they are not live vaccines. This is discussed in detail in other chapters.

Imaging

Contrasted imaging of the abdomen and pelvis is intended to rule out an acute intra-abdominal process or complications related to IMC in those with grade ≥2 colitis such as perforation, abscess, and bleeding. However, there is a poor negative predictive value and correlation between imaging and endoscopic findings. Three imaging signs have been established for IMC, namely, a diffuse colitis pattern, segmental colitis with diverticulosis, and isolated recto-sigmoid colitis without diverticulosis with a good positive predictive value [28]. Our group also has speculated that diverticulitis can occur after ICI use and appeared to occur more often after anti-CTLA-4 therapy. Clinical manifestations present very similarly to non-ICI-related diverticulitis [29]. However, there is a higher complication rate related to diverticulitis in this particular population than non-ICI-treated patients.

Endoscopic Evaluation

Early endoscopic evaluation has been established to be key in prompt identification of patients with high-risk features of colitis which facilitates rapid and efficacious management, thereby decreasing steroid dependency and improving overall outcomes (prolonged hospitalization, recurrence rates) in a critically ill patient population [17, 19].

Broadly, one may classify endoscopic features as normal, non-ulcerative inflammation and mucosal ulcerations [17], with the latter being the most severe with a worse prognosis (Fig. 5.1). Furthermore, it is noteworthy that up to one third of patients may have normal-appearing colonic mucosa with ≥ grade 2 diarrhea. At our institution, we tailor management based on the endoscopic disease severity as seen in Table 5.1.

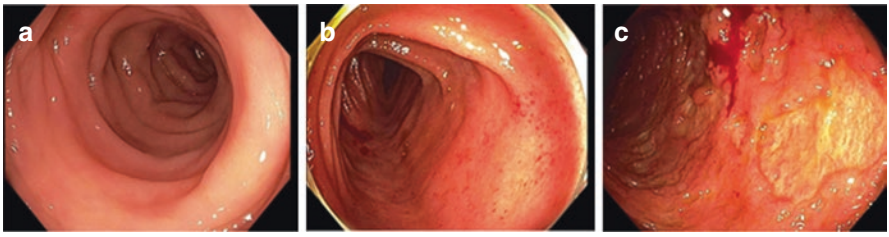


Fig. 5.1 (**a**) Normal-appearing colonic mucosa. (**b**) Moderate-risk endoscopic features characterized by edema, erythema, and non-ulcerative inflammation. (**c**) High-risk endoscopic features characterized by deep ulcerations

Table 5.1 MD Anderson Cancer Center grading of endoscopic inflammation [30]

Severity	Endoscopic features
Mild	Normal endoscopy and normal histology
Moderate	Normal colon appearance with pathology showing inflammation; small ulcer <1 cm, shallow ulcer <2 mm, and/or number of ulcers <3; inflammation limited to the left colon only, non-ulcer inflammation
High	Large ulcer ≥1 cm, deep ulcer ≥2 mm, and/or number of ulcers ≥3; extensive inflammation beyond the left colon

Histologic Evaluation

Acute colitis, chronic colitis, and microscopic colitis are the three established distinct histologic patterns of IMC. It is the third type, albeit rare, that may present with clinically aggressive disease necessitating systemic immunosuppression [31]. Acute colitis pattern is the most frequently encountered histologic subtype characterized by the presence of neutrophil and/or eosinophil infiltration, epithelium apoptosis, cryptitis, and crypt micro-abscesses. Chronic colitis pattern demonstrates features similar to inflammatory bowel disorders such as crypt architectural distortion, basal lymphoplasmocytosis, granulomas, and Paneth cell metaplasia [17]. The microscopic colitis pattern resembles lymphocytic or collagenous colitis. A detailed description of the histopathology of this process is described separately in a separate chapter.

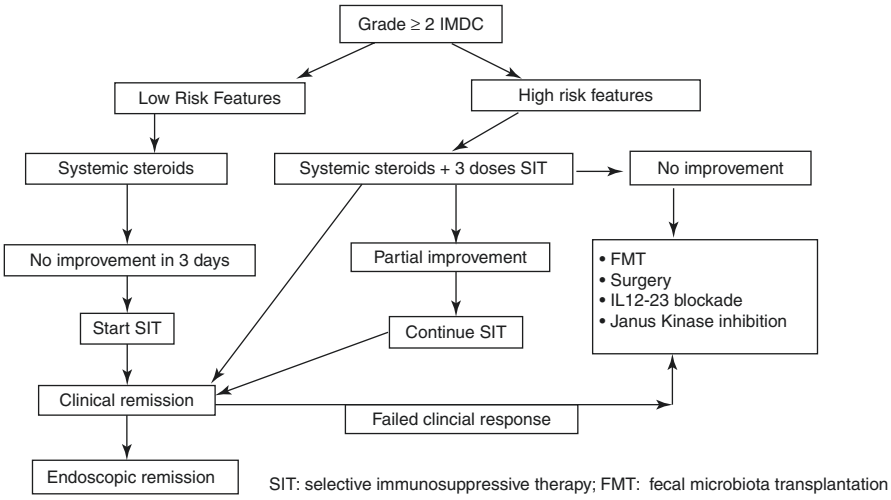
Similar to IBD, there appears to be no correlation between clinical presentation and histologic inflammation in IMC [32, 33]. It has been speculated that the onset of histologic inflammation likely precedes clinical symptomatology [17].

Treatment of IMC

Prompt, appropriate, and efficacious management of IMC ensures avoidance of complications, recurrence, and delay in cancer care.

Grade 1 IMC generally manifests as a mild and self-limiting diarrhea that is managed with supportive care, i.e., hydration, correction of electrolyte imbalances, bland diet, anti-diarrheals (once infection has been ruled out), or 5-ASA-based therapies. In particular, patients with delayed onset of grade 1–2 IMC after PD-(L)1 monotherapy and lower colonic inflammatory burden confirmed by calprotectin and endoscopy/histology evaluation may benefit from 5-ASA-based therapies with cholestyramine [34]. Furthermore, the use of mesalamine can minimize the use of IMS and its related complications given its favorable safety profile. In most cases, ICI therapy may be resumed after resolution of the acute episode, thereby avoiding frequent interruptions in cancer care [35].

Management of grade ≥2 IMC requires expeditious immunosuppression. ICI therapy is paused temporarily for grades 2 and 3 and permanently for grade 4 [36,



Algorithm 5.1 MD Anderson Cancer Center ICI colitis management

37]. Low-risk endoscopic features are treated with weight-based systemic corticosteroids (prednisone or equivalent with a dose of 1–2 mg/kg) with a taper over a duration of 4 weeks after symptom resolution to ensure fewer complications secondary to infections [17]. In the rare absence of improvement in 3 days from steroid initiation, patients may be administered selective immunosuppressive therapy (SIT) with either infliximab or vedolizumab to reach clinical remission. Early introduction of SIT for moderate to severe IMC is associated with favorable clinical outcomes in patients with IMC regardless of steroid response.

Please refer to Algorithm 5.1 for current MD Anderson guidelines on the evaluation and management of checkpoint inhibitor colitis [38]. In subtle contrast to the current NCCN [39] and ASCO guidelines [40] on management of irAE which is based solely on the CTCAE grade of symptoms, MD Anderson strategies are incorporating:

A. Findings of high risk endoscopic features which serve as important markers of disease severity with clinical implications [17].
B. Early initiation of SITs in the management of IMC to ensure favorable outcomes [41].
C. Maintenance SIT therapy to prevent recurrence of IMC, facilitate resumption of ICI, and ensure continued cancer care and better overall survival [42].

Infliximab (IFX), a chimeric human mouse IgG monoclonal antibody, targets the TNF-α receptor and thereby suppresses inflammation. The evidence for this biologic is favorable as concerns the significantly decreased time to symptom resolution and steroid titration with this drug [26]. However, it does bear an increased risk of infection and is contraindicated in the setting of congestive heart failure,

hepatotoxicity, and demyelinating disease. It has also been implicated in an increased risk of malignancy/lymphoma with long-term usage [43].

Vedolizumab (VDZ), a gut-selective fully humanized monoclonal antibody, targets the α4β7 integrin and halts inflammation. It has shown encouraging clinical outcomes, comparable efficacy, and favorable safety profile [44].

In a two-center retrospective study of patients with IMC who received these two SITs following steroids, the comparative efficacy of IFX and VDZ on IMC and their impact on cancer outcomes were measured. While IFX had a significantly favorable shorter median duration from first dose to symptom improvement compared to VDZ (13 versus 18 days, $P = 0.012$), the latter faired significantly better in terms of median duration of symptoms (35 versus 51 days, $P < 0.001$), hospitalization (10 versus 14 days, $P = 0.043$), histological remission ($P = 0.011$), and recurrence of IMC ($P = 0.009$). The higher doses of VDZ over longer duration for the IMC maintenance compared to IFX group could have contributed to better outcome. A prospective clinical trial is underway to compare and contrast the efficacy of these biologics in the management of GI toxicities in a cancer patient population [45].

Ustekinumab, a human monoclonal antibody to p40 subunit of interleukin (IL)-12/IL-23, is approved for management of moderate to severe Crohn's disease (CD) by antagonizing essential components of the Th1 and Th17 inflammatory pathways and facilitating mucosal healing, i.e., inducing and maintaining clinical remission, as has been demonstrated previously in the UNITI 1/2 trials [46]. Opposing roles of IL-23 and IL-12 in maintaining outgrowth and dormancy of tumors in mice raise concerns regarding the use of ustekinumab in patients with cancer. Nevertheless, most clinical trials did not find an unexpected increase in cancer across approved indications. While the role of this IL-12/IL-23 antagonist in immune-related adverse effects and the implications of therapeutic inhibition of IL-12 in cancer is yet to be established, a few case series speculate that this inflammatory pathway may serve as a therapeutic target and alternative to long-term steroid dependency in IMC management [47, 48].

Tocilizumab is an IL-6 receptor antagonist which has shown clinical improvement in a variety of steroid-refractory irAEs. Stroud et al. demonstrate a clinical improvement in ~80% of their cohort of cancer patients that received ICI therapy and developed varied irAEs requiring immunosuppression with reserved similar overall survival among those that received ICI with and without IL-6 blockade [49]. At low levels, IL-6 activates anti-inflammatory pathways via classic signaling, while at high levels, this cytokine may have pro-inflammatory effects via trans-signaling [50–52]. In a case series of two ulcerative colitis patients with concomitant autoimmune disorders treated with tocilizumab, IL-6 blockade worsened colonic inflammation [53]. While this pathway could potentially serve as a target to treat irAEs without interfering with checkpoint blockade, this complex pathway is also implicated in promoting tumor progression and metastasis [54]. Hence, while caution is necessary when targeting this pathway, well-designed clinical trials are imperative in order to practice evidence-based medicine in this complex disease process.

Tofacitinib, a Janus kinase inhibitor, was established as a highly efficacious therapy for ulcerative colitis refractory to alternative biologic therapies in the OCTAVE

trials [55]. The JAK-STAT regulatory pathway integrates the innate and adaptive immunity and may play a role in autoimmunity and cancer immune surveillance. Bishu et al. recently report a small case series of four males successfully treated with tofacitinib for IMC [56]. Three of these patients who had achieved cancer remission prior to tofacitinib therapy remained cancer-free 12 to 71 weeks after tofacitinib. One had preexisting inflammatory bowel disease and did not achieve cancer remission before Janus kinase inhibition and had cancer progression. Given its oral route of administration and fast onset of action, tofacitinib is a promising target to be further explored in refractory IMC [57]. However, its risk for thromboembolic phenomenon in a cancer population as well as the loss-of-function mutations in *JAK1* associated with resistance to PD-1 blockade in melanoma patients requires thorough evaluation and clinical validation of this class of medications [58].

Fecal microbiota transplantation: Gut dysbiosis is linked closely to host responses and is implicated in cancer initiation and progression as well as sensitivity to chemotherapeutic agents in the tumor microenvironment [59–62]. Differential gut microbiome bacterial signatures have been established among responders versus non-responders to ICI therapy as well as those with a lower threshold for IMC [63, 64]. Animal studies demonstrate that modulation of the gut microbiome in gnotobiotic mice via FMT from cancer patients alters anti-tumor immunity and response to ICI therapy [65]. Similarly, it has been proposed that targeting specific bacterial taxa may abrogate ICI-related toxicity [66–69]. Fecal microbiota transplantation (FMT) has been proposed to be effective in patients with ICI-induced enterocolitis refractory to the abovementioned immunosuppression [48, 70–73]. Prospective FMT clinical trials also demonstrate improved cancer response among melanoma patients who previously failed ICI therapy after receiving FMT from melanoma responders [74, 75].

Recurrence of IMC

Moderate- to high-grade endoscopic features pose a significantly higher risk of prolonged hospitalization and recurrence [19] and are managed with early initiation of at least three doses of SIT [41] with maintenance in conjunction with a weight-based systemic corticosteroid taper. Once clinical remission is attained, it is highly recommended that SIT therapy should continue especially if ICI is resumed. A prior study [41] demonstrated an IMC recurrence can be significantly reduced if patients receive ≥3 doses of SIT or endoscopic and histologic remission.

Surveillance

IMC, at most cancer centers, is closely monitored post therapy by evaluating clinical symptoms. Deep remission is determined by endoscopic and histologic evaluation of the disease process. Partial endoscopic improvement and/or residual

histologic inflammation should prompt continuation of SIT, and PD-1/PD-L1 blockade may be reinstituted with caution. Repetitive endoscopic evaluations with bowel preparation can be particularly cumbersome for immunocompromised cancer patients. FCal concentration testing may serve as an attractive alternative noninvasive biomarker of endoscopic or histologic remission. A retrospective analysis of a cohort of 77 cancer patients found a cutoff FCal concentration of ≤116 μg/g and ≤80 μg/g to predict endoscopic and histologic remission respectively, with an optimal specificity (94% and 85% respectively) [20]. Large prospective studies may provide more information on the role of this inflammatory stool biomarker in surveillance of this disease process.

Maintenance Therapy

Up to a third of patients who resume ICI after IMC experience recurrence. Factors that predispose to IMC recurrence with resuming ICI therapy include CTLA-4 blockade, initial use of anti-PD-1/PD-L1 agents, long duration of the initial IMC episode, and the requirement of SIT [76]. Recent evidence shows a significantly lowered risk of IMC recurrence with maintenance SIT therapy in comparison to the absence of the same with resumption of ICI therapy cancer care (17% versus 37%, $P = 0.027$). We also demonstrate similar overall survival of these two groups of patients, thereby favoring the judicious use of concurrent SIT with ICI therapy for cancer care [77].

IMC and Its Impact on Cancer Outcomes

Our retrospective review at MD Anderson conclusively showed that patients with IMC have improved survival outcomes. Diarrhea is an independent predictor of an improved survival regardless of immunosuppressive treatment requirement [78]. Thereafter, we also found that when the disease course exceeds 3 months in duration with features of chronicity on colon histology [79], this is associated with improved survival outcomes in terms of cancer and may in fact reflect persistent anti-tumor activity of the ICI therapy. As we learn more about this disease process, it appears that striking a fine balance between ICI therapy and toxicity is key to ensure the maximum benefit of this revolutionary class of drugs in advanced malignancies. However, to date, evidence on the incidence of GI irAEs in patients with luminal GI cancer receiving ICIs and its impact on cancer outcomes is limited. Our recent analysis suggests that GI irAEs occur in 2.4% of patients with cancer involving luminal GI tract receiving ICI and endoscopic evaluation for GI symptoms. Lower GI irAE is more prevalent (66%) and often responds well to immunosuppressant therapies. Immunosuppressive treatment with vedolizumab for GI irAE is safe and not associated with further GI luminal cancer progression and recurrence or a subsequent poor response to ICI therapy [80].

Future Direction and Scope

Data is greatly limited in terms of the true natural history of this disease process as well as long-term outcomes such as risk of fibro-stenotic disease and colon cancer mostly due to the critically ill patient population who eventually succumb to progression of underlying aggressive malignancy. However, we acknowledge a need to formulate a validated scoring tool that incorporates clinical, biochemical, endoscopic, and histologic features of IMC to determine severity and therefore guide management as well provide prognosis and need for maintenance/prophylactic therapy.

Conclusion

IMC is a frequently encountered irAE. Early recognition with clinical, biochemical, imaging, and prompt endoscopic evaluation bears favorable outcomes. In patients with ≥ grade 2 IMC, prompt introduction of SIT with a minimum of three doses is associated with a faster symptom resolution and decreased steroid exposure with a goal for endoscopic remission demonstrated on surveillance evaluation. Fecal calprotectin is a reasonable noninvasive biomarker of inflammation that may be considered as a surveillance tool post therapy of IMC. Maintenance SIT is strongly preferred with resumption of ICI. IMC is associated with better cancer outcomes.

Immune-Mediated Upper GI Toxicity (from the Mouth to the Ligament of Treitz)

Upper GI (mouth to ligament of Treitz) toxicity secondary to ICI use is rare, and consequentially, the literature related to the same is sparse. Upper GI symptoms occur far more commonly in conjunction with IMC, and isolated upper GI involvement is rare. PD-1/PD-L1 blockade has been more frequently implicated in toxicity involving the upper GI tract compared to CTLA-4 blockade [81–83], which may be attributed to variable expression of targets in different tissues [83, 84]. However, the distribution of CTLA-4 and PD-1/PD-L1 expression along the GI tract has not been well described.

ICI Mucositis (IMM)

ICI-related irAEs may involve the oral cavity and presnet with xerostomia, dysgeusia, odynophagia, dysphagia, lichenoid mucositis, or stomatitis [85, 86]. While IMM remains a diagnosis of exclusion, this toxicity is often mild in severity. A retrospective study of patient with this irAE suggests a need for immunosuppression in as high as 25% of cases with recurrence noted in 38% of patients [83].

ICI-Related Esophagitis

A retrospective analysis of cancer patients who received ICI therapy and developed esophagitis concluded that toxicity isolated to the food pipe is rare and often occurs in conjunction with other upper gastrointestinal toxicities. Clinical presentation is similar to other causes of esophagitis such as nausea, emesis, dysphagia, and rarely hematemesis. While the diagnosis is one of exclusion, the disease often remains mild, is rarely associated with complications, and may be managed with supportive therapies, namely, proton pump inhibitors or H_2 receptor blockers [81].

ICI-Related Gastroenteritis

Similar to toxicity involving the esophagus, irAE involving the stomach and proximal small bowel is rare and may present clinically with abdominal pain, intractable nausea and emesis, and GI bleeding [81, 87, 88]. Endoscopic features include erythema, edema, friability, erosions, and ulcerations. On histology, commonly described features in the gastric mucosa are lamina propria expansion and intraepithelial neutrophilic infiltration. Villous blunting, lymphoplasmacytic lamina propria expansion, plasma cell and eosinophilic infiltrates, neutrophilic cryptitis, and/or villitis have been reported on duodenal biopsies [89, 90]. Mild symptoms are effectively managed with non-immunosuppressive treatments, e.g., proton pump inhibitors or H_2 receptor blockers. Anecdotal reports favor the use of systemic steroids or vedolizumab in patients with aggressive disease refractory to supportive management [91]. Larger prospective studies are needed to help further characterize this disease process longitudinally and determine optimal management of the same.

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Chapter 6
Hematology

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Abstract Immune checkpoint inhibitors (ICIs) are a distinct class of immunotherapeutic agents that have altered the treatment of many cancers for over a decade. This type of treatment has shown beneficial and clinically meaningful effectiveness against many types of cancers, such as melanoma; kidney, lung, and bladder cancers; and lymphomas [1]. ICIs target suppression receptors such as programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) on the surface of immune cells, as well as receptors on the tumor cells such as programmed cell death ligand-1 (PD-L1). Immune checkpoint blockade leads to downregulation of innate breaks on the immune system and stimulates the adoptive immune response. The activated T cells are not antigen specific and thus may lead to immune-related adverse events (IRAEs) [1]. Common IRAEs include dermatologic, gastroenterologic, hepatic, pulmonary, renal, neurologic, and cardiac manifestations as well as endocrinopathopathies [2–7]. Less commonly, hematologic IRAEs such as autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), autoimmune neutropenia (AIN), pure red cell aplasia (PRCA), aplastic anemia (AA), hemophagocytic lymphohistiocytosis (HLH), and hemostatic complications have been reported [8, 9].

Chapter debriefing: Power point video presentation is provided at the end of the chapter.

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Hematologic IRAEs are estimated to be around 3.6% for all grades and 0.7% for grades III–IV according to a review of large clinical trials of ICIs. Frequency of hematologic toxicities appears to be higher with anti-PD-1 or anti-PD-L1 therapies than with anti-CTLA-4 therapies. The mean time to the onset was 10 weeks after the initiation of ICIs, and the adverse events could occur at any time after ICI treatment [1]. Herein, we discuss the epidemiology, clinical characteristics, diagnosis, treatment, and long-term complications of the hematologic IRAEs.

Keywords Autoimmune hemolytic anemia · Immune thrombocytopenic purpura · Autoimmune neutropenia · Aplastic anemia · Pure red cell aplasia · Hemophagocytic lymphohistiocytosis · Macrophage activation syndrome · Hemostatic complications

Abbreviations

AA	Aplastic anemia
AIHA	Autoimmune hemolytic anemia
AIN	Autoimmune neutropenia
ANA	Antinuclear antibodies
APTT	Activated partial thromboplastin time
ATG	Antithymocyte globulin
BM	Bone marrow
CAT	Cancer-associated thrombosis
C3	Complement C3
CRP	C-reactive protein
CTLA-4	Cytotoxic T lymphocyte antigen-4
DAT	Direct antiglobulin test
DIC	Disseminated intravascular coagulation
G-CSF	Granulocyte colony-stimulating factor
HLH	Hemophagocytic lymphohistiocytosis
ICI	Immune checkpoint inhibition
IgG	Immunoglobulin G
IRAE	Immune-related adverse event
ITP	Immune thrombocytopenic purpura
IVIG	Intravenous immunoglobulin
MAS	Macrophage activation syndrome
NK	Natural killer
PBS	Peripheral blood smear
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand-1
PRCA	Pure red cell aplasia
PT	Prothrombin time

RBC	Red blood cell
TMA	Thrombotic microangiopathy
VTE	Venous thromboembolism

Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia (AIHA) is characterized by erythrocyte destruction by autoantibodies with or without complement activation, leading to shortened erythrocyte survival [10, 11]. AIHA can be primary (no obvious initiating and/or underlying cause) or secondary. ICI therapy is an emerging cause of secondary AIHA. There are two subtypes: warm AIHA and cold AIHA.

Epidemiology

Warm AIHA is due to formation of autoantibodies (IgG, rarely IgM and IgA) against erythrocytes. An imbalance between regulatory T cells and an excessive activity of B and T lymphocytes cause AIHA [12–14]. The incidence of ICI-related AIHA is estimated to be <1% [15]. The onset of ICI-related AIHA ranges from 7 to 10 weeks after the initiation of ICI therapy [8, 16]. Both males and females are equally affected [8, 15]. The median age is 65 [15]. The underlying malignancies commonly include melanoma, lymphoma, renal and lung cancers, and chronic lymphocytic leukemia [8, 15]. Frequently used ICIs are nivolumab, pembrolizumab, ipilimumab, and atezolizumab [8, 9, 15]. ICI-related cold AIHA is exceedingly rare, and there have been only two cases of cold AIHA reported in the literature [17, 18].

Clinical Characteristics

Patients with AIHA may present with symptoms of anemia (tiredness, fatigue, dizziness, dyspnea), hemolysis (jaundice and dark urine) [11], and symptoms of underlying malignancies. The physical examination may reveal pallor, icterus of varying degrees, hepatosplenomegaly, hemoglobinuria, and signs of heart failure [11]. Cold AIHA can present with cold-induced acrocyanosis (dusky coloration of digits, nose tip, or ears) or Raynaud phenomenon [11]. Other hematologic as well as non-hematologic IRAEs may present concurrently with AIHA. Concurrent hematologic IRAEs that have been reported in the literature include AIN, ITP, and PRCA [8, 15]. Concurrent non-hematologic IRAEs include rash, hypothyroidism, hepatitis, diabetes mellitus, colitis, pneumonitis, arthritis, and acute kidney injury [8, 15].

Evaluation

Laboratory findings revealed features of hemolysis such as reticulocytosis, elevated unconjugated bilirubin and lactate dehydrogenase, and low haptoglobin. Hemoglobinuria and hemosiderinuria can occur if there is element of intravascular hemolysis. In mild compensated hemolysis, some parameters may be normal [11]. A positive direct antiglobulin test (DAT) indicates immune hemolysis mediated by IgG (commonly), IgM and IgA (rarely), or complement bound to the RBC membrane. Nonspecific anti-IgG and anti-C3 antibodies are generally used in the initial workup [11].

In warm AIHA, hemolysis is caused by autoantibodies which bind RBCs in vitro at 37 degrees C. DAT may be positive with immunoglobulin G (IgG) only, IgG + complement C3 (C3), or C3 only [11]. Rarely, patients with AIHA may have negative DAT test due to small numbers of IgG molecules below the level of detection of standard DAT, or an Ig not tested for (e.g., IgM or IgA) or elution of low-affinity IgG autoantibodies during routine washing of the erythrocytes prior to the detection phase of the standard DAT. In those scenarios, "super Coombs test" can be performed in specialized laboratories [19]. Peripheral blood smear (PBS) examination reveals polychromasia and microspherocytes. It is interesting to note that ICI-related warm AIHA has a high incidence of DAT negativity (38%) in a large case series [8].

In cold AIHA, hemolysis is caused by autoantibodies (usually IgM) which bind erythrocytes in vitro at 4 degrees C. DAT is usually positive for C3 only; however, a quarter of cases are also positive with IgG. Marked erythrocyte agglutination on the PBS is classically seen. The thermal amplitude (the maximal temperature at which antibody binds red cell in vitro) is usually <25 degrees C [11].

Treatment

ICI-Related Warm AIHA

The American Society of Clinical Oncology (ASCO) consensus clinical practice guideline recommends permanent discontinuation of ICIs if the patient develops grade 3 or 4 toxicities. In grade 2 toxicity, ICI should be held, whereas in grade 1 toxicity, ICI can be continued [20]. Management includes initiation of corticosteroids (prednisone 1–2 mg/kg daily or intravenous equivalent in grade 3 and 4 toxicities) and supportive care such as folic acid supplementation and red blood cell (RBC) transfusions [8, 20]. According to a case series of 14 patients with ICI-related warm AIHA, 3 patients (21%) required additional immunosuppressive therapies (ISTs) such as rituximab, intravenous immunoglobulin (IVIG), and azathioprine. The median interval from hemoglobin (Hb) nadir to complete Hb recovery (defined as an increase in Hb to within 0–1.0 g/dL of the pre-ICI treatment value) was 47 days [8]. Review of the 12 published patients also reported a similar trend; all were treated with corticosteroids and 3 patients (25%) required additional ISTs with IVIG or rituximab [15].

ICI-Related Cold AIHA

This is exceedingly rare and only two cases were reported in the literature. Both cases were successfully treated with rituximab [17, 18]. The addition of fludarabine may be considered. Other supportive care management includes initiation of folic acid, RBC transfusions, keeping warm, and avoidance of cold exposure [11].

Long-Term Complications and Follow-Up

The treatment outcome of ICI-related warm AIHA is fairly good. In a large case series of 14 patients, 86% achieved a complete Hb recovery, while 14% achieved a partial Hb recovery (defined as an increase in Hb to within 1.1–2.0 g/dL of the pre-ICI treatment value). 57% of patients achieved a complete remission (defined as an increase in Hb to within 0–1.0 g/dL of the pre-ICI treatment value in the absence of immunosuppression or ongoing hemolysis). 7 out of 14 patients (50% of patients) could be rechallenged with ICIs. 14% (1 out of 14 patients) developed recurrent warm AIHA [8]. In another literature review of 12 patients, 2 (8%) patients had fatal outcome [15]. It is our usual practice to follow up the patients every 1–2 weeks during the induction phase of steroid therapy. Once the patients respond to ISTs, the patients should be followed up every 3–4 weeks.

Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura (ITP) is an autoimmune disease characterized by isolated thrombocytopenia [21]. ITP can be primary (no obvious initiating and/or underlying cause) or secondary. ICI therapy is an emerging etiology for secondary ITP

Epidemiology

Overall, the incidence of typical ITP ranges from 2 – 4 cases per 100,000 person-years, with 2 peaks: the first between 20 and 30 years of age (female > male) and the second peak after 60 years of age (female = male) [22, 23]. The pathogenesis of ITP is complex. Some cases are platelet antibody mediated with antibody-coated platelets prematurely destroyed in the spleen, liver, or both via the interaction with Fcγ receptors [24]. Autoantibodies can also induce complement-mediated platelet destruction as well as inhibition of megakaryocytic function [25, 26]. Abnormalities in the T cells including skewing of helper T (Th) cells towards a type 1 helper T (Th1) and type 17 helper (Th17) phenotype and reduced regulatory T cell numbers

and function [27, 28]. The incidence of ICI-related ITP is estimated to be <1%. The time to onset of ICI-related ITP ranges from 1 to 20 weeks (median 6 weeks). Most patients were treated with anti-PD1 or anti-CTLA4 agents or a combination of both. The median age is 54 [9]

Clinical Characteristics

Patients with ITP may be without symptoms at presentation, or they may present with mild mucocutaneous (e.g., petechiae, purpura) to life-threatening bleeding. The patients often report fatigue and impaired quality of life [29]. Other hematologic as well as non-hematologic IRAEs may present concurrently with ITP [8, 30, 31]. Concurrent hematologic IRAEs that have been reported in the literature include AIHA and autoimmune pancytopenia [32].

Evaluation

Most of the time, the laboratory features reveal isolated thrombocytopenia. ITP is defined as platelet count <100,000/cmm in patients after other causes of thrombocytopenia have been excluded [21]. PBS examination shows thrombocytopenia with no other abnormalities (e.g., schistocytes, dyspoietic changes, immature white blood cells). Some patients with ITP may exhibit large platelets. Antiplatelet antibodies are detectable in only 50–60% of patients. In patients with ICI-related ITP who simultaneously develop warm AIHA, microspherocytes can be seen on PBS examination [8, 31]. Bone marrow (BM) biopsy may be required to exclude other causes of thrombocytopenia in difficult clinical scenarios [21].

Treatment

The ASCO consensus clinical practice guideline recommends continuing ICI with close follow-up if the patient has grade 1 toxicity. If thrombocytopenia is grade 2 (50–75,000/cmm), ICI should be held or interrupted until platelet count reaches >75,000/cmm. Corticosteroids (e.g., prednisone 0.5–2 mg/kg/day for 2–4 weeks) followed by tapering over the next 4–6 weeks should be considered. For grade 3 (25–50,000/cmm) and grade 4 (<25,000/cmm) thrombocytopenias, hematology consultation should be obtained and corticosteroid should be started. Additional therapies such as IVIG, rituximab, and thrombopoietin mimetics (e.g., romiplostim, eltrombopag) can be considered. In grade 3 and 4 toxicities, ICIs should be permanently discontinued if ITP status worsens or does not improve with treatment [20].

Long-Term Complications and Follow-Up

The treatment outcome of ICI-related ITP is fairly good according to a recent literature review [9]. About 71% of patients with ICI-related ITP responded to corticosteroids (57% complete response and 14% partial response). The remaining patients required additional therapies with rituximab or romiplostim achieving a good outcome [9]. It is our usual practice to follow up the patients every 1–2 weeks during the induction phase of steroid therapy. Once patients have responded, the patients should be followed up every 3–4 weeks.

Autoimmune Neutropenia

Autoimmune neutropenia (AIN) is an autoimmune disease characterized by isolated neutropenia. AIN can be primary (no obvious initiating and/or underlying cause) or secondary [33]. ICI therapy is an emerging etiology for secondary AIN [9].

Epidemiology

Overall, the incidence of garden variety AIN is rare [33, 34]. AIN is caused by antibodies directed against the neutrophil antigens [35]. Antineutrophil antibodies are directed against a defined group of neutrophil-specific antigens such as HNA-1a, HNA-1b, HNA-1c, HNA-2a, HNA-3a, HNA-4a, and HNA-5a [33]. AIN also occurs as part of combined immune cytopenias. 14% cases of AIN were associated with AIHA or ITP. About 50% of cases were also found to have some other diseases such as systemic lupus erythematosus, myelofibrosis, and common variable immunodeficiency [36]. The incidence of ICI-related AIN is extremely low with only less than 20 cases reported in the literature [9, 37]. The time to onset of ICI-related AIN ranges from 2 to 44 weeks (median 10 weeks). The median age is 63 [9].

Clinical Characteristics

The degree of ICI-related AIN was profound and severe, with absolute neutrophil counts close to 0/cmm in many cases and all cases were diagnosed with grade 3 and 4 neutropenias [9]. Severe neutropenia was complicated by severe sepsis in over 50% of cases with median duration of neutropenia <500/cmm (grade 4) was 16.5 (range 3–57) days [9]. In some cases, antineutrophil antibodies were detected [31, 38–40].

Evaluation

Clinical evaluation for AIN involves PBS examination and requisition of antineutrophil antibodies (if available). Other tests that may be useful include workup for underlying diseases such as rheumatoid factor, antinuclear antibodies (ANA), or anti-double-stranded antibodies [33]. BM biopsy may be required to exclude other causes of neutropenia in difficult clinical scenarios. The ASCO also published an updated clinical guideline on management of febrile neutropenia (FN) for adult neutropenic oncology patients in 2018 [41]. Patients should undergo systematic assessment with a validated risk index (e.g., Multinational Association for Supportive Care in Cancer [MASCC] score or Talcott's score). Patients with MASCC score $\geq$ 21 (or Talcott's group 4), Clinical Index of Stable Febrile Neutropenia (CISNE) score of <3, and absence of clinical judgement criteria are considered low risk and can be managed as outpatients. Other patients should be managed hospitalized [41].

Treatment

Supportive care management for those with AIN who develop FN should follow recent ASCO clinical guidelines. Outpatient management for low-risk patients includes performing blood cultures, symptom-directed workup, and administering the first dose of intravenous antibiotics, observation for $\geq$4 hours, and subsequent oral empiric therapy with fluoroquinolone plus amoxicillin/clavulanate. Inpatient management for the high-risk patients includes performing symptom-directed workup, taking blood cultures, and administering empiric intravenous antibiotics based on institutional antibiogram [41, 42].

Since ICI-related AIN is very rare, general consensus for specific management does not exist. Recent systematic review revealed that almost all patients received granulocyte colony-stimulating factor (G-CSF) for neutropenia. ISTs included corticosteroids, IVIG, cyclosporine, rituximab, mycophenolate, or antithymocyte globulin (ATG) [9, 43]. A recently published Chinese clinical guideline suggested discontinuation of ICIs once grade 3 or 4 neutropenia occurs [43].

Long-Term Complication and Follow-Up

About 80% of patient with AIN recovered completely according to a recent systematic review [9]. However, few patients succumbed to complications of severe neutropenia [37]. It is our usual practice to follow up the patients every 1–2 weeks during the induction phase of steroid therapy. Once patients have responded, the patients should be followed up every 3–4 weeks.

Bone Marrow Failure Syndromes

They comprise aplastic anemia (AA), pure red cell aplasia (PRCA), megakaryocytic hypoplasia or aplasia, agranulocytosis, or the combination of those entities.

Epidemiology

The only currently available population based-registry data on hematologic IRAEs is the REISAMIC registry [38]. REISAMIC describes IRAEs in 745 patients who were treated with anti-PD-1 or anti-PD-L1 therapies for cancer. Among those, there were a total of 35 patients who experienced hematologic IRAEs. Besides the REISAMIC registry, bone marrow failure (BMF) case reports have been anecdotal [32, 40, 44–58].

Clinical Characteristics

In the REISAMIC registry, two patients experienced bicytopenia and one patient had PRCA. All the patients were investigated with BM biopsy that confirmed the central mechanism for the cytopenias in two cases. One of the bicytopenia cases had a normal BM cellularity and positive neutrophil autoantibodies, ANA, and antiphospholipid antibodies. The onset of the hematologic IRAEs was variable from 12 days to 322 days from ICI initiation [38]. Another 17 cases have been reported in the literature with diagnoses of BMF following ICI [32, 40, 44–58]. Anti-CTLA-4 and anti-PD-1 have been the most frequent agents involved in those reports, and mainly, in patients with advanced melanoma or lung malignancies.

Evaluation

The diagnostic strategies described in the literature have been extrapolated from the evaluation steps for primary immune cytopenias. In cases of BMF syndrome or multiple concurrent cytopenias, a BM biopsy is a commonly used diagnostic method. It is important to emphasize that the evaluation of patients with suspected hematologic IRAEs from ICI should be a diagnostic process of exclusion. Patients with advanced malignancy commonly have cytopenias from other etiologies far more frequent than IRAEs. Those etiologies include micronutrient deficiencies [59–61], chemotherapy, myelophthisis, and myelosuppression from other medications, and sometimes as manifestations of other cancer-associated processes, such as disseminated intravascular coagulation (DIC) and thrombotic microangiopathy (TMA)

syndromes [62]. Therefore, the diagnostic approach to cytopenias following ICI should also include the evaluation of micronutrient status (serum iron studies, red blood cell folate, serum cobalamin, serum copper, and pyridoxine), coagulation parameters (prothrombin time [PT], activated partial thromboplastin time [APTT], fibrinogen, and fibrin split products), and the review of the PBS.

Treatment

Clinical consensus guidelines on the management of ICI related-hematologic IRAEs have recommended the interruption of ICI accompanied by the use of IST [20]. The grading of the severity of the IRAEs has followed the Common Terminology Criteria for Adverse Events (CTCAE) criteria. For CTCAE grade 2 cases, the initiation of steroids, 0.5–1 mg per kg daily of prednisone equivalent, is the recommendation. For those CTCAE grades 3–4, the recommended dose of prednisone equivalent is higher, oscillating between 1 and 2 mg per kg per day.

For BMFs, those guideline recommendations extrapolate from regimen used in primary AA, including horse ATG and cyclosporine with the supportive care of G-CSF agents. Interestingly, in the case reports of ICI-aplastic anemia, the treating physicians have used prednisone with or without G-CSF agents as the most common strategies for those cases [32, 40, 44–58]. Similarly, in the REISAMIC registry, those patients were treated with oral prednisone or prednisolone 1 mg/kg per day in combination with G-CSF. One case required IVIG, rituximab, and romiplostim. After clinical response to IST (stable peripheral blood counts and absence of blood product transfusion), steroid taper can be initiated. Clinical consensus guidelines recommend to complete steroid taper within 4–6 weeks, similar to the recommendations for the management of other organ-specific IRAEs [20].

Long-Term Complications and Follow-Up

The reported duration of follow-up of cases with ICI related-BMF syndrome has ranged from 2 weeks to 9 months [32, 40, 44–58]. The event resolves in 30%–45% of the cases. Blood product transfusion support is frequent and permanent in some patients. To date, the paucity of data does not allow to infer the appropriate duration and frequency of follow-ups. From strategies used in primary AA and other similar BMFs, relapse occurs in 30%–60% of patients and usually responds to further immunosuppression. Long-term (years) continuation of IST is commonly required. Responses and outcomes are typically better in younger patients than in older adults [63].

Macrophage Activation Syndrome/ Hemophagocytic Lymphohistiocytosis

Macrophage activation syndrome (MAS)/ hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome that consists of a pathologic immune activation with clinical features of extreme inflammation and heterogeneous organ injury. First recognized as an inherited disorder, it can also debut in adulthood as a result of different triggers of the immune system, including cancer and its therapies [64]. Diagnostic criteria have been developed through consensus by the Histiocyte Society to standardize enrollment on clinical trials, HLH-94 and HLH-2004, and through clinical prediction models validated in pediatric and adult populations (H-score) [64].

Epidemiology

In regard to ICI-related toxicity, ten individual cases have been published to date describing MAS/HLH [65–71]. All the cases received anti-CTLA-4, anti-PD-1, anti-PD-L1, or combinations of those agents. The events occurred between 3 weeks to 17 months from the initiation of ICI.

Clinical Characteristics

The case definition criteria of the ICI-related cases followed an extrapolation from the HLH-2004 or the H-score criteria [72, 73]. Those criteria included the following clinical features: fever (peak temperature ≥ 38.5 C for >7 days); splenomegaly or hepatosplenomegaly; >2 cytopenias; hypertriglyceridemia (fasting triglycerides >177 mg/dL); elevated serum ferritin (>500 ng/mL); decreased serum fibrinogen levels (<250 mg/dL); elevated transaminase levels (AST >30 U/L); elevated soluble interleukin-2 receptor levels (>2400 U/mL); the presence of hemophagocytosis in biopsies from BM, spleen, or lymph nodes; and low or absent natural killer (NK) cell activity.

Three cases related to ICI had tissue diagnosis (two had BM biopsies, and one had liver biopsy) of hemophagocytosis [66, 67, 70]. One case had natural killer (NK) cell activity studies that showed decreased NK cell function [69]. One case without tissue diagnosis for hemophagocytosis had next-generation sequencing for 15 genes associated with familial HLH and was found to be heterozygous for PRF1 c.272C >T (p.A91V). Two cases had BM biopsy that did not show hemophagocytosis and had a high probability H-score and increased level of activated NK cells with decreased perforin expression by flow cytometry in one. The syndrome was

attributed to MAS in those cases. In the third MAS case, the BM biopsy procedure could not be done. The patient had a high probability H-score [68]. Two cases of MAS were defined by elevated interferon-γ levels along with high serum ferritin, C-reactive protein, and interleukin-6 levels. Tissue diagnosis was not performed [71].

Evaluation

Similar to the cases with multiple cytopenias, if MAS/HLH is suspected, the evaluation should include the approach to other etiologies of cytopenias and systemic inflammation (sepsis, drug hypersensitivity, DIC, liver failure, and myelophthisis among others). In cancer patients, it has been shown that the conventional clinical criteria for HLH may not be sensitive nor specific, and tissue diagnosis is crucial [74, 75]. Patients with malignancies commonly have different etiologies for elevated serum inflammatory markers (including serum ferritin), hepatosplenomegaly, coagulopathy, and liver dysfunction. The use of BM, liver, or lymph node biopsy methods can be helpful to confirm HLH.

Treatment

Data from the available case reports showed that high doses of steroids (dexamethasone 10 mg per m^2, methylprednisolone 1.5 mg per kg every 8 hours, prednisone 2 mg per kg per day) in combination with etoposide 150 mg/m^2 were the regimen used for some patients [65–71].

Most recently, expert consensus recommendations from the American Society of Hematology, on the management of HLH in adults, have stated that HLH syndromes induced by novel immunotherapies (ICI and also other T-cell-engaging strategies) require specific treatment. Besides interruption of the trigger agent and the use of steroids, anti-IL-6 antibody (tocilizumab) has been used with notable clinical resolution in HLH cases induced by other immunotherapies for cancer [76] (Table 6.1).

Traditionally, the first goal for HLH treatment is to suppress the overactive immune system and prevent further end-organ damage. Extrapolation from the HLH-94 protocol includes an 8-week regimen with etoposide intravenous (150 mg/m^2 twice weekly for 2 weeks and then weekly), dexamethasone intravenous or oral (20 mg/m^2/day, followed by 5 mg/m^2 for 2 weeks, 2.5 mg/m^2 for 2 weeks, 1.25 mg/m^2 for 1 week, and 1 week of tapering), and intrathecal methotrexate administered for a maximum of four doses only if there are neurological symptoms [77]. Typically the protocol is followed by consolidation bone marrow transplant (BMT). The consolidation strategy may be limited in ICI-hematologic IRAE, since ICI toxicity is not a standard indication for BMT procedures [78].

Table 6.1 Cytopenias associated with immune checkpoint inhibitors

Conditions	Common clinical features	Salient laboratory features
Warm autoimmune hemolytic anemia	Onset: 7–10 weeks Median age: 65 Symptoms: Anemic and hemolytic symptoms Signs: Pallor, icterus, hepatosplenomegaly, hemoglobinuria	Hemoglobin ↓ haptoglobin ↓ Indirect bilirubin ↑, lactate dehydrogenase ↑ DAT test: Positive with IgG +/− C3 in the majority PBS: Polychromasia, microspherocytes, small erythrocyte aggregates
Immune thrombocytopenic purpura	Onset: 6 weeks Symptoms: Petechiae, purpura, mucocutaneous bleeding	Platelet <100,000/cmm PBS: Isolated thrombocytopenia with no schistocytes, dysplastic changes, immature cells or clumping BM biopsy may be required Antiplatelet antibodies may be positive
Autoimmune neutropenia	Onset: 10 weeks Median age: 63 Symptoms: Fever, chills, and specific symptoms of the infected organs	Grade 3/4 neutropenia PBS: Isolated neutropenia with no immature cells, dysplastic changes BM biopsy may be required Antineutrophil antibodies may be positive
BM failure syndromes	Onset: 12–322 days Symptoms: Anemic symptoms, symptoms of infection or bleeding	Uni-cytopenia to pancytopenia PBS: No immature cells, dysplastic changes, or platelet clumping BM biopsy shows aplasia or hypoplasia
MAS/HLH	Onset: 3 weeks to 17 months Symptoms and signs: Fever, hepatosplenomegaly	≥ 2 cytopenias Serum ferritin ↑, CRP ↑, transaminases ↑, soluble interleukin-2 ↑, PT ↑, APTT ↑ Fibrinogen ↓ Tissue biopsies show hemophagocytosis

Abbreviations: *DAT* direct antiglobulin test, *IgG* immunoglobulin G, *C3* complement C3, *PBS* peripheral blood smear, *BM* bone marrow, *MAS* macrophage activation syndrome, *HLH* hemophagocytic lymphohistiocytosis, *CRP* C-reactive protein, *PT* prothrombin time, *APTT* activated partial thromboplastin time

Long-Term Complications and Follow-Up

From the available case reports to date, approximately 40% of cases demonstrated clinical response to IST. The majority of the patients succumbed to complications after the hematologic IRAE [65–71].

Thrombophilia and Hemostasis Complications

Cancer-associated thrombosis (CAT) is a common complication of malignancy; it carries a significant degree of morbidity and represents one of the main causes of mortality in ambulatory cancer population [79, 80]. Certain genetic factors, tumor histologies, types of chemotherapy, and laboratory parameters have been identified as risk factors for CAT, among others [81–83]. Traditionally, the CAT risk has been evaluated using the Khorana score and derivations of it [84]. The Khorana score (KS) has been widely used in clinical studies to assess the effect of primary ambulatory thromboprophylaxis for the prevention of CAT [85].

Epidemiology

Recently, two retrospective studies from single-center cohorts showed that patients who received ICI had a substantial risk of CAT [86, 87]. In those studies the incidence of CAT, specifically venous thromboembolic (VTE) complications, occurred in 13–24% of those patients. Arterial thrombotic events were infrequent, and occurred in 1% of patients at 1 year since the initiation of ICI [87]. Among the clinical factors, a prior history of CAT, younger age at cancer diagnosis, and metastatic disease were associated with higher incidence of CAT [86, 87]. Among biomarkers and laboratory parameters, a myeloid-derived suppressor cell phenotype of the peripheral blood mononuclear cells, higher interleukin-8, and soluble vascular cell adhesion protein-1 levels were associated with an increased risk to develop CAT [86]. Interestingly, one of the studies assessed the performance of the KS prediction of ICI-related CAT. The results showed that the KS did not predict the risk of CAT in those patients [87].

Other reported hematologic complications associated with thrombosis, such as TMA, have been rarely reported and only as anecdotal cases [88–91]. Complications of hemostasis and bleeding, such as acquired hemophilia, have been also part of exotic case reports [92].

Clinical Characteristics

The great majority of cases of thrombophilic complications during ICI are VTE events [87]. Approximately one third of them are deep venous thrombosis (DVT) of the limbs and another third complicated with pulmonary embolism (PE). Mesenteric and portal venous circulation events comprise 10% of events. The classic symptomatologies of DVT/PE following the Wells rule (calf swelling >3 cm compared to contralateral leg, collateral-non-varicose-superficial veins, leg edema, and localized tenderness along the deep venous system) are good clinical predictors of VTE in

general population [93, 94]. In cancer patients who are symptomatic the use of the Wells rule is appropriate. However, it is known that in the cancer population, approximately one third to a half of VTE are incidentally found in cancer staging imaging studies [95]. For those patients who present with arterial thrombotic events, symptoms of angina, transient ischemic attack, or acute arterial vascular occlusion (pain, coldness, paresthesias, pallor, and pulselessness) may be present.

Evaluation

The diagnostic evaluation should focus on the diagnostic imaging confirmation if the clinical suspicion of thrombosis is high. Conventional venous or arterial Doppler studies are useful. Computed tomography (CT) of the pulmonary artery would be indicated if the symptoms of DVT are accompanied by hypoxia or unexplained sinus tachycardia. When anemia and thrombocytopenia are observed during the acute thrombotic complication, evaluation for TMA is indicated. The evaluation of the PBS to search for schistocytes, PT, APTT, fibrinogen, and fibrin split products (e.g., D-dimer) are additional diagnostic tools.

In cases of major venous thrombotic events in unusual locations (brain, splanchnic circulation), other diagnostic imaging modalities such as magnetic resonance venogram imaging of the brain and CT imaging of the abdomen with intravenous contrast may be indicated. If arterial cerebrovascular or myocardial events are suspected, diagnostic approaches for acute cerebrovascular event and acute coronary syndrome should follow.

Treatment

The treatment of ICI-related thrombotic complications is derived from the recommendations of society guidelines for the treatment of CAT [96–98]. Long-term anticoagulation for at least 6 months is indicated for the great majority of DVT/PE cases in the cancer population. Low molecular weight heparins and direct oral anticoagulants (factor Xa inhibitors) are now available treatment options for the cancer population. In cases of arterial thrombotic complications, revascularization strategies as indicated and long-term use of antiplatelet therapies are also recommended [99–101].

Long-Term Complications and Follow-Up

The risk and benefit index of antithrombotic strategies in cancer patients is dynamic. The long-term follow-up of CAT involves periodic outpatient visits to assess complications to antithrombotics (mainly bleeding) and the evaluation of new

symptomatology of recurrent CAT. Thrombotic complications are associated with a negative overall survival impact in cancer patients. In those patients who develop thrombotic complications during ICI therapy, the incidence of CAT is also associated with a decreased overall survival. In subgroup analyses, there were no differences in CAT by tumor types or the different ICI agents [87].

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Chapter 7
Hepatology (Liver and Bile Duct)

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Abstract Immune-mediated hepatobiliary toxicity is one of the immune-related adverse events that could occur after initiating treatment with an immune checkpoint inhibitor. Importantly, it is a diagnosis of exclusion. Three important phenotypes of this toxicity have been recognized: hepatitic, cholangiopathic, and an "overlap" of both features. Although no pathognomonic features have yet been defined in this entity, published analyses on the histologic features can aid in building confidence toward the diagnosis - particularly when committing patients to immunosuppressive therapy - while excluding alternative diagnoses such as autoimmune hepatitis, which must be distinguished from an immunotherapy-mediated cause. Immunotherapy-mediated hepatobiliary toxicity is traditionally treated with corticosteroids in cases of moderate-to-severe disease. The severity of injury affects the management. Mild injury can be monitored closely while continuing immunotherapy, whereas more severe cases require the cessation of immunotherapy in favor of immunosuppressive treatment. Emerging clinical experience and new literature are changing the landscape of approaches to diagnosis and optimal treatments. Complex cases often relate to unsatisfactory response to standard treatment with steroids, particularly if remission is not achieved after adjunctive therapies are added, or if the patient has a pre-existing underlying chronic liver disease condition. While many patients successfully respond to steroid-based immunosuppressive therapy, a subset of steroid-refractory or steroid-dependent cases represents an

Chapter debriefing: Power point video presentation is provided at the end of the chapter.

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important area of unmet need. Several aspects of immune-mediated hepatobiliary toxicity require ongoing research, including its pathophysiologic mechanisms, risk factors for onset, and optimal treatments.

Keywords Immune checkpoint inhibitors · Immunotherapy · Hepatitis · Hepatobiliary toxicity · Cholangiopathy

Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CTCAE	Common Terminology Criteria for Adverse Events
d	Day
DILI	Drug-induced liver injury
GGT	Gamma-glutamyl transferase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
ICI	Immune checkpoint inhibitor
IMCp	Immune-mediated cholangiopathy
IMH	Immune-mediated hepatobiliary toxicity
INR	International normalization ratio
irAE	Immune-related adverse event
LBTs	Liver biochemical tests
mg	Milligrams
PCP	*Pneumocystis* pneumonia
ULN	Upper limit of normal

Introductions

The expanded approval of immune checkpoint inhibitors (ICIs) for the treatment of multiple cancer types has offered patients more opportunities in treatment selection and survival.

Hepatotoxicity is a well-recognized immune-related adverse event (irAE) associated with treatment with ICI. It is considered an “indirect” type of drug-induced liver injury (DILI). Depending on the specific ICI and whether the patient is treated with a single ICI or combination ICI, the incidence of hepatotoxicity could be as high as 29%. As more patients receive treatment with ICI, more cases of hepatotoxicity are expected to occur. Therefore, clinicians must exercise close pharmacovigilance to recognize liver-related irAEs early and then direct management.

ICI-mediated hepatobiliary toxicity (or "IMH") generally presents as asymptomatic elevation of alanine transaminase and aspartate transaminase, with or without alkaline phosphatase elevation. Some cases could be symptomatic, with associated jaundice, fever, malaise, and, rarely, death from liver failure. The diagnosis of IMH is made after careful exclusion of other etiologies of acute hepatitis based on medical history, laboratory evaluation, imaging, and histologic findings. In clinically significant cases of IMH, the management involves discontinuation of ICI followed by close monitoring and possible initiation of immunosuppression. Current society guidelines delineate specific recommendations depending on the grade of liver injury according to the Common Terminology Criteria for Adverse Events (CTCAE).

Because concomitant histologic bile duct injury has been observed, ICI-mediated cholangiopathic disease probably exists on a spectrum within IMH. Even extrahepatic biliary ductal involvement has been observed. The cases involving cholangiopathy present additional treatment challenges.

Nomenclature

The nomenclature used to describe hepatotoxicity associated with immune checkpoint inhibitors (ICIs) is variable. In referring to the general phenomenon, "immune-mediated liver injury caused by checkpoint inhibitors (ILICI)" may be used, particularly in the absence of histologic proof of hepatitis [1]. Other examples of terms that have been used include "hepatic irAE" and "immune-mediated hepatitis." The terms "immune-mediated hepatotoxicity" (or IMH) and "immune-related hepatotoxicity" (IRH) were utilized by Peeraphatdit et al. and Ziogas et al., respectively [2, 3]. Because bile ducts derive from the liver and with the knowledge that bile duct injury can occur simultaneously (or overlap) with hepatocellular injury, "immune-mediated hepatobiliary toxicity" or "ICI-mediated hepatobiliary toxicity" captures a broader spectrum of its heterogeneous presentations while maintaining the same abbreviation of "IMH" for consistency and brevity. Additional comments will be made in this chapter regarding the nomenclature for patients with cholangiopathic forms of this disease.

In describing the clinical course of IMH, we propose the following terminology and definitions:

1. Biochemical remission
    - Normalization or near-normalization of liver biochemistries, either naturally or with the implementation of immunosuppressive agents.
    - Can be defined as the status when the patient is either no longer on immunosuppressive medications or on only low doses of steroids (i.e., prednisone 5 mg/d or less) with anticipation for discontinuation; near-normalization (such as improvement to CTCAE grade 1) is regarded as sufficient if the

patient no longer requires ongoing immunosuppression and/or if it will not hinder considerations for ICI resumption.
- In clinical practice, sustained remission of a duration greater than 4 weeks on the equivalent of prednisone 5 mg/d or less, with stable liver biochemistries of CTCAE grade 1 or better after, may be considered a reasonable definition.

2. Relapse or resurgence
   - Worsening changes in biochemical trends, during observation for natural improvement, during the immunosuppressive phase in treating IMH, or after completion of immunosuppression but without resuming ICI therapy
3. Recurrence
   - Interval abnormal changes to liver biochemistries after resuming ICI

Epidemiology

IMH is a well-recognized irAE [4, 5]. The incidence of IMH varies depending on the ICI agent and whether monotherapy or dual ICI therapy is being employed. For instance, one pharmacovigilance study reported the incidence of IMH varies from 11% to 29% [6].

The incidence of hepatotoxicity associated with anti-CTLA-4 inhibitor ipilimumab is reported to be as low as 0.3% to even as high as 70.4% (if higher-than-standard doses are used) depending on the specific study [5]. The overall incidence of hepatotoxicity associated with anti-PD-1/L1 inhibitors is reported to be up to 12%, in which the incidence of IMH secondary to anti-PD-1 inhibitors (specifically pembrolizumab and cemiplimab) is considered to be relatively lower at 0.7–2.1% [2]. In data analyses including nivolumab, pembrolizumab, atezolizumab, and durvalumab, the estimated risk was 1–4% [7]. On the other hand, in patients treated with anti-CTLA-4 inhibitors, the risk of hepatotoxicity has been suggested to be 1–7% (for ipilimumab) and even up to 16% [2, 8–10].

The risk of IMH increases up to 30% in patients receiving ICI combination therapy (i.e., ipilimumab and nivolumab) [8, 9, 11]. In melanoma patients, the incidence of IMH can be as high as 49% in the cohort studied who received combination therapy [12]. Combination ICI exposure is thought to act in synergy to induce hepatocyte injury and hepatocyte death, as demonstrated in mice models [13].

Grade 3–4 IMH was reported in 1–3% of patients receiving ICI monotherapy and in 8–14% of patients treated with a combination of anti-PD-1 and anti-CTLA-4 therapy [10, 11, 14–20]. A single-center retrospective study at a cancer hospital corroborated similar patterns, where IMH of any grade occurred in 5.9% (of any grade) for anti-PD-1/L1, 9.5% (of any grade) in anti-CTLA-4, and 18.7% in combination ICI treatment [21]. Overall, the incidence of at least grade 3 IMH occurred in 1.1%, 1.7%, and 9.2%, associated with anti-PD-1/L1, anti-CTLA-4, and combination ICI treatment, respectively [21].

IMH is clearly not a rare or uncommon phenomenon. The diagnosis of grade 3–4 IMH has important implications for the patient's treatment course and prospects for future ICI candidacy, which will be discussed below.

Pathophysiology

Aside from T-cell activation pathways that affect hepatocytes, the specific mechanism by which IMH develops is not understood. No specific clinical factors have been defined as predictive for who is at higher risk of developing IMH. Hypotheses for mechanisms include the notion of a dose-dependent risk and permissive hepatotoxicity in those with pre-existing autoimmune disease, although no studies have included those with autoimmune hepatobiliary disease [2]. Because IMH is an immune-mediated process by a pharmacologic agent, the liver injury is considered DILI of an "indirect type" [2]. The relative expression of PD-1 vs. CTLA-4 and the duration of blockade may also have a role toward the onset of IMH [22].

Interleukin-6 (IL-6) has a well-established role in the normal physiologic pathways in liver biology, including regeneration and metabolism [23]. Inflammatory cytokines interleukin-1 and TNF-alpha may influence production of IL-6, where IL-6 can subsequently lead to induction of acute phase proteins. This is part of the IL-6 "classic signaling." Downstream signaling by IL-6 depends on the IL-6/IL-6R complex being able to associate with glycoprotein (gp) 130 with downstream signaling via the JAK1, MAPK, PI3 kinase, and STAT3 pathways. IL-6 receptor (IL-6R) expression can be found on hepatocytes, hepatic stellate cells, and biliary epithelial cells. Metalloprotease cleavage of IL-6R, called "shedding" yields sIL-6R, the soluble form, which can bind to IL-6, and the IL-6/sIL-6R complex can still associate gp130 and influence the downstream effects. This represents with trans-signaling pathway. Tocilizumab, which is a humanized anti-IL-6R antibody, blocks both the IL-6 classic and trans-signaling pathways, whereas an anti-IL-6 agent would not bind sIL-6R. The roles of these cytokines and signaling pathways have yet to be elucidated in the pathogenesis of IMH.

Proinflammatory cytokines play a role in both IMH and classical idiopathic autoimmune hepatitis (AIH). In AIH, T-cell-mediated responses involve key players such as T_{reg} cells, T_H2 cells, and T_H17 cells, eventually leading to an inflammatory response in the liver yielding interface hepatitis which includes plasma cells and lymphocytes [24, 25]. As will be discussed in the histologic observations of IMH, the lymphocytic predominance over plasma cells and the less common findings of interface hepatitis can differentiate IMH from AIH. Since CTLA-4 is expressed on peripheral T_{reg} cells, inhibition of the CTLA-4 checkpoint pathway causes escape of self-tolerance which can predispose to inflammation in the liver.

The cholangiopathic phenotypes of IMH, which will be discussed further, manifest due to special aspects of cholangiocyte biology. This is particularly important in patients treated with anti-PD-1/L1 inhibitors. Cholangiocytes express PD-L1 that can interact with PD-1 on activated T cells. In this fashion, inhibitory signals by cholangiocytes themselves can inhibit T-cell proliferation, but cholangiocytes can

also release inflammatory modulators [26]. SH2-containing phosphatase 2 (SHP2), which is downstream of the PD-1 signaling pathway for the T cell, suppresses T-cell activation [27, 28]. This forms the basis for examining the role of SHP2 inhibitors as a potential immunotherapy agent [28–30]. Intuitively, PD-1 blockade not only allows for antitumor effects by T cells but consequently makes inflammatory injury upon cholangiocytes permissive. Curiously, SHP2 is also part of the IL-6/JAK-STAT3 signaling pathway when SHP2 is recruited by the IL-6/IL-6R/gp130 complex as previously described [28].

Clinical Characteristics

IMH develops through an immune-mediated mechanism which manifests on a spectrum of hepatocellular and/or cholestatic injury [18, 31–33]. The clinical presentation of IMH remains highly heterogeneous, ranging from an asymptomatic state with mild rise in liver enzymes to, rarely, death as a consequence of acute liver failure [34–36]. Although hepatotoxicity is commonly an incidental finding on routine laboratory screening during the course of ICI treatment, clinical signs and symptoms of IMH can occur. Symptoms such as jaundice, changes in stool color, malaise, abdominal pain, and fever have been reported [31, 37, 38]. In the latest multicenter study examining characteristics of 146 patients diagnosed with IMH, 46% were asymptomatic. Other symptoms reported include fatigue/anorexia (17%), fever (14%), nausea/emesis (14%), and abdominal pain/back pain (12%). Jaundice has a low overall frequency of 3–4% [39].

Increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin are the commonly used biomarkers of IMH as suggested by society guidelines, regardless of the class of ICI [4, 10, 31, 35].

IMH can occur at variable times for different patients, most often becoming clinically evident at 5–13 weeks after initiation of ICI therapy [2, 20, 32, 35, 40]. However, the time to onset may be as early as 1 week after the initial administration of ICI, so routine laboratory monitoring remains important even before the next cycle of ICI [2]. Sudden onset of severe hepatitis can potentially occur despite the patient having tolerated long-term ICI treatment [41]. As such, relatively delayed onset of IMH can occur despite having tolerated long-term ICI treatment, attesting to the importance of pharmacovigilance.

Evaluation

Initial Assessment

The approach to the diagnosis of IMH is similar to the approach with other cases of suspected DILI. IMH is a diagnosis of exclusion. The clinician should perform a careful evaluation of the patient's medical history including concurrent medications, supplement (including herbal medications) use, and alcohol use history. Other

differential diagnoses should be explored and excluded [2, 10, 42]. When the level of suspicion for IMH is high after review of the medical history associated with a compatible chronology, the liver biochemical profile should be further characterized. Three major categories of liver injury pattern are hepatocellular, cholestatic, and mixed. The R factor (or "R-value") provides a quantitative approach to categorizing the liver injury pattern [43]:

$$\text{R factor} = \frac{\left(\text{ALT} / \text{ALT}_{\text{ULN}}\right)}{\left(\text{ALP} / \text{ALP}_{\text{ULN}}\right)}$$

Hepatocellular-predominant injury corresponds to an R factor greater than 5.0. Cholestatic-predominant injury corresponds to an R factor less than 2.0, when the ALP is at least 2× ULN. Mixed hepatocellular and cholestatic injury corresponds to an R factor from 2.0 to less than 5.0, when the ALT and ALP are both at least 2× ULN.

Based on both the magnitude of liver biochemical tests and the clinical presentation, grading Common Terminology Criteria for Adverse Events (CTCAE) grading should be employed since it determines the later management decisions for either observing or treating IMH [44].

Liver enzymes include two transaminases, ALT and AST, and alkaline phosphatase. Liver function tests are the international normalization ratio (INR), total bilirubin, and albumin. We will use the term "liver biochemical tests" (LBTs) to refer to the combination of liver enzymes and liver function tests.

In current society guidelines, the grading of IMH relies on the ALT, AST, and total bilirubin. CTACE grading also exists for alkaline phosphatase and gamma-glutamyl transferase (GGT), although these parameters are *not* traditionally included for influencing management, except for their inclusion in the diagnostic algorithm proposed by in a recent review of IMH published in 2020 in *Hepatology* [2]. The standard criteria for CTCAE grading are summarized in Table 7.1.

The correct interpretation of the liver biochemical profile affects the assessment of the patient's clinical status and the frequency of follow-up [38]. ALT is more specific than AST as an indicator of hepatocellular injury, although in general the magnitude of both liver enzymes is expected to be similar and track in proportion. In DILI, the ALT level is generally higher than the AST level. Depending on the clinical signs and symptoms, disproportionate elevation in the AST or new isolated AST elevation without ALT elevation may prompt evaluation for ICI-mediated myositis or myocarditis. When AST is more than double the ALT value, alcoholic hepatitis should especially be excluded. Variability in the upper limit of ALT will influence the categorization of the CTCAE grade, since the ULN varies depending on the lab facility where the population resides. While the AASLD previously adopted the ULN ALT of 19 U/L in women and 30 U/L in men, the latest AASLD guidelines suggest using ULN ALT of 25 U/L in women and 35 U/L in men [45–47]. Because there is otherwise no universal AST standard for its ULN, we recommend using the upper limit of AST reported by the interpreting laboratory. The level of lactate dehydrogenase (LDH) alone is not particularly helpful, except when utilized in calculating the ALT:LDH ratio, which can provide predictive categorization for viral infection, hypoxic hepatopathy, or acetaminophen-related liver injury [48].

Table 7.1 CTCAE version 5 grading schema for liver biochemical laboratory tests and for clinical assessment of liver function [44]. An expanded list of pertinent liver biochemistries or clinical assessment that should be assessed in patients with suspected IMH or while being managed for IMH, based on CTCAE version 5. Total bilirubin can only be reliably used to assess the state of cholestasis or the state of liver function if direct bilirubin is at least 50% of the total bilirubin; the analysis does not apply if the patient presents with indirect hyperbilirubinemia from the standpoint of hepatobiliary disease. GGT may act as a surrogate marker for cholestasis when analyzed in conjunction with the alkaline phosphatase level. Hepatic dysfunction can be assessed using parameters such as INR, total bilirubin, and albumin levels, but hepatic failure is a clinical diagnosis which requires physical examination. Abbreviations: *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *GGT* gamma-glutamyl transferase, *ULN* upper limit of normal, *CTCAE* grade 5 represents death

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
ALT	>ULN to 3.0× ULN	>3.0–5.0× ULN	>5.0–20.0× ULN	>20.0× ULN
AST	>ULN to 3.0× ULN	>3.0–5.0× ULN	>5.0–20.0× ULN	>20.0× ULN
ALP	>ULN to 2.5× ULN	>2.5–5.0× ULN	>5.0–20.0× ULN	>20.0× ULN
GGT	>ULN to 2.5× ULN	>2.5–5.0× ULN	>5.0–20.0× ULN	>20.0× ULN
Total bilirubin	>ULN to 1.5× ULN	>1.5–3.0× ULN	>3.0–10.0× ULN	>10.0× ULN
Hepatic failure assessment	–	–	Asterixis; mild hepatic encephalopathy	Life-threatening consequences; moderate-to-severe hepatic encephalopathy; coma

The alkaline phosphatase (ALP) level can be directly influenced by age, ethnicity, and the presence of metastatic disease to the liver or bone [49]. Traditional society guidelines exclude the ALP in the overall CTCAE grading. However, elevations should be characterized further to determine whether the contribution is predominantly from a cholestatic condition or from bone turnover, which could be differentiated by first checking the GGT level. In patients without bone metastases, elevation in the ALP can be observed in conjunction with ALT and AST elevation in IMH. Profound elevations may be a sign of possible simultaneous bile duct injury. As part of the initial serologic liver disease workup, primary biliary cholangitis (PBC) is part of the differential. An ALP level of at least 1.5× ULN is part of the traditional criteria for the diagnostic certainty of PBC. Therefore, we suggest ascribing significance to the ALP value when the following three parameters are observed: ALP at least 1.5× ULN (still within CTCAE grade 1 but even before approaching grade 2), any GGT above upper limit of normal, and an R factor of less than 2.0. The most recent review of IMH in *Hepatology* reprise the evaluation of both ALP and GGT in the initial evaluation [2]. Alkaline phosphatase isoenzyme evaluation may also be helpful in some circumstances.

Total serum bilirubin level is also specified in current published guidelines to be used as part of the overall grading schema. Bilirubin is one of the three major parameters for assessing liver function. However, fractionation of the bilirubin must be performed in those with hyperbilirubinemia because unconjugated hyperbilirubinemia may point toward a hematologic process (such as hemolysis) instead of impaired liver synthetic function. Therefore, this CTCAE grading should only be used when the direct bilirubin proportion is at least 50% of the total bilirubin. Like ALP, the burden of any metastatic disease in the liver could cause the bilirubin to be elevated. In IMH, whether or not the liver synthetic function is impacted by the toxic liver injury should rest on not only the cross-sectional interpretation of the other two LFTs (serum albumin and INR) but also the trends across time. Some patients with advanced cancer, cachexia, and malnutrition may at baseline have relatively low serum albumin or very mild elevations in the INR. A patient presenting with jaundice could also reflect unrelated cholestasis, a hemolytic disorder, or acute liver dysfunction. In the case of frank biliary obstruction, as in the case of choledocholithiasis or tumor impeding bile outflow duct, the total and direct bilirubin will be elevated due to obstructive jaundice. In a patient with hepatic metastases, the degree of metastatic burden to the liver organ should be carefully assessed.

To build confidence toward the diagnosis of IMH, and as part of the *initial* evaluation for the cause of either acute liver injury or acute on chronic liver injury, a comprehensive serologic workup must be considered, especially in those with at least grade 2 IMH (Table 7.2) [2, 4].

In cases of profound elevations in the ALT categorized as CTCAE grade 4, and particularly when ALT >1000 U/L, the clinician should evaluate for acute viral hepatitis, AIH, other competing causes of DILI, acute choledocholithiasis (especially when abdominal pain is present with ALP elevation, with or without jaundice), and hypoxic hepatopathy (particularly in the critically ill patients). Patients diagnosed with choledocholithiasis would follow a separate trajectory of management such as consideration for endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP), and/or endoscopic retrograde cholangiopancreatography (ERCP).

In patients who have had a prior history of pancreatitis (whether presumed to be related to ICI or without obvious relationship to biliary stones) associated with new alkaline phosphatase elevation and/or cross-sectional imaging implicating bile duct disease, we recommend checking IgG4 subtype to evaluate for any possibility of IgG4-related cholangiopathy, which bears the advantage of excellent response to corticosteroids. As this will be discussed further, the clinician should bear in mind the implications of diagnosing ICI-mediated cholangiopathy that is not associated with classical IgG4-related disease.

There is no relationship between autoimmune serologic markers such as ANA and the diagnosis of IMH [2, 20]. As this will be discussed in the histologic observations of IMH, IMH is an entity that is distinct from idiopathic AIH and drug-induced AIH [50, 51]. AIH may be excluded when histologic features on liver biopsy are not compelling for AIH in conjunction with a normal total serum IgG level. The AIH scoring systems can be used to gauge this further [52]. The expectation would be that cases with true IMH should actually yield low-probability AIH scores. No

Table 7.2 Pertinent laboratory studies to consider in the initial assessment of suspected IMH

General
Antinuclear antibody (ANA)
Anti-smooth muscle antibody (ASMA)
Anti-liver-kidney microsomal type 1 (LKM-1) antibody
Total serum IgG
Viral hepatitis A IgM
Viral hepatitis A IgG
Viral hepatitis B surface Ag
Viral hepatitis B core IgM
Viral hepatitis B core IgG
Viral hepatitis B surface antibody
Viral hepatitis B DNA quantitative
Viral hepatitis C RNA quantitative
Viral hepatitis C IgG
Viral hepatitis E IgM
Viral hepatitis E IgG
Viral hepatitis E RNA quantitative
Serum ferritin, iron, transferrin, and TIBC (assess transferrin saturation percentage)
Ceruloplasmin (especially when low levels of ALP are observed)
Anti-transglutaminase IgA and IgG with total serum IgA
HIV-1/HIV-2 antibodies
CMV serologies and quantification
HSV serologies and quantification
EBV serologies and quantification
If cholestatic pattern present
Gamma-glutamyl transferase (GGT)
Alkaline phosphatase isoenzymes
Anti-mitochondrial antibody (AMA) (M2 type)
Total serum IgM
IgG4 (as part of the IgG subclasses testing)
Depending on specific circumstances
Lactate dehydrogenase (LDH)
Creatine kinase (CK)
Acetaminophen level
Less valuable labs
CRP
ESR
Antineutrophil cytoplasmic antibodies (ANCA)

Quantitative viral tests should be checked initially for hepatitis B and hepatitis C; hepatitis E viral quantification can be checked if the Hepatitis IgM is detected. The clinician should decide whether quantification for CMV, HSV, and EBV is necessary depending on the medical history and risk factors for these viral entities, especially if acute hepatitis A, B, C, and E are excluded

scoring system exists otherwise for diagnosing IMH. In the absence of positive AMA M2 type, normal total serum IgM level, and lack of typical histologic features such as florid duct lesions and ductopenia, PBC can be excluded. Overall, the correct diagnosis of the observed laboratory derangements must be made as it would inform indications for steroid treatment and its duration, clinical outcomes, prognosis related to this irAE, and candidacy for ICI re-challenge.

Imaging

Abdominal imaging such as computerized tomography (CT), magnetic resonance imaging (MRI), and abdominal ultrasound (US), must be part of the initial evaluation although findings in patients diagnosed with IMH are usually nonspecific [53]. Imaging can help detect other etiologies that lead to abnormal liver biochemical tests such as liver metastasis, intra- and extrahepatic biliary tree abnormalities, or a vascular event such as hepatic vein or portal vein thrombosis [31, 54]. In patients who present with cholestasis suspicious for biliary tract disease, high-quality imaging targeting the biliary tree such as MRCP must be performed to exclude entities such as choledocholithiasis or other reasons for obstructive jaundice.

In general, IMH alone is associated with normal appearance of the liver or no new interval changes compared to prior liver imaging [31, 55]. However, reported radiological features in IMH that could manifest include periportal edema, hepatomegaly, periportal MRI T2 hyperintensity, attenuated liver parenchyma, and enlarged periportal lymph nodes on CT or MRI in severe IMH [31, 56, 57]. In one retrospective study related to IMH secondary to ipilimumab, where associated abdominal imaging abnormalities were present, subsequent treatment of IMH led to resolution of hepatomegaly and improvement of periportal lymphadenopathy [31].

The Role of Liver Biopsy and Histopathologic Features

The role of routine liver biopsy for diagnosing IMH is considered controversial since the liver biopsy is an invasive procedure not without some degree of risk to the patient [2, 58, 59]. There is with no standardized criteria across published guidelines. The latest NCCN guidelines and ESMO guidelines suggest pursuing liver biopsy in those patients diagnosed with grade 4 IMH [59–61]. The SITC guidelines published in 2017 recommend considering liver biopsy in grade 3 or grade 4 IMH [62]. No specific recommendations are made about when to refer for liver biopsy in the ASCO guidelines published in 2018 [38]. In clinical practice, if liver biopsy is not initially performed during the diagnostic phase, it may be considered in those patients who do not exhibit satisfactory LBT improvement, either spontaneously or in response to systemic corticosteroid treatment, depending on the CTCAE grade.

A major limitation in the interpretation of the histological features is that there are no known pathognomonic findings specific to IMH. Despite this limitation, the histologic evaluation from a liver biopsy offers several advantages in select patients without contraindications to liver biopsy, those with grade 3–4 liver injury, and those with concomitant or predominantly cholestatic biochemical liver injury pattern. As with serologic testing, the histologic findings serve to exclude other causes of liver injury when the serologic data may not be revealing. Whether or not the patient has positive autoimmune antibodies, the pattern of histologic inflammation could differentiate IMH from AIH, even though there are *also* no pathognomonic

histologic features specific to AIH. In cases with cholestatic injury LBT patterns, the biopsy can confirm whether there is cholestasis and whether bile duct injury is seen in conjunction with hepatitis. In a study of melanoma patients to gauge the utility of liver biopsy for suspected IMH, 58 patients with grade 3–4 liver injury underwent liver biopsy, 3 of whom were diagnosed with a condition other than IMH [63]. Although the conclusion derived from this study questioned the utility of liver biopsy in relation to the ultimate clinical outcome, the authors acknowledged that some biopsies (21.8% of the remaining 55 patients) revealed bile duct injury, corroborating the need for attention to those with cholestatic liver injury [63].

In the latest review of IMH in *Hepatology*, the authors suggest the utilities of biopsy include finding granulomas (which may support IMH especially if the ICI used was an anti-CTLA-4 inhibitor), capturing undiagnosed metastatic disease that may not be seen on imaging, and evaluating the histologic severity of liver injury [2]. One case series proposes that liver biopsy could hold an important role in determining whether steroids should or should not be initiated [20]. Furthermore, some patients could have undiagnosed chronic liver disease prior to starting ICI such as NAFLD including NASH or even cirrhosis (particularly in patients with HCC). Although severe liver fibrosis is also *not* expected to be directly related to new-onset liver enzyme abnormalities or to IMH, finding of severe fibrosis or cirrhosis will contribute to the clinician's view of prognosis and candidacy for ICI re-challenge. In echoing the notion of arriving at the correct diagnosis, particularly in patients who may have established liver metastasis or if there is concern for "silent" metastasis in the liver not identified on imaging, additional data, specifically a liver biopsy, will help determine if steroids should be initiated at all [64].

The most common histologic descriptions attributed to patients with IMH include nonspecific features of lobular or pan-lobular hepatitis, necroinflammatory findings that are either spotty or confluent, fibrin ring granulomas (particularly in those with anti-CTLA-4 exposure), central vein endotheliitis, prominent sinusoidal lymphohistiocytic infiltrates, and bile duct injury [17, 35, 37, 65, 66].

One case series observed that the histopathology of IMH associated with anti-CTLA-4 inhibitors could manifest as granulomatous hepatitis with fibrin ring deposits, whereas cases associated with anti-PD-1/L1 inhibitors tend to exhibit more heterogeneous patterns as it relates to lobular and periportal inflammation, but microgranulomas could be seen [20, 58, 66–68]. Although interface hepatitis could potentially be present in some cases of IMH, it is neither a universal nor a specific finding, and the inflammatory population in IMH is not of plasma cell predominance as in AIH [1, 35]. The finding of hepatic steatosis or steatohepatitis is not expected to be a direct consequence of IMH; such a finding may prompt revisiting the patient's history to determine the likelihood of having prior alcoholic liver disease or NAFLD prior to initiation of ICI [35, 69]. Patients who undergo initial liver biopsy after several weeks or more of steroid therapy could develop fatty liver, which may confound the clinical picture [70].

Although the diagnosis of IMH traditionally addresses hepatocellular injury, the observation of bile duct injury should not be overlooked. In a case series of patients as regarded as having immune checkpoint inhibitor-mediated hepatotoxicity, 9 out of 16 (56%) histologic evaluations had evidence of bile duct injury. Three of those nine cases were associated with jaundice, and one of those three cases required very high

doses of corticosteroids with a protracted course of treatment [20]. Vanishing bile duct syndrome has been reported in two cases in the published literature to date [71, 72]. In differentiating ICI-mediated duct injury from PBC, florid duct lesions and ductopenia are *not* typical histologic findings associated with ICI exposure. Multiple reports of secondary sclerosing cholangitis associated with ICI, especially anti-PD-1 inhibitors, have been published [73, 74]. Both intrahepatic bile duct involvement (best ascertained by histologic evaluation through liver biopsy) and extrahepatic biliary ductal disease (best evaluated via MRCP) have been described [66, 68, 75–78]. It is possible for cross-sectional imaging to mimic that of primary sclerosing cholangitis (PSC) or even IgG4-related disease involving the bile ducts. Such conditions should be considered in the differential diagnosis during initial evaluation. Demonstration of histologic bile duct injury may be important during the diagnostic investigation. The implications of cholangiopathic phenotypes will be discussed further.

In immunohistochemical analyses, IMH exhibits increased numbers of CD3+ and CD8+ lymphocytes and decreased CD20+ B cells and CD4+ T cells, which can be a distinguishing features compared to AIH and potentially other drug-induced liver injury [2, 20, 35, 58, 66]. These immunohistochemical stains are not routinely employed with liver biopsies for patients suspected of having IMH, but the current data points to potential value for such tests to add another layer of diagnostic certainty.

Current society guidelines suggest that liver biopsy may be considered if the patient with ILICI does not demonstrate improvement *after* initiation of steroids. One concern of obtaining a biopsy after starting moderate-to-high dose steroids is whether this would attenuate the histologic features that would have otherwise been seen as previously described. Although this can occur, a delayed biopsy after starting immunosuppression can still be helpful in excluding an alternative cause and, by exclusion, corroborate the clinical diagnosis of IMH. Another advantage to obtaining the initial diagnostic liver biopsy before starting steroids is to correlate whether the histologic changes are as severe as the CTCAE grade might make it seem. For instance, a patient with grade 2 levels of liver injury can have significant necroinflammatory changes and apoptotic bodies, whereas a patient with grade 4 levels of liver injury might show only mild lobular inflammation. This phenomenon of "histobiochemical discordance" might provide insight into the true severity of liver injury that cannot be accurately judged from liver biochemistries alone. It could also explain why severe IMH can just as well respond to corticosteroid doses less than 1–2 mg/kg/d.

Management and Treatment Options

The severity of liver injury is graded according to (CTCAE) version 5.0. These grades are used to determine the preferred treatment approach to IMH [38, 79].

A comparison of the latest society recommendations is displayed in Table 7.3, which features an abridged summary of recommendations from each of the following sources:

- American Society of Clinical Oncology (ASCO), *Journal of Clinical Oncology* [38]

Table 7.3 Summary and comparison of different published guidelines offered to manage IMH

CTCAE grade	ASCO	NCCN	ESMO	SITC	Peeraphatdit et al. in *Hepatology*	AGA
1	Continue ICI with close monitoring Labs 1–2×/week	Nomenclature: G1 "mild" Monitor labs with increased frequency Continue ICI depending on lab trend	Continue ICI Repeat labs in 1 week if increase to >G1	Continue ICI Weekly labs; reduce frequency of labs upon improvement or with stability	Continue ICI Labs 1–2×/week No CS	Continue ICI if asymptomatic Close lab monitoring If symptoms or lab results worsen, follow management of higher-grade liver injury
2	Hold ICI Monitor for recovery to G1 *Consider CS 0.5–1 mg/kg/d pred equiv*. ICI resumption if G1 or prednisone 10 mg/d or less	Nomenclature: G2 "moderate" Hold ICI Monitor labs q3–5d *Consider pred 0.5–1 mg/kg/d*	Hold ICI Labs q3d *Start pred 1 mg/kg* Liver disease panel Imaging for mets or clot When G1, wean pred over 2 weeks; resume ICI once pred ≤10 mg	Hold ICI Start *pred 0.5–1 mg/kg/d* then 4 weeks taper Monitor labs twice weekly When G1 or less, and/or pred dose 10 mg/d or less, resume ICI	Hold ICI Labs q3d No CS initially, unless labs do not improve: *Pred 0.5–1 mg/kg/d* Resume ICI when G1	Hold ICI Consider *liver biopsy* Start *oral pred 0.5–1 mg/kg/d* Taper steroids >= 1 month if condition improves Resume ICI if condition improves to = < G1

3	G3 “symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis” Permanent discontinuation of ICI *Start CS 1–2 mg/kg* methylprednisolone or equiv. If not better after 3 days, consider MMF or azathioprine CS taper attempt around 4–6 weeks; optimal duration unclear	Nomenclature: G3 “severe” Permanent discontinuation of ICI *Start pred 1–2 mg/kg/d* Labs q1–2d Liver consult If not better after 3 d, consider MMF	“Cease treatment” ALT or AST <400 with normal LFTs: *Pred 1 mg/kg* ALT or AST >400 or abnormal LFTs: *IV CS 2 mg/kg* ALT 400 U/L ≈ 11–16× ULN	Discontinue ICI Monitor labs every 24–48 h Start *pred 1–2 mg/kg/d* Taper off steroid over 4 weeks when G1 or less Consider *liver biopsy* Consider MMF if no response after 72 h of steroids	Hold ICI Labs q2d *If no lab improvement, then start pred 0.5–1 mg/kg/d* When G2, taper steroid over 4–6 weeks Consider resuming ICI/switch ICI class	Discontinue ICI permanently Consider admission Consider *liver biopsy* Start *IV MP 1–2 mg/kg/d* Taper steroid > = 1 month if condition improves If refractory × 3 days, consider alternative agents: MMF, tacrolimus, or azathioprine If fulminant hepatitis, consider ATG
4	G4 features of liver failure Permanent discontinuation of ICI *Start CS 2 mg/kg MP or equiv.* If not better after 3 days, consider MMF CS taper after 4–6 weeks when G1 or less; optimal duration unclear	Nomenclature: G4 “life-threatening” Permanent discontinuation of ICI *Start pred/MP 2 mg/kg/d* Inpatient care Daily labs Liver consult *Liver biopsy* If not better after 3 days, consider MMF (0.5–1 g q12h)	Permanent discontinuation of ICI *IV CS 2 mg/kg*	Discontinue ICI Monitor labs every 24–48 h Start *pred 1–2 mg/kg/d* Taper off steroid over 4 weeks when G1 or less Consider *liver biopsy* Consider MMF if no response after 72 h of steroids	Hold ICI Labs q1d Consider admission Start *IV MP 1–2 mg/kg/d*	As in G3

(continued)

Table 7.3 (continued)

CTCAE grade	ASCO	NCCN	ESMO	SITC	Peeraphatdit et al. in *Hepatology*	AGA
Additional comments	G2/3/4: Avoid infliximab	G3/4: Infliximab should not be used If G3 and was on combination CTLA-4 and PD-1/PD-L1 inhibitors, then could resume with PD-1/PD-L1 only	G3/4: Once G2, change to oral prednisolone and wean over 4 weeks; G3, re-challenge with discretion If worsening despite steroids, change PO to IV steroids; add MMF 500–1000 mg twice daily; if worse on MMF, consider adding tacrolimus; consider ATG		Proposes incorporation of ALP and GGT into the grading schema G4: If labs do not improve, consider MMF, azathioprine, tacrolimus, UDCA, and ATG G4: Infliximab to treat IMH controversial	

Society guidelines published by ASCO, NCCN, ESMO, SITC, and the AGA, and management approach proposed by Peeraphatdit et al. in *Hepatology*, the journal of the AASLD, are featured in this table. There are some variations in the steroid dosing and the approach to escalation of treatment beyond corticosteroids. The recommendations offered in the current published algorithms are currently based on expert consensus. Abbreviations: *CS* corticosteroids, *pred* prednisone, *MP* methylprednisolone, *PO* per oral, *IV* intravenous, *MMF* mycophenolate mofetil, *UDCA* ursodeoxycholic acid, *ATG* anti-thymocyte globulin

- Society for Immunotherapy of Cancer (SITC) [62, 80]
- National Comprehensive Cancer Network (NCCN) [59]
- European Society for Medical Oncology (ESMO) [60]
- Peeraphatdit et al.'s review of IMH in *Hepatology* (journal of the American Association for the Study of Liver Diseases or AASLD) [2]
- American Gastroenterological Association (AGA) [81]

A primary limitation in the current guidelines is that the recommendations are based on expert consensus without robust data. Guidelines published before the year 2020 also have not accounted for interval new insights that have been either published or presented in society conferences. Therefore, monitoring and treatment strategies should be tailored to the patient's specific scenario. We offer our treatment recommendations based on both existing guidelines, appraisal of the latest published evidence, and outcomes from our own clinical experience (Fig. 7.1).

In patients for whom IMH is being treated with steroids, the treatment pathway would include initial induction with corticosteroids, with routine monitoring until transaminases approach either complete biochemical remission or near biochemical remission (i.e., ALT of 2× ULN or less), followed by steroid taper and establishment of ongoing favorable lab trends or of normal values over an additional 2 months.

Summary of Initial Management Recommendations

Grade 1
Patients may continue ICI treatment with close monitoring of the LBT. Liver biopsy is not necessary to make the diagnosis.

Grade 2
ICI should be temporarily withheld with close monitoring of the trends in LBT. Like in many cases of DILI, because spontaneous improvement could be observed in the short term, the first week may be used to initiate a more comprehensive liver disease workup including the need to exclude acute infectious hepatitis before deciding on steroid initiation. If LBTs do not improve or worsen while remaining within grade 2 parameters, oral prednisone dosed at 0.5–1 mg/kg/d (see more details below) can be considered with a subsequent taper. Weekly lab monitoring is recommended.

Grade 3
The CTCAE schema defines a wide range of transaminase elevations (5–20× ULN) within this grade. Minor variability exists among the different society recommendations regarding management in this range. ICI must be first withheld entirely. A comprehensive liver disease workup should be promptly initiated. Liver biopsy should be considered to increase confidence for the diagnosis of IMH. Because grade 3 IMH has the potential to demonstrate spontaneous improvement, it is reasonable if not encouraged to monitor for signs of improvement in LBT for 1–2 weeks after recognition of LBT, during the diagnostic testing phase, before deciding to

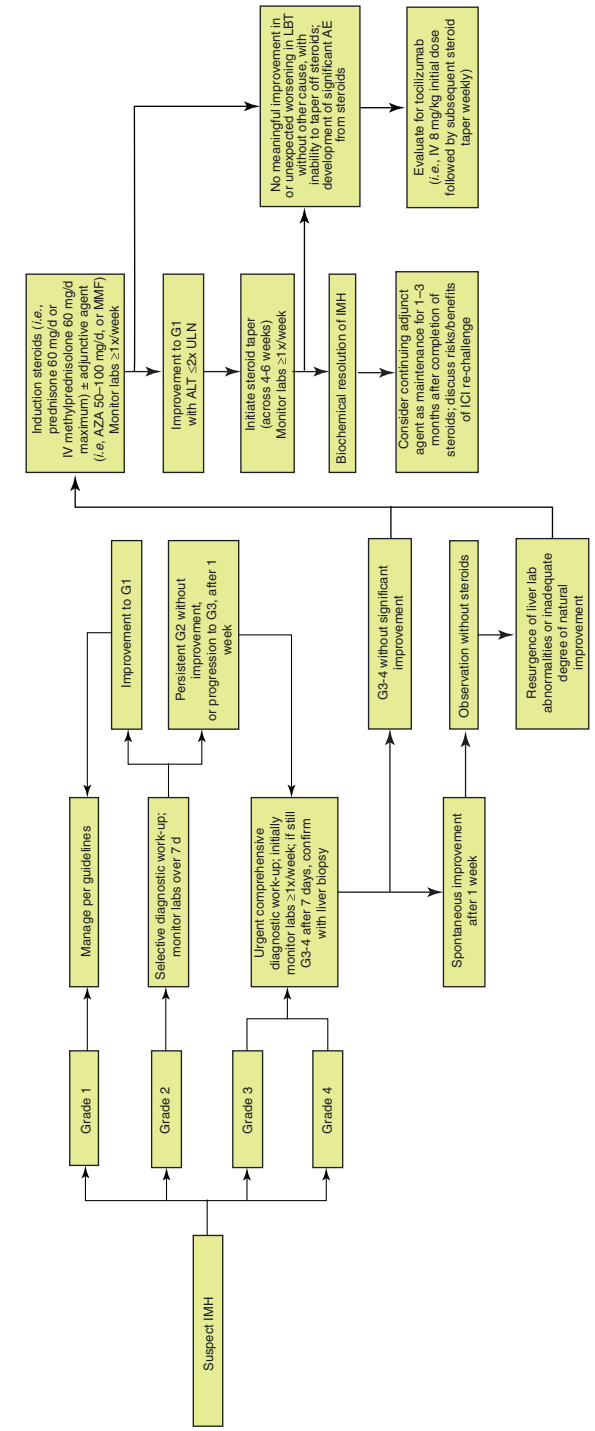

Fig. 7.1 During the initial work-up for suspected IMH, the initial overall CTCAE grade of liver injury affects whether ICI should be withheld or whether it can be continued (such as in the case of grade 1). Initial identification of grade 2 IMH can be closely monitored to determine the trajectory after 1 week, without immediately resorting to steroid therapy. The indication for initiating steroid therapy in grade 3-4 IMH is more compelling. However, because it is possible for grade 3-4 IMH to resolve naturally without the use of steroids, we propose a "grace period" during which the initial work-up is implemented to exclude other forms of acute liver disease, offer time to arrange for a potential liver biopsy, and confirm the diagnosis histologically, before deciding to commit to steroids. Abbreviations: *G* grade, *AZA* azathioprine, *MMF* mycophenolate mofetil, *ICI* immune checkpoint inhibitor

initiate steroids [21]. However, initiation of steroids should not be delayed once infection is confidently excluded and if LBTs are not already improving.

Traditionally, a steroid dose range equivalent to either IV methylprednisolone or oral prednisone 1–2 mg/kg is suggested, according to guidelines. The necessity of this dosing paradigm has been challenged [2, 82–84]. It is important to recognize that well-established infectious etiologies should be excluded before initiating high-dose steroids. ESMO guidelines subcategorize grade 3 IMH into those with ALT above or below 400 U/L, to aid in determining whether corticosteroid doses of 1 or 2 mg/kg/d should be employed. In *Hepatology*, the authors of the review adopt an overall lower steroid range of 0.5–1 mg/kg/d. Close lab monitoring, even as often as every 1–2 days, should be considered to track the evolution of changes in LBT. Weekly labs are generally adequate in those who exhibit favorable changes in LBT. Steroids are eventually to be tapered over 4–6 weeks or longer, depending on LBT trends [10, 80, 85].

Grade 4

ICI must be withheld. Thorough liver disease workup should be immediately pursued. Liver biopsy should be highly considered. Grade 4 IMH also has the potential to demonstrate spontaneous improvement, so it is reasonable if not encouraged to monitor for signs of improvement in LBT for 1–2 weeks after recognition of abnormal LBT during diagnostic testing and before deciding to initiate steroids [21]. However, as with grade 3 IMH, if the LBT trends are not favorable after the first week, initiation of corticosteroids should not be delayed if infection is already excluded or not suspected. Similar to grade 3, grade 4 IMH has been traditionally treated with high-dose corticosteroids as high as 2 mg/kg/d (per guidelines by ASCO, NCCN, ESMO, SITC, AGA). The review of IMH in *Hepatology* suggests a range of steroids from 1 to 2 mg/kg/d. This dosing paradigm has also been challenged [82, 83]. Steroids are eventually to be tapered over 4–6 weeks [10, 80, 85] but may take longer depending on starting dose of steroids and evolution of LBT. Of note, NCCN guidelines categorize grade 4 IMH as "life-threatening," which is not universally true, since the magnitude of transaminase elevation alone does not equate to active liver synthetic dysfunction. Therefore, precise interpretations of the LBT and careful physical exam for jaundice and hepatic encephalopathy are important to make conclusions about true hepatic failure.

Especially for grade 3–4 IMH, the decision may be whether to initiate steroids at all. Not cases of this severity require urgent initiation of steroids. Given that some patients may experience natural improvement without the need for steroids, and given that no specific clinical factors have been defined to predicts who will need steroids or who would not, even when histology can be obtained, a 7-day observation period may be beneficial to identify the patients who may demonstrate spontaneous biochemical improvement as long as the ICI is withheld. Because gaps may be present in the available liver biochemistries at the time of first identification of abnormal liver enzymes, the patient may fall into one of these four categories (Fig. 7.2):

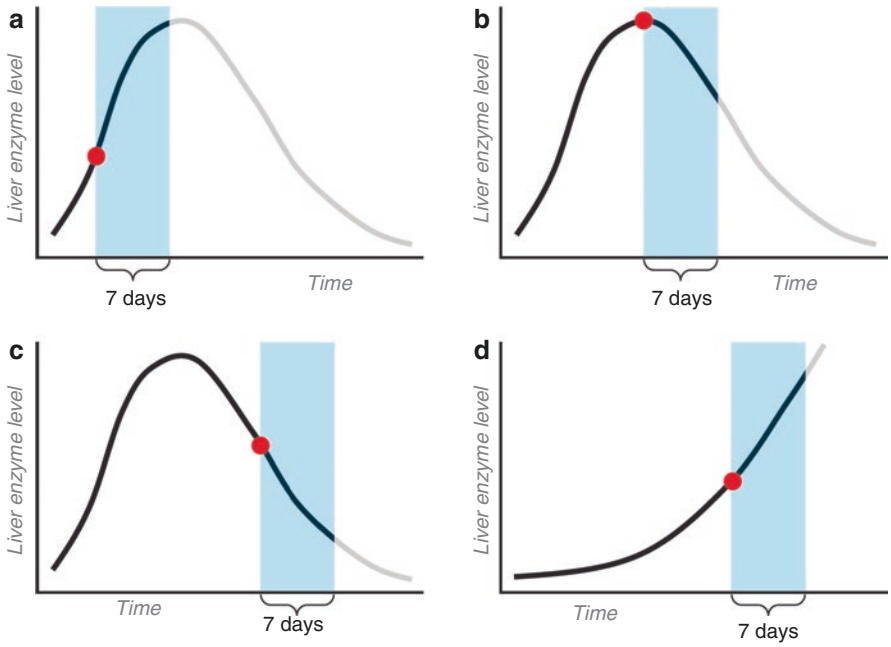

Fig. 7.2 The red dot indicates the time of initial identification of LBT abnormalities. In scenario (**a**), the patient's liver enzymes may continue to rise after 7 days but potentially peak. The increase of liver enzymes will decelerate. A decision can be made at 7 days whether to initiate steroid therapy or opt to monitor an additional 7 days for potential improvement; there may still be a high likelihood of requiring steroid induction to encourage improvement of IMH. In scenario (**b**), the initial liver enzyme elevation is captured at its peak, and monitoring for 7 days will allow for time to observe the natural improvement potentially without the need to initiate steroids, with close ongoing observation of LBT trends. In scenario (**c**), elevated liver enzymes are initially detected by the clinician, but data could be missing for values between baseline or normal values. Therefore, the peak may have already occurred hypothetically, since this data may not be available, and the behavior could appear indistinguishable from scenario (**b**). Monitoring labs for 7 days demonstrate natural improvement, and this initial may be defined as the peak value, similar to scenario (**b**). In scenario (**d**), liver enzymes demonstrate consistent elevation without a trend to suggest deceleration. Even if there is a possibility of natural improvement in the future, the urgency to control increasing inflammation acutely, and to allow earlier consideration of future cancer treatments, steroids should be promptly initiated in this case

Commentary on Steroid Treatment Strategies

Systemic steroids bear the well-established risk of serious adverse effects, such as developing impaired glycemic control or even diabetes, and infection. The effects of steroids used to treat irAE have not been clearly shown to affect ICI's antitumor response, although limited retrospective data intimates at the potential to influence overall survival, which was observed to be different between low-dose and high-dose steroid groups [86, 87]. The decision to initiate steroids, including in grade 3–4 IMH, should rest on a high confidence of diagnosis of IMH after ensuring that a

broad liver disease workup, as previously delineated, has not revealed a competing cause for new-onset abnormal LBT.

No systematic studies are available to endorse the superiority of efficacy of steroid doses that range 1–2 mg/kg/d of corticosteroids, since the current published guidelines are based on expert consensus without high-quality evidence, and no specific references are cited to support these doses. The risk of steroid-related AE rises with higher dosage (such as 2 mg/kg/d), which also subsequently lengthens the duration of steroid taper schedule, ultimately resulting in a much higher cumulative steroid dose. Therefore, potentially safer and alternative routes of management can and should be considered, especially since real-world clinical experiences have already demonstrated efficacy of alternatives, even observation without steroids, for grade 3–4 IMH.

In treating classic idiopathic AIH, the initial starting dose considered is up to 60 mg/d maximum for monotherapy, or a starting dose of prednisone 30 mg/d (or 20–40 mg/d) with azathioprine for combination therapy [88, 89], regardless of patient weight. A similar dosing strategy has recently been explored. In Cheung et al., which included nine patients (43%) with grade 3 IMH and five patients (24%) with grade 4 IMH, patients who received the equivalent of prednisolone 50–60 mg/d were compared with those treated with more than 1 mg/kg/d. Importantly, higher prednisolone doses did *not* appear to shorten the time to normalization of ALT, concluding that higher doses may not confer additional therapeutic benefit [82]. In a case series of nine patients with grade 3–4 IMH, eight patients were treated with initial dose of prednisone 60 mg/d, and one patient was treated initially with IV methylprednisolone 60 mg/d, with improvement to grade 1 by a median of 13 days [83]. Of note, in this cohort, seven patients also received concurrent azathioprine [83]. Based on this small case series, it remains unknown whether concurrent azathioprine adjunct compensated for a relatively lower dose of prednisone for the initial induction to achieve response, which still would likely yield a relatively lower cumulative dose and duration of prednisone exposure, compared to higher doses that these patients may have otherwise received if guidelines were to have been strictly followed.

Whichever induction dose of steroids is selected, the goal of treatment should be biochemical remission (and prompt reversal of any hepatic dysfunction if initially present). The ALT, AST, and total bilirubin can serve as the markers for assessing biochemical improvement in the majority of cases. The patient must first able to reach grade 1 parameters of these parameters during the steroid-induction phase and then eventually fully normalize all liver enzymes and/or associated elevation in bilirubin. Steroid responsiveness should be identified within the first 7 days, if not the first 3 days, as this would influence the decision to initiate adjunctive treatments which will be later discussed. Immune-mediated inflammatory conditions including both AIH and IMH are subject to potential for relapse or uncontrolled inflammation particularly during the steroid tapering period. No specific guidance has been offered by societies as to when to begin the taper after the initial steroid dose has been implemented. We generally continue the initial steroid dose until LBTs at least attain grade 1 parameters. When the ALT has achieved 2× ULN or less, a slow

steroid taper can be implemented over 4–6 weeks, depending on starting dose and LBT progression. The reason ALT is selected over AST is due to the more specific nature of ALT in relation to liver inflammation, compared to AST. Alkaline phosphatase values may fluctuate, so no explicit goal is defined for this parameter. A threshold of 2× ULN of the ALT value is selected based on the notion that grade 1 elevations in liver parameters are regarded as mild and even allowable for ongoing ICI treatment; from the standpoint of improvement from liver injury that was greater than grade 1, a threshold too close to an ALT of 3× ULN is not considered near biochemical remission, as there may still be an opportunity for the ALT to increase >3× ULN, at which point a premature steroid taper can even lead to resurgence in the inflammation.

Once induction steroids are started, we strongly advise against initiating the steroid tapering process too early (i.e., if the patient has not yet achieved stable CTCAE grade 1 parameters or better), which may lead to uncontrolled IMH and resurgent elevation of the liver enzymes. Depending on the rate of kinetics of the improvement of the liver enzymes, for example, a patient who started on high-dose steroids should not automatically taper after 7 days without sufficient improvement. As such, we do not advise starting with a fixed weekly taper schedule, since the patient may not approach grade 1 parameters after the first 7 days, and this could lead to uncontrolled IMH which may then require escalation of the steroid dose and prolongation of the steroid duration. Furthermore, the lack of adequate improvement may be a predictor of steroid unresponsiveness. These aspects of treatment response are still being studied.

Because ALT is more specific for hepatocellular injury than AST, preference is given for using ALT instead of AST. During recovery from liver injury, the AST may improve relatively more quickly than ALT, so the ALT becomes the limiting factor to ensure that the taper is not initiated too soon. Depending on the CTCAE grade and trends, labs twice a week or once weekly should be decided by the clinician. When LBT trends are favorable, weekly labs should be continued during the steroid taper, in order to identify early any indication of inefficacy of the steroid dose or for unexpected relapse.

The taper schedule may be influenced by several factors, including initial steroid responsiveness, comorbidities, and whether ICI re-challenge is being considered. An oral prednisone taper, once deemed appropriate, for instance, may involve a decrement of either 20 mg/d or 10 mg/d every 7 days, with a final week of 5 mg/d (Fig. 7.1). Relapses present a particular challenge to patients during the steroid taper as it could entail either extending the duration of the active steroid dose or temporarily increasing the dose. Currently, there are no systematic studies or randomized control trials to show the optimal approach for steroid taper in IMH. Therefore, steroid treatment strategies should be guided by clinical experience and/or with expert consultation with hepatology.

During the steroid taper phase, there may be cases where the ALT may not improve further or show small fluctuations that might suggest resurgence. We suggest one of the three options:

1. Prolong the current steroid dose for another 7 days.
2. Increase the current steroid dose by 10–20 mg/d for another 7 days.
3. Administer "pulse steroids" at a higher dose than the initial induction dose of steroid (can be equivalent of intravenous methylprednisolone or oral prednisone) for a maximum of 3 days and reassess response.

Nonresponse to these approaches may be a clue to change treatment strategies. A hepatologist should be consulted to provide further guidance.

In all patients initiated on the path of steroid treatment for IMH, we recommend prophylaxis against *Pneumocystis* pneumonia (PCP) (previously known as *Pneumocystis jirovecii* pneumonia) and for gastric protection to prevent steroid-associated peptic ulcer disease. Common options for PCP prophylaxis include atovaquone, dapsone, and trimethoprim-sulfamethoxazole. Trimethoprim-sulfamethoxazole may be less favored in the setting of IMH due to its well-known potential for hepatotoxicity, including cholestatic liver injury. If dapsone is selected, glucose-6-phosphate dehydrogenase (G6PD) level should be checked before starting the medication to determine the risk of dapsone-induced hemolytic anemia. In our practice, atovaquone (750 mg twice daily) is preferred. Once the steroid dose is tapered down to less than the equivalent of prednisone 20 mg/d (with the expectation to complete the steroid regimen soon), PCP prophylaxis may be discontinued. Proton pump inhibitors (PPI) for gastric protection may be continued until the completion of corticosteroids, if no other indication exists.

Patients with previously impaired glycemic control, whether prediabetes or frank diabetes, should be closely monitored for uncontrolled hyperglycemia and with routine follow-up with hemoglobin A1c at the usual 3-month intervals if steroids are initiated. Even patients with risk factors for developing diabetes should undergo vigilant glycemic monitoring at the beginning of steroid therapy, which at high doses can precipitate onset of diabetes and even diabetic ketoacidosis.

Cholangiopathic Phenotypes: Immune-Mediated Cholangiopathy or Cholangiohepatitis

The early recognition of ICI-mediated cholangiopathy or cholangiohepatitis is important to guide expectations on response to immunosuppressive therapy and prompt vigilance for morbid sequelae of bile duct injury. This entity probably exists on a spectrum with typical cases of IMH or cases of IMH in which histologic bile duct injury or alkaline phosphatase elevation may have been regarded as "collateral" manifestations in IMH [20, 68]. The nomenclature for this entity is not yet standardized; "irCH" for immune checkpoint inhibitor-related cholangiohepatitis was used by Moi et al. [90]. Other descriptive nomenclature that could be used to describe the diagnosis includes immune checkpoint inhibitor-mediated cholangiohepatitis (IMCH) which describes a hepatobiliary "overlap" condition or immune checkpoint inhibitor-mediated cholangiopathy (IMCp).

One of the first cases published revealing the possibility of developing cholangiopathic disease secondary to ICI was described in patient who underwent treatment with nivolumab for metastatic non-small cell lung cancer [91]. In this case study, the patient presented with jaundice and grade 3 elevation in alkaline phosphatase after exposure to nivolumab. Histopathologic analysis from liver biopsy demonstrated bile duct injury in conjunction with portal and periportal inflammation, and prevalence of CD8+ lymphocytes.

Since then, multiple case reports and case series have corroborated the phenomenon of cholangiopathic phenotypes. The majority of cases are reported in association with an anti-PD-1 inhibitor, such as nivolumab or pembrolizumab, or with an anti-PD-L1 inhibitor, such as atezolizumab [74, 78, 90–98]. A case series of 13 patients revealed anti-PD-1 inhibitor exposure in 100% of cases (nivolumab and pembrolizumab) [78]. Ten of 13 cases had R factor <2.0, 2 cases had R factor between 2 and 5, and 1 case had R factor >5.0. Eleven of 13 cases presented with no hyperbilirubinemia. There was also no association between this phenotypic variant with autoimmune serologies such as AMA, and, in cases where tested, there were no elevations in total serum IgM, IgG, or IgG4 levels. In 12 cases where liver biopsy was performed, all cases exhibited bile duct injury, and no cases exhibited ductopenia. As previously stated, the presentation of vanishing bile duct syndrome as a consequence of ICI exposure is rarely reported [71, 72]. In a histopathologic study by Cohen et al., mixed hepatitic and cholangitic patterns accounted for 8 of the 60 cases examined (13%); predominantly cholangitic pattern accounted for 16 of 60 cases (27%) [69]. The accumulation of ongoing cases emphasizes the need for dedicated recognition of this phenotype [92, 93]. The analysis by Takinami et al. reinforces the notion of histologic "overlap" of hepatitis and cholangiopathy [96]. In summary, the radiographic findings can mimic findings of primary sclerosing cholangitis, and histologic analysis less resembles primary biliary cholangitis.

With regard to treatment response, the medical literature also highlights the profound propensity for steroid refractoriness in these cases [74, 78, 90, 95, 99–102]. This observation is in direct contrast to IgG4-related diseases involving the biliary tree where IgG4-related sclerosing cholangitis cases, albeit rare, are deemed to have good response to steroids. In a review of 26 patients with IMCp where responsiveness to steroids was assessed, 8 patients (31%) were considered poorly responsive, and only 3 of 26 patients (12%) of patients were considered to have good response to steroids [74]. Several cases in the literature describe requiring the addition of one or two adjunctive therapies, such as mycophenolate mofetil and ursodeoxycholic acid (UDCA, or ursodiol) [103]. Even with adjunctive treatment, patients may still experience a protracted course of immunosuppression and recovery time, thereby precluding their ability to be re-challenged with ICI. In an aforementioned case series described by Eyada et al., 7 of 13 cases exhibited initial steroid responsiveness but then experienced relapse requiring escalation of therapy [78]. Moi et al. described three cases of steroid-refractory ICI-mediated cholangiohepatitis associated with pembrolizumab that were treated successfully with IV tocilizumab (two of three patients required repeat infusions) [90]. Reddy et al. described one case that was treated eventually with IV tocilizumab (4 mg/kg infusion) for large-duct biliary cholangiopathy secondary to nivolumab exposure [95]. The observed differences in

steroid responses compared to typical cases of hepatocellular IMH may suggest the need for initial parenchymal liver biopsy to provide a prognostic role. For instance, the clinician may choose to escalate therapy sooner if inadequate response to combination steroid and an adjunct is identified within the first 1–2 weeks. There is concern that although steroids may help encourage improvement in the hepatitic aspect of this irAE, it may not prevent the biliary sclerosing sequelae even after completion of steroids [78, 96, 101, 104].

The current society guidelines currently do not offer specific guidance for diagnosis or treatment for cholangiopathic disease induced by ICI. In the most recent review of IMH in *Hepatology*, the proposed algorithm suggests incorporating the grading of both ALP and GGT but does not explicitly offer management guidelines should these values be abnormal [2]. Because such patients often have simultaneous liver enzyme abnormalities with or without elevation in bilirubin, IMH treatment algorithms are initially implemented. As previously discussed, an initial evaluation that also focuses on characterizing patients with elevated ALP (i.e., 1.5× ULN) with or without hyperbilirubinemia, when the R factor is less than 5.0, is warranted to increase sensitivity for detecting this variant. Since histologic bile duct inflammation can be present or arise even when ALP is <1.5× ULN, we do not recommend waiting for the ALP to reach grade 2 levels or above 2.5× ULN before initiating the workup.

Unlike in patients with typical hepatocellular injury, bile duct inflammation could cause biliary stricturing disease which may involve intrahepatic and/or extrahepatic bile ducts, as discussed earlier (Fig. 7.3). This in turn could pose the risk of developing progressive jaundice and even acute bacterial cholangitis. Even in the absence of cholangitis, severe stricturing disease would warrant ERCP with intent for therapeutic interventions [101, 105]. Therefore, patients with the cholangiopathic phenotype are prone to greater morbidity. We recommend expert consultation with gastroenterology/hepatology when the diagnosis of ICI-mediated cholangiopathy is made. Additional longitudinal studies are needed to ascertain whether sclerosing cholangitis or bile duct stricturing is a permanent sequela.

No systematic studies or randomized control trials exist on an evidence-based approach to treating ICI-mediated cholangiopathy or cholangiohepatitis. Although the natural history of this disease is not fully characterized, published clinical experience brings to light the propensity for an aggressive course of disease. Therefore, it is reasonable to adopt initial strategies from the treatment of typical IMH with the following considerations. Early addition of adjunct therapy may be necessary. UDCA may be favored as an adjunct to steroids in cholestatic disease given its favorable side effect profile. A dose of 13–15 mg/kg/d in divided doses, like that used for patients with PBC, can be considered when steroids are also initiated. After recovery and completion of immunosuppressive therapy, if morbid sequelae of cholangiopathic disease have already occurred, we recommend permanent discontinuation of ICI.

For the diagnosis of ICI-mediated cholangiopathy, a systematic, algorithmic approach should be considered as detailed in Fig. 7.3.

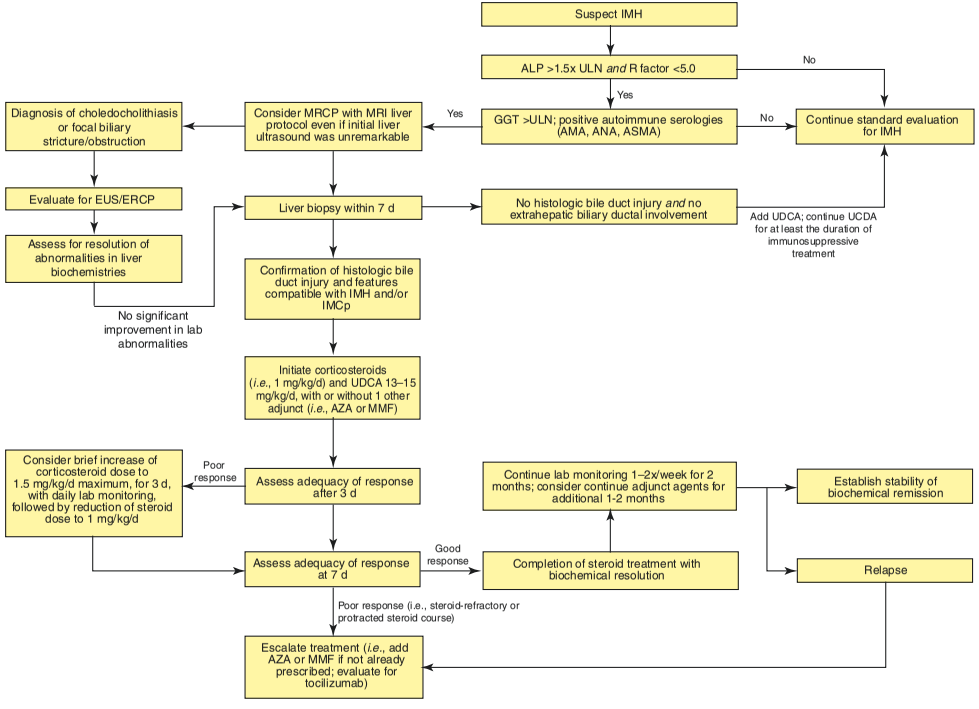

Fig. 7.3 Detailed approach to evaluating the patient who presents with a component of cholestatic liver injury. Autoimmune serologies do not need to be positive to continue pursuing this work-up, but positive results may strengthen the indication for liver biopsy. The propensity for steroid-refractoriness or a protracted duration of systemic steroid use should prompt consideration for early escalation of alternative treatment options or adjunct therapy.
Abbreviations: *IMH* immune checkpoint inhibitor-mediated hepatobiliary toxicity, *ALP* alkaline phosphatase, *ULN* upper limit of normal, *GGT* gamma-glutamyl transferase, *AMA* anti-mitochondrial antibody, *ANA* anti-nuclear antibody, *ASMA* anti-smooth muscle antibody, *EUS* endoscopic ultrasound, *ERCP* endoscopic retrograde cholangiopancreatography, *IMCp* immune-mediated cholangiopathy, *UDCA* ursodeoxycholic acid, *IV* intravenous, *ATG* anti-thymocyte globulin, *IVIG* intravenous immunoglobulin

Adjunctive Treatments

In patients initiated on steroids who do not respond satisfactorily after 3 days of treatment, clinicians should consider addition of adjunctive agent(s) or alternative nonsteroidal treatments to control IMH [2, 38, 40, 59–62, 103]. To date, steroid-refractory cases of IMH are considered rare. As discussed below, cholangiopathic variant of IMH represents a subtype of IMH which predicts a higher risk for steroid refractoriness. Many adjunctive therapies have been selected in real-world clinical use based on knowledge of an agent's theoretical effects on targeting T-cell subpopulations; Ziogas et al. feature a summary of the current scope of the alternative strategies that have been employed [103]. Early adjunct treatment may also confer the benefit of a shorter time to ALT improvement in those with grade 3 IMH, thereby potentially reducing overall steroid exposure by augmenting the rate of improvement in liver enzymes [106]. A review of adjunctive agents employed in IMH is presented in Table 7.4 with associated references in which the agent was employed for hepatobiliary irAE. One primary limitation with proposed strategies is that none of these agents have been studied systematically in comparison with each other.

Although rituximab, an anti-CD20 agent, may be considered in the context of idiopathic autoimmune hepatitis, no studies or case reports are available to show its efficacy specifically in IMH, which may interfere with the T-cell-mediated mechanism that also underlies the pathophysiology of IMH. Based on lack of knowledge about the role of rituximab in IMH, we do not recommend its routine use for treatment of steroid-refractory IMH; instead, we would favor options such as MMF, azathioprine, and tocilizumab.

Kinetics of Biochemical Improvement

Usually, treatment with corticosteroids will achieve improvement or normalization of liver enzymes in most patients [35, 41, 66]. Particularly in those with CTCAE grade 3–4 IMH, favorability of response to steroids is assessed over the first 3 days before reassessing the need to escalate treatment with higher steroid dose, immunomodulators, or other adjunctive agents.

The median time from corticosteroid initiation to biochemical resolution is approximately 8 weeks [129]. In one case series, patients with grade 3–4 IMH achieved grade 1 parameters after a median time of 13 days, but with median duration of steroid use of 69 days (9.9 weeks) to maintain biochemical remission [83]. In another case series, time to normalization of liver enzymes ranged from 2 weeks to 3 months after initial presentation [35]. Clinicians may observe that the serum AST may improve slightly quicker than the serum ALT. However, if the magnitude of the ALT is higher than AST, then the CTCAE grade of the ALT level is still used to judge the status.

As previously suggested, early addition of adjunct treatment could augment the rate of recovery and shorten the time to improvement of ALT [106]. In a recent study by Li et al., the clinical courses of steroid treatment were examined in 94

Table 7.4 List of adjunctive agents and their published clinical applications

Agent	Commentary
Mycophenolate mofetil (MMF) [20, 21, 36, 50, 58, 72, 82, 99, 100, 103, 106–110]	The suggestion to prescribe MMF is consistently featured in society guidelines as an adjunct to steroids when inadequate responses to steroids are observed after the first 3 days. Its application is common in post-liver transplantation patients to prevent graft rejection. AE profile includes bone marrow suppression, CMV infection, herpetic infections, and shingles. The starting dose to consider is 500–1000 mg every 12 hours [40, 59]. The optimal time to discontinue MMF after achieving biochemical remission and after completion of steroids has not been established. Published cases in which MMF is featured are proportionately higher than other agents probably due to its consistent inclusion in society guidelines.
Azathioprine [78, 83, 106, 111–113]	Azathioprine is well-recognized as the first-line adjunct treatment in idiopathic AIH where combination strategy is selected. Azathioprine serves as an immunomodulator as steroids are tapered to lower doses while maintaining remission from active inflammation [88, 89]. To ensure proper dosing and to minimize effects of AE, thiopurine S-methyltransferase level (or genotype assessment) should be checked in order to determine if the patient has any evidence of reduced capacity for azathioprine metabolism. Two well-recognized AE include bone marrow suppression (like MMF) which in the case of azathioprine specifically could cause leukopenia (as a result of 6-thioguanine nucleotides or 6-TGn) and elevation in liver enzymes (as a result of 6-methyl-mercaptopurine or 6-MMPR). In cases of unexpected increase of liver enzymes during steroid taper, metabolite testing can be performed to exclude azathioprine toxicity. Another well-recognized AE includes pancreatitis [114]. The optimal dose of azathioprine for IMH is unknown, although depending on the patient's weight and TPMT level, azathioprine 50–100 mg/d, or 1–2 mg/kg body weight, can be considered. The optimal time to discontinue azathioprine after achieving biochemical remission *and* after completion of steroids has not been established. The decision to select azathioprine as an adjunct may also depend on the patient's history of lymphoma, specifically non-Hodgkin's lymphoma. Thus far, short-term utilization of azathioprine has not yet been shown to increase the future risk of developing non-Hodgkin's lymphoma. No data exists on whether routine monitoring of azathioprine metabolites and adjusting the dose to meet a specific target concentration has any specific role in determining its efficacy in treating IMH. Azathioprine is given consideration as an adjunct in the ASCO and AGA guidelines [38, 81].
6-Mercaptopurine (6-MP) [35]	Within a case series of 11 patients, 1 patient was initiated on 6-MP in conjunction with prednisone, with eventual normalization of liver enzymes after 6 months. Because 6-MP is a metabolite of azathioprine, similar pharmacovigilance applies when using this agent.
Tacrolimus [82, 103, 110]	Its application in hepatology has traditionally been in post-liver transplant patients to prevent graft rejection. AE profile includes hypertension, neurotoxicity, renal insufficiency, neurotoxicity, and diabetes. Tacrolimus levels should be monitored (suggested target blood level of 8–10 ng/mL) [103]. The optimal time to discontinue tacrolimus after achieving biochemical remission *and* after completion of steroids has not been established.
Ursodeoxycholic acid (UDCA or ursodiol) [72, 115, 116]	This may be preferentially selected for patients with cholestatic disease with or without jaundice, particularly those with biliary duct injury. The benefits have not been systematically studied, but based on its mechanism and low risk of AE, patients with cholangiopathic phenotypes of hepatobiliary irAE may represent candidates in addition to steroids. The optimal dose is unknown, although 13–15 mg/kg/d in divided doses can be adopted from understanding of its efficacy in PBC.

Tocilizumab [90, 95, 101, 102, 117–119]	As previously discussed, the IL-6/IL-6R pathway is an important mediator in the physiology and biology of hepatocytes, including hepatic regeneration. As an anti-IL-6 receptor antagonist and a biologic agent, tocilizumab is approved to treat rheumatoid diseases such as rheumatoid arthritis and juvenile idiopathic arthritis. Its application in the context of immunotherapy was expanded to treat cytokine release syndrome (CRS) in patients who had undergone chimeric antigen receptor (CAR) T-cell therapy [59, 120]. Tocilizumab is also a treatment option for patients with immunotherapy-mediated rheumatoid disease such as inflammatory arthritis and polymyalgia-like syndrome [38, 59]. The current published literature features favorable outcomes in managing different types of irAE [118]. Four published cases have demonstrated efficacy in treating severe or steroid-refractory cases of ICI-mediated cholangiohepatitis [90, 95]. One patient with IMH was featured in a study featuring the application of tocilizumab in a variety of irAEs of different organ systems associated with anti-PD-1 exposure [117]. In a recent abstract, a small case series of heterogeneous presentations of IMH demonstrate tocilizumab's potential utility for treating patients who fail to achieve biochemical remission even when initial adjuncts are added to corticosteroids, in order to subsequently allow for tapering of the steroid dose after administration of tocilizumab [119]. Of note, tocilizumab-induced hepatotoxicity can occur and may present a dilemma in the interpretation of LBT trends after administration. This form of DILI could potentially lead to initial paradoxical increase of liver enzymes before net improvement is later observed [119]. In summary, tocilizumab's application in hepatobiliary irAE appears promising as a steroid-sparing agent. Tocilizumab may increase lipids/cholesterol, so fasting lipid profile testing is strongly encouraged before administering tocilizumab. However, this effect does not generally confer increased cardiovascular risk [121]. Leukopenia and thrombocytopenia are potential adverse events related to tocilizumab, so a complete blood count with differential should be routinely monitored. Screening for latent tuberculosis is strongly recommended before administering tocilizumab. An intravenous dose can be administered as 8 mg/kg or 4 mg/kg as a single infusion [90, 95, 101, 102, 119]. If no compelling need for dose adjustment exists, the initial infusion may be given at 8 mg/kg. Because patients might be regarded as steroid-refractory by the time tocilizumab is considered, the steroid dose can be reduced the next day, followed by a gradual taper to completion, without regard to specific LBT trends. A second and third infusion can also be administered at 8 mg/kg or 4 mg/kg depending on the magnitude of liver enzymes while continuing to taper the steroid dose (or while already off steroids). Administration of subcutaneous tocilizumab for the application of IMH has not been specifically studied. Based on data from available case series or case reports, tocilizumab may be favorable to consider in the following scenarios: (A) patients who do not adequately respond after several weeks of either monotherapy steroids or with adjuncts already on board; (B) patients who may initially respond to steroids but relapse during the steroid taper, which may lead to escalation of steroid doses and thereby extend the steroid exposure further; (C) recurrent IMH after ICI re-challenge; and (D) ICI-mediated cholangiopathy who do not demonstrate early improvement with traditional therapies. Monotherapy tocilizumab without steroid induction has not yet been studiedl.
Antithymocyte globulin (ATG) [36, 108, 122]	ATG was employed as third-line treatment after treatment failure with both corticosteroids and MMF. The current literature comprises of three total cases demonstrating ATG's efficacy.
Plasma exchange [123]	One case report described a patient who developed severe IMH after treatment with nivolumab and subsequently ipilimumab. Plasma exchange was employed after the patient developed acute liver failure, despite treatment with corticosteroids and MMF. The patient developed clinical improvement. This treatment strategy has yet to be studied further [124].

(continued)

Table 7.4 (continued)

Agent	Commentary
Cyclosporine [111]	Its application in hepatology has traditionally been in post-liver transplant patients to prevent rejection. AE profile includes hypertension, hypercholesterolemia, renal insufficiency, gingival hyperplasia, and hirsutism.
Budesonide [113, 115]	Budesonide (9 mg/d) was prescribed for two patients who developed grade 3 IMH with cholestatic features, in the context of nivolumab and pembrolizumab. In both cases, adjunct agents with UDCA and N-acetylcysteine were given. In another case report, initial treatment with budesonide (9 mg/d) in combination with azathioprine and ursodiol yielded relatively early response toward resolution of immune-mediated cholangiohepatitis. Budesonide may be considered in a specific scenario where a patient had previous significant adverse events or intolerance to oral prednisone or prednisolone. For instance, if a patient has uncontrolled diabetes or if surgery is anticipated, budesonide may offer benefits over prednisone. No published data exists to systematically show whether an adjunct agent must in general accompany budesonide to yield efficacy. When the ALT improves to <2× ULN, budesonide can be slowly tapered to 6 mg/d (for at least 14 days), followed by 3 mg/d (for at least 14 days).
Intravenous immunoglobulin (IVIG) [99, 100]	One case report described a patient treated with combination ipilimumab and nivolumab that failed initial attempts in treatment of IMH with cholestasis (including jaundice) with both corticosteroids and MMF. Subsequently, IVIG was administered in combination with steroids without MMF.
N-acetylcysteine [115]	Potential benefits have been studied for application in both acetaminophen- and non-acetaminophen-related DILI; its role has not been specifically studied in the context of ICI-mediated hepatobiliary injury, other than report of its adjunct use in Ziemer et al. in two patients.
Infliximab [82, 110]	Infliximab is a biologic anti-TNF-α inhibitor with applications in traditional inflammatory bowel disease (IBD) and immunotherapy-mediated diarrhea/colitis (IMDC). In general, infliximab for established indications is well-tolerated. However, hepatotoxicity secondary to infliximab, albeit infrequent, is a recognized part of its AE profile [125]. Hepatotoxicity can even present in the form of drug-induced autoimmune hepatitis [126, 127]. Because other options are available while avoid its use which can confound the issues related to the active IMH that is being treated, infliximab is *not* considered a favored agent to attempt to treat steroid-refractory IMH [37, 38, 128].

Different adjunctive agents and alternative therapies have been reported in clinical practice for patients who do not initially demonstrate adequate response to methylprednisolone or prednisone treatment. This table delineates "options" that can be considered, with respective associated published material, to guide clinical decision-making when weighing the strength of the available data with the risks and benefits of each therapy. There are no prospective studies that demonstrate superiority of one approach over another

patients with melanoma diagnosed with grade 3–4 IMH. The 33 patients deemed to be steroid-refractory had common factors including higher peak ALT values and comparatively higher ALT values after 1 week of steroid initiation. These patients also exhibited a longer time to ALT improvement to <100 U/L and to <50 U/L. Thirty-one of 33 patients required escalation to the additional of MMF, and the other 2 patients were treated with the addition of azathioprine [106].

As such, the biochemical response is highly variable. Ultimately, considerations such as the urgency to resume ICI (especially in the absence of other cancer treatment options) and the anticipated duration of exposure to corticosteroids should influence the need to escalate therapy or consider steroid-sparing strategies. As previously mentioned, tocilizumab, an IL-6R antagonist, may serve as a potential treatment for patients who are not demonstrating satisfactory overall improvement or rate of improvement while still on steroids.

Moreover, each ICI has its own pharmacokinetic properties, as outlined in Table 7.5 [130–133]. However, there are no dedicated studies to date examining the relationship of a particular ICI with the rate of resolution of IMH whether the patient was treated with steroids or not. In those with features of steroid refractoriness, patients may require prolonged duration of treatment for many months.

Tremelimumab, an anti-CTLA-4 inhibitor, not yet an approved ICI agent, has a half-life of 22 days. The length of an ICI's half-life and washout period (generally regarded at 10 half-lives) could have implications on the risk of relapse during the recovery phase of IMH or delayed initial presentations of IMH [131]. Ipilimumab's clearance may be impacted by body weight and baseline serum LDH level [133]. Interestingly, flow cytometry studies showed that PD-1 blockade (PD-1 receptor occupancy) by nivolumab may persist beyond 57 days, even when serum concentrations of nivolumab may not be detectable, which relates to the observed affinity of nivolumab for PD-1, with a dissociation constant of 1.45 nM, less than that of ipilimumab [22, 133]. These observed properties might serve as a hypothesis for delayed presentations or relapse in IMH (and potentially a wide variety of irAEs), although simultaneously support the notion that patients may continue to derive benefit from

Table 7.5 Pharmacokinetic properties of approved ICI agents

ICI	Class	Half-life (λ) (d)	Steady state with ongoing treatment	Dissociation constant
Ipilimumab	CTLA-4	14.7–15.4	9 weeks (about 2.3 mo)	5.25 nM
Nivolumab	PD-1	25	12 weeks (about 3 mo)	1.45 nM
Pembrolizumab	PD-1	14–27.3	18 weeks (about 4.5 mo)	29 pM
Cemiplimab	PD-1	12–19	4 mo	–
Atezolizumab	PD-L1	27	6–9 weeks (about 2.3 mo)	–
Avelumab	PD-L1	6	4–6 weeks (about 1.5 mo)	–
Durvalumab	PD-L1	21	16 weeks (about 4 mo)	667 pM

Different ICI agents (ones that are currently approved) have their own respective pharmacokinetic properties such as half-lives and steady states. However, serum concentrations may not correlate with active checkpoint blockade which also depends on the agent's dissociation constant or binding affinity. Abbreviations: *d* days, *mo* months, *nM* nanomoles, *pM* picomoles

the previously ICI administration even after its discontinuation [134]. The relative behavior in this aspect for anti-PD-1 inhibitors compared to anti-CTLA-4 inhibitors has not been systematically described, as PD-1 expression is different than the transient CTLA-4 expression on the T-cell surface.

Approach to Suspected or Confirmed IMH in the Context of Intrahepatic Primary Tumors or Metastatic Liver Lesions

A diagnostic challenge may arise in cases where intrahepatic lesions - whether a primary tumor, solitary or multifocal, or metastatic disease in the liver - might cause abnormal liver enzymes including those with cholestatic patterns and/or hyperbilirubinemia. Cross-sectional liver imaging findings should be correlated with the temporal acuity during which the liver enzymes, and bilirubin, increased, as well as exclusion of a vascular event such as portal vein thrombosis or hepatic vein thrombosis. It is important to note that the healthy remaining liver parenchyma and bile ducts are still susceptible to immune-mediated injury, and the correct diagnosis can influence whether immunosuppression can be started. The main concern in these cases is if the abnormal liver enzymes were incorrectly attributed to liver tumor burden, untreated IMH may continue to escalate, and even hinder potentially resuming either ICI or another chemotherapeutic agent. By correctly identifying superimposed IMH, immunosuppression can be initiated with close observation to determine any improvement of liver enzymes and bilirubin levels, although complete normalization may not be expected depending on the baseline lab results or if there is concurrent progression of malignant disease in the liver. If feasible, a liver biopsy of the parenchymal tissue, with care to avoid sampling a liver lesion, can be informative to make the diagnosis. The rest of the management otherwise would be similar to typical cases of IMH.

A specific scenario of such a challenge in diagnosis and management is the patient with hepatocellular carcinoma (HCC). Treatment of HCC with ICI, particularly with agents like nivolumab, pembrolizumab, durvalumab, and atezolizumab, does introduce the risk of developing a hepatobiliary irAE [135–137]. Furthermore, patients with HCC may also have underlying chronic liver disease such as cirrhosis, chronic hepatitis C infection, or chronic hepatitis B infection. An algorithm similar to current guidelines was proposed by Sangro et al., with induction starting doses of oral prednisone 0.5–1.0 mg/kg/d even for grade 3–4 IMH [135].

Outcomes and Follow-Up

Overview

In clinical practice, spontaneous resolution of IMH without any corticosteroid therapy, particularly in cases with grade 3–4 liver injury, has been reported in a reproducible fashion [20, 21, 39, 84, 138]. In a retrospective study by Miller et al., 31 of

85 patients (36%) with grade 3 IMH and 2 of 15 patients (13%) with grade 4 IMH did not receive steroids (overall 33%). In a case series by de Martin et al., 6 of 16 patients (38%) were managed without steroids [20]. In another case series by Gauci et al., five of ten patients (50%) exhibited improvement without the use of steroids [138]. These observations were summarized in Peeraphatdit et al.'s systematic review of the published literature which corroborated the range of 38–50% of cases of severe IMH that may resolve without requiring corticosteroids [84]. Patrinely et al.'s multicenter study of IMH reported an overall smaller percentage of 7.9% of cases of IMH that did resolve with observation alone without the use of steroids [39].

To date, there are factors not yet defined for predicting such a favorable conservative approach with observation. Therefore, most patients will likely continue to receive corticosteroids as suggested by the guidelines unless future guidelines change the paradigm. However, in clinical practice, circumstances may exist that disfavor the initiation of steroids at the time of diagnosis (i.e., active infection requiring treatment, prior steroid intolerance). As such, clinicians should exercise flexibility in managing new cases of even severe IMH.

For patients undergoing steroid treatment, the first week after recognition of abnormal LBT offers a reasonable window to gauge whether the liver enzymes have or will soon reach its peak. LBT should be monitored at least once a week depending on the trends, since rebound elevation of AST and ALT can occur even after completion of corticosteroids therapy and clinical resolution; the frequency at which this occurs is not yet studied.

Unlike in IMDC, where repeat endoscopic evaluation with biopsies can offer objective information about the degree of histologic improvement or even resolution of the irAE at the level of the tissue, the role of definition histologic remission in IMH has not yet been studied. Yet, demonstration of deep histologic remission even in IMDC is not mandatory nor an expectation, with more practical reliance on endoscopic healing,

Because of the expected duration of steroids used to treat IMH, a theoretical concern may exist as it pertains to whether corticosteroids may counteract the efficacy of ICI [139]. The impact of corticosteroids on cancer outcome in the context of IMH has not been studied.

The Risk of Relapse or Flare During the Management of IMH

In idiopathic autoimmune hepatitis, discontinuation of steroids carries a very high risk of resurgence of inflammation, ascertained by the increase in liver enzymes [2]. Similarly, in IMH, relapse or recurrence could occur in some patients who initially exhibit improvement in LBT after ICI withdrawal without steroid therapy, during a steroid taper, or even after a successful regimen of corticosteroids. In a retrospective study by Miller et al., clinical outcomes were documented for patients who were diagnosed with grade 3–4 IMH [21]. For patients with grade 3 IMH, 56 patients were *not* re-challenged with ICI. Yet, seven patients (13%) had recurrence in IMH. For patients with grade 4 IMH, 13 patients were not re-challenged with ICI, but 3 of those patients (23%) exhibited recurrent IMH. Overall, the proportion of

these patients who experienced spontaneous relapse or flare was 15%. Additional studies are needed to describe the incidence and prevalence of spontaneous relapse after resolution of IMH. When relapses or flares occur, and if the patient's steroid exposure is expected to be prolonged, the clinician should discuss with the patient alternative strategies to control the liver enzyme elevations. Namely, if not already implemented, adjuncts such as azathioprine and MMF should be considered, and if these adjuncts fail, tocilizumab can be considered as a "rescue" option which can allow for subsequent tapering off of the steroids, without relying on steroids to dictate the liver enzyme trends.

Not all interval elevations in liver enzymes and/or bilirubin necessarily equate to a relapse or flare during or after treatment of IMH. The clinician should review the patient's case to ascertain whether a non-ICI drug culprit is possible, as patients may be on alternative pharmacologic agents or chemotherapies which may also carry a hepatotoxic risk. For example, high-dose steroid treatment may elicit new steatosis and steatohepatitis, which may in turn case LBT elevation or lack of improvement. The risk of interval infection, including that of CMV, should also be considered and tested if deemed necessary. Each scenario may bear its own complexity with several active variables which may influence the strength of attribution of unexpected abnormal changes in LBT to ICI. This in turn could influence the decision about steroid doses or escalating to alternative agents to treat IMH. If the diagnostic attribution remains uncertain, a liver biopsy may be warranted (even if it was already performed during the onset of IMH).

Re-challenging with ICI After Recovery from Grade 3–4 IMH

Society guidelines from NCCN, ASCO, SITC, and ESMO guidelines recommend permanent discontinuation of ICI for those who are diagnosed with grade 3 and grade 4 IMH [38, 59–62]. This recommendation is based on expert consensus, but real-world experience and clinical practice challenge this paradigm. In a single-center retrospective study at a cancer hospital by Miller et al., the retrospective data showed that recurrent IMH after ICI re-challenge occurred in 28% (8 of 29 patients) who initially had grade 3 IMH and in 0% (0 of 2 patients) who had grade 4 IMH, with an overall proportion of recurrence of 13%. The future clinical course of those patients is not delineated. In Pollack et al., 17% (5 of 29) of patients experienced recurrent hepatitis after resuming anti-PD-1. In Li et al., 31 of 102 patients (30%) with melanoma who recovered from grade 3–4 IMH were re-challenged with ICI [140]. Only 13% of these cases (4 out of 31) required subsequent discontinuation of ICI due to recurrence. Increased survival was observed in patients who were re-challenged. Of note, this study was limited by selection bias for the patients who were re-challenged [140].

Nonetheless, these preliminary data encourage the clinician to remain flexible about ICI re-challenge or resumption in selected patients. In efforts to attenuate the theoretical risk of IMH recurrence, the clinician may opt for ICI monotherapy rather than dual therapy or a modified dose at the time of ICI re-challenge. The data

suggests the opportunity for flexibility in patients where ICI was deemed effective but suffered grade 3–4 IMH. The risks/benefits should be discussed with the patients, with expectation for very close pharmacovigilance.

Currently, biochemical remission (i.e., normalization or improvement toward baseline of the ALT, AST, and total bilirubin) is regarded as an adequate assessment for resolution of IMH. There are no studies examining whether histologic remission is important or necessary in relation to the risk of relapse or recurrence in IMH after ICI re-challenge.

Prophylactic use of tocilizumab combined with ICI for melanoma patients, to reduce the overall incidence of irAEs, is still being studied [141]. There are no studies examining the role of secondary prophylaxis or maintenance therapy when patients resume ICI after recovering from grade 2–4 IMH.

Mortality in IMH

Although rare, acute liver failure and death associated with ICI use have been reported [50, 71, 123, 142–146]. The largest published evaluation of fatalities associated with ICI adverse effects showed that in a comprehensive query of the World Health Organization's pharmacovigilance database, 613 such deaths occurred from years 2009–2018, and 124 of them (20%) were associated with IMH [144]. It is unclear how much of the deaths involving IMH also involved adverse reaction in other organs. The same article also examined 122 published cases of fatal ICI-associated adverse events and found that only 6.5% (8 cases) involved IMH. As these databases do not capture the number of total patients who used ICIs during the time periods examined, the true incidence of IMH-related fatality is unknown. However, risk of death associated with ICI use as a whole is thought to be comparable or lower than traditional cancer treatments including platinum-based chemotherapy (0.9%) [147]. The incidence of IMCp-related fatalities is unclear: At least one published case of IMH with vanishing duct syndrome resulted in death [71]. In Smith et al.'s multicenter study examining IMH associated with combination ICI therapy, none of the deaths (11 of 31 patients) were attributed to IMH itself [12]. The role of underlying liver disease such as metastatic tumor burden or cirrhosis (especially in patients with liver cancer) in the risk of IMH fatality has yet to be examined.

Evaluation for Pre-existing Liver Disease and Viral Infections Before Initiating ICI

The past medical history is undoubtedly a crucial element in the clinician's initial evaluation of the patient when deciding to pursue treatment with ICI. The presence of an established autoimmune hepatobiliary disease likely will preclude the patient from becoming a candidate for treatment with ICI. However, patients may

frequently have either diagnosed or unknown underlying chronic liver disease at the time of ICI treatment. One retrospective study examined the clinical outcomes of patients who had pre-existing chronic infections by viral entities (HIV, hepatitis B, and hepatitis C); the results revealed no appreciable differences compared to those without these infections, and no hepatitis B reactivation events were observed [148]. A systematic review of the published literature also concluded that ICI treatment appears to be safe in those patients with hepatitis B or C infection [149]. In this review, 89 patients had HBV infection; 22 of these patients did not receive antiviral therapy, and 2 of those patients experienced reactivation with viral load increase. The review also reported 98 patients who had hepatitis C virus (HCV) infection, wherein hepatitis C viral load increased in 1 patient. A small prospective report of four patients at a single-center cancer hospital examined patients with chronic hepatitis C infection who were treated with ICI; no cases of HCV reactivation of HCV-associated hepatitis were reported during a 9-month follow-up period [150]. Later, additional prospective data from the same center continued to support the notion that ICI can be safely employed in patients with chronic hepatitis C [151].

There is a paucity of data about IMH in the setting of chronic liver disease. Only one study to date has proposed a potential relationship between nonalcoholic fatty liver disease (NAFLD) and the impact on development of IMH. In Sawada et al., a retrospective study performed in Japan involving 135 patients treated with anti-PD-1 inhibitors, attribution of liver injury (at least grade 2) was made in 8 patients; data analysis revealed that NAFLD could be a potential risk factor for developing PD-1 inhibitor-associated DILI [152]. No data is available regarding the outcomes after ICI treatment in other types of chronic liver disease including alcoholic liver disease, Wilson's disease, alpha-1 antitrypsin disease, and hereditary hemochromatosis. Only one case of ICI treatment (with pembrolizumab) for newly diagnosed melanoma in a patient with pre-existing primary biliary cholangitis (PBC) with overlap with autoimmune hepatitis (AIH) has been described [153].

Before initiation of ICI, screening for chronic liver disease, including for chronic hepatitis B or prior exposure to hepatitis B, and recommended adult screening for HIV and HCV are valuable. Although there is no compelling data to support routine prophylaxis against hepatitis B virus (HBV) reactivation before, during, and after treatment with ICI, patients who meet standard criteria for treatment should be managed accordingly. Nivolumab has even been studied as a method of controlling chronic hepatitis B infection with suppression of hepatitis B surface antigen, by leveraging an ICI's effect on T-cell immunology [154]. In general, a careful clinical assessment is necessary to determine the presence of any underlying hepatobiliary disease that may need to be clarified before starting ICI. Because ICI-based regimen (i.e., nivolumab; atezolizumab in conjunction with bevacizumab) might be employed in patients with hepatocellular carcinoma (HCC), the patient's baseline liver function and fibrosis status, especially since HCC is frequently seen in the context of cirrhosis, must be clarified before initiating treatment with ICI [155, 156]. In some cases, before the initiation of ICI, parenchymal liver biopsy may be warranted to provide a more accurate assessment.

Conclusions

IMH is increasingly encountered as ICI use in a variety of malignancies becomes more expansive. IMH can occur as early as 1 week after the initiation of ICI therapy. In most cases, IMH is asymptomatic and found only via elevations in ALT, AST, and alkaline phosphatase. Potential symptoms, including abdominal pain, fever, and malaise, are rare. Jaundice may not be universal in those with cholangiopathic disease. Pharmacovigilance is paramount to allow for early diagnosis. Mortality associated directly with IMH is rare.

As IMH remains a diagnosis of exclusion, other etiologies for new abnormal liver tests must be explored. IMH is distinct from both idiopathic autoimmune hepatitis and drug-induced autoimmune hepatitis [42]. No relationship to autoimmune markers is observed. Liver biopsy can be beneficial in select cases to corroborate a suspected case of IMH. Although no pathognomonic findings are defined in the histopathology of IMH, commonly described histologic findings can help distinguish IMH from autoimmune hepatitis or primary cholestatic liver diseases such as PBC. Once the diagnosis of IMH is made, management and treatment will depend on the overall CTCAE grade. Some patients, even those with grade 3–4 IMH, can exhibit spontaneous improvement without steroids upon ICI withdrawal. Liver injury with cholestatic features (i.e., ALP >1.5× ULN with elevated GGT) should prompt specific investigation for bile duct pathology, as both intra- and extrahepatic biliary tract involvement have been documented after ICI exposure. ICI-mediated cholangiopathy may manifest as a more aggressive condition than typical IMH, often requiring escalation of treatment and prolonged duration of immunosuppression. In summary, diagnoses of IMH should be characterized by the pattern of liver injury, presence or absence of histologic bile duct involvement in those with elevated alkaline phosphatase and/or bilirubin, and presence or absence of extrahepatic biliary duct involvement.

The goal of steroid treatment is biochemical remission with return of liver enzymes to baseline or normal values. The duration of corticosteroids should take into account the trends in the liver enzymes, comorbidities, and prospects of being re-challenged with ICI while minimizing the risk of adverse events from steroids. The role and implications of histologic remission are not yet studied. Additional research is needed to establish the efficacy, timing of initiation, and the selection of adjunctive treatments in IMH, such as with MMF or azathioprine, or a steroid-sparing approach with tocilizumab.

Current society guidelines suggest that ICI can be continued in cases of grade 1 or resolving grade 2 IMH. Published clinical experiences show that not all patients who recover from grade 3–4 IMH experience recurrent IMH. Therefore, the recommendation for permanent discontinuation of ICI in those categories may need to be revisited, particularly in cases where the patient's cancer had responded well to ICI therapy.

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Chapter 8
Infectious Diseases

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Abstract The use of immune checkpoint inhibitors (ICIs) has revolutionized cancer care and improved the outcomes for patients affected by an ever-expanding list of malignancies. The efficacy and adverse reactions to ICIs depend on a series of complex interactions between the type(s) of ICIs agents used, the host's immune system and microbiota, and the environment. In this chapter, we discuss the infectious diseases considerations that clinicians need to know when confronting a patient with ICI-related immune adverse events that present with symptoms suggestive of infection (i.e., pneumonitis, encephalitis, colitis, and mucositis) or develop infection following immunosuppressive therapy for the management of ICI immune adverse events. We also discuss the central role that microbiome has on the efficacy of ICIs, the factors that place patients on ICIs at risk for infection, and, finally, the indications for the screening for infectious diseases prior to initiation of immunosuppression and when is antimicrobial prophylaxis indicated.

Keywords Checkpoint inhibitors · Immunotherapy · Cancer · Infections · Prevention · Microbiome

Abbreviations

ANC	Absolute neutrophil count
BAL	Bronchoalveolar lavage
CDAD	*Clostridioides difficile*-associated diarrhea
CMV	Cytomegalovirus
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease

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COVID-19	Novel Coronavirus Disease 2019
CRP	C-reactive protein
CTLA-4	Cytotoxic T lymphocyte-associated protein 4
HCT	Hematopoietic cell transplantation
HIV	Human immunodeficiency virus
IBD	Inflammatory bowel disease
ICIs	Immune checkpoint inhibitors
INF-γ	Interferon γ
INH	Isoniazid
IQR	Interquartile ranges
irAEs	Immune-related adverse events
LTBI	Latent tuberculosis infection
Mtb	*Mycobacterium tuberculosis*
NAAT	Nucleic acid amplification test
PAMPs	Pathogen-associated molecular patterns
PCR	Polymerase chain reaction
PD-1	Programmed cell death receptor
PD-L1	Programmed cell death ligands
SARS-CoV-2	Severe acute respiratory syndrome Coronavirus 2
TMP-SMX	Trimethoprim-sulfamethoxazole
TNF- α	Tumor necrosis factor-alpha
Treg	Regulatory T cells
VZV	Varicella zoster virus

Overview

Background

Cancer is a major burden on public health and is associated with high morbidity and mortality rates in the general population. Cancer remains the second leading cause of death in the United States after heart disease [1]. The vital interplay between infection and cancer was first recognized by Sir William Coley in 1893 who demonstrated that injections of *Streptococcus* spp. into sarcoma cells elicited a favorable tumor response [2], presumably by eliciting an inflammatory or immune response. However, it took more than 100 years to identify the molecular mechanisms by which cancerous cells evade the host anticancer immune surveillance system, specifically, the central anticancer role of T cell-mediated immunity. The identification of checkpoint receptors and their ligands and their role in preventing an excessive activation and proliferation of T cells, including programmed cell death receptor (PD-1) or PD-1 ligands (PD-1 L) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), led to the discovery of checkpoint blockade immunotherapy as a mechanism to harness the hosts' anticancer immune response, the molecular basis of which is reviewed in Chap. 8. The discovery of immune checkpoint inhibitors (ICIs) is ushering in a new era of precise and personalized medicine that is exploiting new

targets, adjuvants, combinations of ICIs types, either alone or simultaneously with chemotherapy. Ipilimumab, which targets CTLA-4, was the first approved ICIs for treating patients with advanced melanoma [3]. Since then, the list of FDA-approved ICIs and their indications are expanding for both solid tumors and hematological malignancies [4].

While highly effective for malignancies that express PD-1 and PD-L1, ICIs can be associated with a constellation of exuberant off-target inflammatory responses or immune-related adverse events (irAEs) that can mimic infection and may occur weeks to months following the treatment. The spectrum in terms of incidence, agent-specific organ tropism, severity and types of irAEs associated with ICIs are reviewed in other chapters. Relevant to risk for infection, irAEs may require to be managed with corticosteroids or with immunosuppressive therapies, which increase the risk of infection including those due to opportunistic pathogens [3]. A retrospective study of patients with melanoma who were treated with ICIs monotherapy or dual ICIs therapies (the majority with anti-CTLA-4 antibodies) found that the rate of serious infection was 7.3%. The main risk factor identified in this study was the use of immunosuppressants including corticosteroids alone or in combination with infliximab to manage ICIs-related irAEs [5]. A separate study done in France in patients with melanoma and non-small cell lung cancer showed that 18% of patients treated with ICIs (anti-PD-1/PD-L1) developed an infection with a median onset of 47 days after the initiation of ICIs [6]. In a more informative, comparative, retrospective study done in patients with advanced lung cancer, the overall rate of infection regardless of severity was 15% in patients treated with ICIs plus conventional chemotherapy relative to 22% in patients treated with chemotherapy alone ($P = 0.1$) [7]. Thus, the risk of infection depends on the type of agent used, the underlying malignancy being treated, and the use of immunosuppressants to counter irAEs.

Sources of Infection

Although the study of infections in patients treated with ICIs is in its infancy, a few retrospective and observational studies suggest that the use of ICIs therapies per se does not confer an intrinsic increase in risk of infection. A burgeoning medical literature and anecdotal evidence suggest that patients treated with ICIs are at heightened risk for infection due to either immune dysregulation, use of concomitant drugs associated with neutropenia, or due to immunosuppressive therapies used to manage irAEs [8]. The principal risk factor being the use of immunosuppressive agents such as corticosteroids and/or tumor necrosis factor-alpha (TNF-α) inhibitors such as infliximab for the management of persistent or relapsing irAEs, which will be discussed in further detail later [9].

Upon encountering an antigen, naïve T lymphocytes rapidly express PD-1 and enter an unresponsive state (clonal anergy) in the absence of co-stimulation [10], a condition that is exploited by intracellular infectious agents to avoid detection and remain in latency. In contrast to cytotoxic or conventional chemotherapy, ICIs restore or enhance the host endogenous immune response against tumor cells

through the activation of T lymphocytes [11]. In a subset of patients treated with ICIs, this may result in off-target immune reconstitution inflammatory syndrome (IRIS) with the unmasking of dormant (latent) infections such as latent tuberculosis (LTBI). Various case reports and series describe the paradoxical reactivation of tuberculosis following ICIs therapies in the absence of irAEs, concomitant cytotoxic chemotherapy, or immunosuppressive therapy [9]. Indeed, PD-1 and PD-L1 are relevant during chronic infections, including those due to *Mycobacterium tuberculosis* (*Mtb*). Notably, early studies described multiple cases of *Mtb* reactivation during PD-1 blockade therapy in patients with cancer. Barber et al. reported two cases of *Mtb* reactivation in cancer patients treated with PD-1 checkpoint blockade. This is consistent with data in murine models of infection where enhancement and boosting of T_H1 function result in severe and increased risk for tuberculosis infection [12]. Additional work is needed to fully understand the link between ICIs treatment and the risk of *Mtb* reactivation [13].

In a study conducted by Malek et al. in patients with solid tumors receiving ICIs and/or chemotherapy, pneumonia was the most common infection encountered in patients receiving ICIs and chemotherapy versus those receiving chemotherapy alone and was mainly secondary to bacterial pathogens. Multivariable analysis revealed that among other risk factors neutropenia was an independent risk factor for infection and severe infection requiring hospital admissions ($P < 0.001$). This study also highlights the importance of skin barrier disruption and mucosal-associated bacterial translocation in neutropenic patients receiving ICIs combined with conventional chemotherapy as sources of infection with rates that were similar to the general cancer population receiving cytotoxic chemotherapy alone [7]. Important risk factors that contribute to irAEs development and infection are outlined in Fig. 8.1.

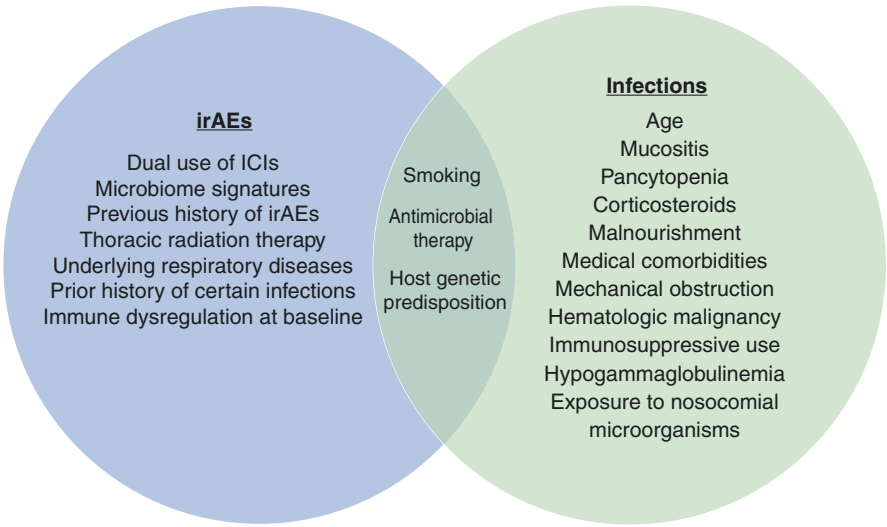

Fig. 8.1 Risk factors that predispose the hosts to irAEs and infections while receiving ICIs

Impact of the Underlying Malignancy

The infectious syndromes seen in patients receiving ICIs vary based on the underlying malignancy and not solely driven by the cancer treatment used. For example, in patients with advanced lung cancer treated with ICIs plus chemotherapy, pneumonia was the most common reported type of infection and is in part explained by bronchial obstruction due to tumor growth and mass effect [7, 14]. In addition, chronic obstructive pulmonary disease (COPD) is a common medical comorbidity in patients with lung cancer that can increase the risk of recurrent pneumonia. In the case of hematological malignancies, where severe neutropenia and lymphopenia due to underlying disease or chemotherapy place patients at risk for aspergillosis, *Pneumocystis jirovecii*, or cytomegalovirus infections, concomitant use of ICIs can result in atypical presentations secondary to irAEs and their associated immunosuppressive therapies. Salient factors germane to the underlying neoplasms and use of ICIs are listed in Table 8.1 and are divided into three categories pre-ICIs, concomitant with ICIs, and post-ICIs.

Risk Factors

Infection in patients with cancer can arise secondary to a constellation of factors, including modifiable factors such as the intensity, duration, and type of cancer therapy used, radiation, surgery, and nonmodifiable factors such as the type of underlying malignancy, medical comorbidities, age, and host-genetic predisposition to infection. In a retrospective noncomparator study that evaluated infections in patients with lung cancer treated with nivolumab, Fujita et al. found that the incidence of infection was 19.2% and that diabetes mellitus was noted as the only independent risk factor associated with infection [14]. In contrast, a study conducted by Malek et al. that included a comparator group of patients receiving chemotherapy alone found that COPD, diabetes mellitus, neutropenia with absolute neutrophils count (ANC) <500 units, smoking history, and the use of corticosteroids prior to chemotherapy were independents risk factors for infections and severe infections [7].

Patients with hematological malignancies are at risk for infection due to a multitude of risk factors, including severe neutropenia, lymphopenia or pancytopenia, hypogammaglobulinemia secondary to B-cell depleting agents, immune cell dysfunction due to alkylating agents and other cytotoxic chemotherapies, mucosal barrier injury from chemotherapy (mucositis), bacterial translocation, dysbiosis, use of central line devices, and indwelling catheters, among others. All these contribute to a net state of immunosuppression that results in susceptibility to conventional and opportunistic pathogens (viral, bacterial, fungi, and parasites). In addition, the use of nivolumab can result in neutropenia as an irAE [15] and further increases the risk of infection. The prevalence, severity, and duration of neutropenia secondary to ICIs therapies are unknown.

Table 8.1 Factors that predispose to infection in patients with solid tumors and hematological malignancies

Solid tumors			Hematological malignancies		
Baseline	During treatment	Post-treatment	Baseline	During treatment	Post-treatment
Age, Performance status, Smoking, COPD, Bronchial obstruction, Aspiration, Diabetes mellitus, Kidney disease, Congestive heart failure, Microbiome composition	Neutropenia, Mucosal barrier injury, Use of corticosteroids, Monotherapy or combination of ICIs, Immunosuppressive therapies, Concurrent conventional and targeted chemotherapy, Central venous lines, Implanted devises, Urinary catheters, Surgical drains, Radiation injury, Dysbiosis	ICIs-related irAEs: Vital organs involved Severity Use of immunosuppression Nutritional state, Tumor progression, Exposure to nosocomial organisms and antimicrobials, Central venous lines, Implanted devices, Urinary catheters, Surgical drains, Radiation injury, Dysbiosis, Cancer Recurrence	Age, Performance status, Profound immunodeficiency, Chronic infection (examples being aspergillosis, CMV), Exposure to chemotherapy, Pancytopenia, Diabetes mellitus, Kidney disease, Congestive heart failure, Microbiome composition	Neutropenia, Corticosteroid use, Mucosal barrier injury, Immunosuppressive therapies, Monotherapy or combination of ICIs, Immune cell depletions (purine analogs, HSCT,CAR-T), Hypogammaglobulinemia, Central venous catheters, Implanted devices, Urinary catheters Dysbiosis, Bacterial dominance	ICIs-related irAEs: Vital organs involved, Severity Use of immunosuppression Nutritional State, Exposure to nosocomial organisms and antimicrobials, Refractory/relapsed cancer

On the other hand, studies have showed that during chronic infection T cells express PD-1 in attempt to protect the host from robust T lymphocytes-mediated tissue destruction and lead to a state of host and pathogen latent coexistence [10]. In mice, the absence of a functional PD-1 pathway results in increased susceptibility to mycobacterial infection with pronounced cytokine storm and exacerbation of the infection [10, 16, 17]. It is hypothesized that T cells PD-1 expression may play a role in fine-tuning the lymphocyte reaction to enhance pathogen clearance with modulation of the immune response to infectious insults [10].

Timing of Infection (Prior, During, and After Checkpoint Inhibitor Therapy)

According to published studies and clinical experiences, the median time between ICIs initiation and infections was 47 days with interquartile ranges (IQRs) of 19.5–132 days [6]. In a separate study, the median time interval between ICIs initiation and infection was 53 days for a group of patients receiving ICIs when compared to 63 days for those receiving conventional chemotherapy groups (P = 0.68). Also, in Fujita and colleagues' paper, the mean time between the initiation of nivolumab therapy and infections was 90.3 days [14]. This is in contrast to Del Castillo and colleagues' study where the average time from starting checkpoint inhibitors to the development of severe infection was 135 days (range, 6–491 days) with the majority of infectious events (79.6%) occurring during the first six months following the initiation of ICIs therapy [5]. An observation derived from a composite analysis of these studies is that relatively early-onset infectious episodes after the initiation of immune checkpoint inhibitors are bacterial, whereas late-onset infections are due to opportunistic pathogens [5].

Microbiome Signatures Associated with Response Cancer Therapy and ICIs-Related Toxicity

There is mounting evidence that the human microbiome plays a fundamental role not only in susceptibility to cancer but also in the responses to cancer therapies, including ICIs [18]. Given that the intestinal microbiota is in continuous interaction with the gut-associated lymphoid tissue, which is the largest component of immune system, it is fairly intuitive that microbiome composition influences local and systemic immune responses to infection and cancer [18]. In preclinical models, gut microbiome composition determines and modulates the tumor response to cancer therapy [19, 20], including immunotherapy [21, 22]. Specifically, the presence of the commensal *Bifidobacterium* promotes antitumor immunity and enhances anti-PD-L1 efficacy. Similarly, *Bacteroidales* play a key role in the immunostimulatory effects and efficacy of CTLA-4 blockade [21, 22]. These preclinical studies have been subsequently validated in several clinical studies that evaluated patients treated

with ICIs. Chaput and colleagues showed that baseline microbiota enriched with *Faecalibacterium* and other Firmicutes promoted beneficial clinical response in patients with metastatic melanoma treated with ipilimumab [23]. Studies by Gopalakrishnan et al. and Matson et al. demonstrated that patients with melanoma who responded well to PD-1 blockade had a greater diversity of gut microbiota abundance of *Clostridiales, Ruminococcaceae*, and *Faecalibacterium* [24, 25]. Large, clinical studies that identify favorable microbiome profiles at baseline and preserve microbiome diversity during ICIs (i.e., microbiome stewardship) by minimizing antibiotic exposure during ICIs (antibiotic stewardship) are needed. Similarly, studies are needed for patients with unfavorable microbiome profiles in whom transplantation of complex microbiome communities or selected microbial constituents could enhance response to cancer therapy.

Use of Antibiotics in Patients on ICIs

The use of antibiotics in patients receiving ICIs has been associated with a negative and poor cancer outcome [24]. As mentioned earlier, the composition and microbial profile of commensal flora in patients receiving ICIs have been linked to therapeutic efficacy [26]. A study by Pinato et al. demonstrated that antibiotic use prior to ICIs therapy resulted in poor response to cancer treatment and worse overall survival [26]. This is explained by the profound antibiotic-mediated alterations and modifications of gut microbiota. A recent study by Routy and colleagues revealed that the use of antibiotics shortly before, during, or shortly after ICIs therapy was associated with lower progression-free survival and poor response to ICIs compared to patients who did not receive antibiotics [27]. Additional fecal profiling using quantitative approaches found that patients that responded poorly to ICIs had low levels of *Akkermansia muciniphila* and that oral bacterial replacement in antibiotic-exposed mice restored the immune response to ICIs [27]. Therefore, judicious and appropriate use of antimicrobials is recommended. To complicate matters, there is clinical overlap between the clinical manifestations of infection and symptoms due to irAE. This is of particular relevance in patients presenting with pneumonitis, encephalitis, or colitis. Additional studies that shed light on clinical-based algorithms or the identification of objective biomarkers specific to infection that aid clinicians in guiding antimicrobial therapy in such clinical scenarios are needed.

Screening for Infectious Diseases Prior to Initiation of ICIs and Potential Use of Immunosuppressants

ICIs therapy has led to a remarkable clinical benefit for a wide array of cancer types but can also cause irEAs and inflammation that can require the use of corticosteroids and other immunosuppressive agents. If prolonged, immunosuppression can

increase the risk of infection and can mask clinical manifestations of some infections [28]. Therefore, it is crucial to identify modifiable risk factors for patients at high risk for infections and ensure a comprehensive strategy based on three aspects: gathering of medical and epidemiological history; physical and radiological examination; and screening for specific infectious agents prior to initiation of immunosuppressive treatment. Screening for latent tuberculosis infection (LTBI) is recommended for two reasons. First, ICIs can lead to *Mtb* reactivation by unleashing a florid immune response in patients with preexisting latent *Mtb*. Second, corticosteroids or immunosuppression are commonly used to control irAEs [29], which can increase the risk of acquiring primary *Mtb* or reactivation of LTBI. Similarly, screening for endemic mycoses (such as *Histoplasma capsulatum* and *Coccidioides immitis* based on local epidemiological data), *human immunodeficiency virus* (HIV), and viral *hepatitis B* and *C* is also recommended [30]. Screening for parasites (such as *Toxoplasma, Strongyloides,* and *Trypanosoma cruzi* based on individual risk factors) and for a history of past infections with herpesvirus such as *herpes simplex virus*, *cytomegalovirus*, *Epstein–Barr virus*, and *varicella zoster virus* can also be helpful in case patients require immunosuppressive therapy for irAEs. Table 8.2 provides recommendations on the screening for infectious diseases in patients receiving ICIs therapy.

Table 8.2 Infectious diseases screening at baseline and prior to immunosuppression and indications for antimicrobial prophylaxis

Routine recommendations at baseline and prior to immunosuppression	Infectious agent	Screening tests	Antimicrobial prophylaxis regimen/ treatment
	Human immunodeficiency virus (HIV)	Fourth-generation immunoassay for HIV antigen and antibody	Refer to infectious diseases specialist
	Hepatitis B virus (HBV)	Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb)	Isolated positive HBcAb, antiviral prophylaxis (entecavir) is only recommended if exposure to anti-CD20 therapies Vaccinate if HBsAb and HBcAb negative
	Hepatitis C virus (HCV)	HCV antibody Enzyme immunoassay (EIA)	Refer to infectious diseases specialist or hepatology for treatment
	Mycobacterium tuberculosis	History of prior disease, exposure. T-spot or quantiFERON-TB	Refer to infectious disease clinic and consider LTBI treatment

(continued)

Table 8.2 (continued)

Preferred testing prior to immunosuppression	*Coccidioides immitis*	History of prior disease or residence in southwestern USA and northern Mexico	Close monitoring for symptoms or reactivation, refer to infectious diseases
	Histoplasma capsulatum	History of prior disease or residence in Midwestern states	Close monitoring for symptoms or reactivation, refer to infectious diseases
	Strongyloides stercoralis	CBC (eosinophilia) Strongyloides serum antibody, stool studies	Consider ivermectin 200 mcg/kg for two doses
	Trypanosoma cruzi (Chaga's disease)	History of prior residence in south and Central America or received transfusion in an endemic area; antibodies to *Trypanosoma cruzi*	Refer to infectious diseases clinic
	Herpes simplex virus (HSV)	History of prior oral or genital ulcerations	Consider (Val)acyclovir prophylaxis when immunosuppression lasts >6 weeks or intense T-cell-depleting agent (alemtuzumab)
	Varicella zoster virus (VZV)	History of prior chickenpox, zoster	Consider (Val)acyclovir prophylaxis when immunosuppression lasts >6 weeks or intense T-cell-depleting agent (alemtuzumab)
	Cytomegalovirus (CMV)	CMV serology*	Close monitoring for reactivation and end organ disease, weekly CMV PCR pre-emptive testing
	Epstein–Barr virus (EBV)	EBV serology*	Monitoring for reactivation
	Toxoplasma gondii	Toxoplasma PCR*	Monitor for reactivation with weekly toxoplasma PCR pre-emptive treatment
	Pneumocystis jirovecii	Baseline screening not recommended	Monitor for symptoms TMP-SMX DS M, W, F for patients receiving ≥20 mg prednisone per day for >4 weeks.

*For patients with underlying hematological malignancies/hematopoietic stem cell transplantation

Antimicrobial Prophylaxis

Indications

Patients receiving high dose of corticosteroids (prednisone 20 mg/day or equivalent for≥4 weeks) should be offered prophylaxis against *Pneumocystis jirovecii* with trimethoprim sulfamethoxazole (TMP-SMX) one tablet (DS), three times per week (M,W,F). Alternatives for patients in whom this drug is contraindicated include either dapsone 200 mg orally plus pyrimethamine 75 mg, plus folinic acid 25 mg once a week (an approach that is also effective in preventing toxoplasmosis), or atovaquone 1500 mg once daily. Pentamidine 300 mg in sterile saline by aerosol inhalation or by IV administration once every 21 days is used by some centers to avoid additional cytopenias in patients with hematological malignancies. Additional studies on the relative impact that the different options described above have on the microbiome and, thus, response to ICIs cancer therapy are needed.

Prophylaxis against *Herpes simplex* and varicella zoster viral should be used in immunosuppressed patients. This can be achieved by using acyclovir 400–800 mg twice daily or valacyclovir 500–1000 mg daily [30].

All patients in whom ICIs therapy is contemplated, particularly if there is preexisting immunosuppression from a hematological malignancy or the potential for new or intensified immunosuppression, should be screened for LTBI. Although in the absence of clear guidance regarding LTBI therapy some cancer centers use isoniazid 300 mg daily plus vitamin B6 for all patients with LTBI. In a small study by Malek and colleagues' done in patients with cancer and LTBI followed for a median of 15 months, patients were divided into three groups. The first group included patients treated with ICIs (n = 32) and was compared to a second group of patients receiving hematopoietic cell transplantation (n = 37) or a third group receiving conventional chemotherapy (n = 37). Although only 50% of patients received LTBI therapy with isoniazid (INH), reactivation of *Mtb* was rare. However, a significant proportion of patients experienced elevation in liver function tests (20%) when receiving ICIs along with INH. Therefore, caution, close laboratory, and clinical monitoring are warranted to avoid liver toxicity and interruption of LTBI therapy and oncological therapy [31]. This finding should be explored further in prospective studies to better understand the pathophysiology, incidence rate, severity, and use of an alternative LTBI regimen with the least drug–drug interaction with other antitumor agents.

The evidence of using antifungal prophylaxis (such as fluconazole 400 mg daily to prevent candidiasis) in the setting of prolonged corticosteroid use (>12 weeks) in patients with solid tumors remains unclear, and clinicians should proceed according to institutional guidelines that consider the risk for infection due to molds in patients with underlying hematological malignancies and hematopoietic stem cell transplant [32, 33]. The preferred agents used for the antimicrobial prophylaxis against common pathogens in patients receiving ICIs are outlined in Table 8.2.

Management and Outcomes of Common Infections in the Patient Receiving ICIs

Infections Related to ICIs Use

Combination Therapy Versus Monotherapy

ICIs clinical trials typically include patients with specific cancer stages and exclude patients with active infections and findings may not reflect "real-life" experiences. Although clinical trials report the frequency and types of infections that emerge during ICIs therapy, they usually do not provide detailed information on the infection such as pathogen, timing relative to ICIs administration, or response to therapy. Therefore, infection-focused registries during ICIs therapy could greatly enhance our understanding of the risk for infection that is associated with ICIs. A better understanding of the interplay between CPIs, irAE, immunosuppression, and infection risk may help devise strategies for improved recognition, diagnosis, and treatment of infections in ICIs-treated patients with cancer [34]. The largest study to date reported the experience at Memorial Sloan Kettering Cancer Center in treating 740 patients with melanoma with ICIs therapies [5]. In this study, investigators evaluated the risk of developing severe infections requiring hospitalization and/or the use of parenteral antibiotics. Serious infections were found in 7.3% of patients. Most infections (85%) were secondary to bacterial pathogens with bacteremia reported in 28% of cases. Pneumonia and intra-abdominal infections were the mostly commonly reported infectious syndromes. The remaining infections were due to varicella zoster virus (VZV), cytomegalovirus, and Epstein–Barr virus or other opportunistic fungi, including *Pneumocystis jirovecii*, *Aspergillus*, and *Candida,* and one case described a *Strongyloides* hyperinfection syndrome. Of interest, most patients (85%) who experienced serious infections received corticosteroids during the follow-up time period. It is noteworthy that the difference in the incidence of infection among the various ICIs regimens used was related to their propensity and likelihood risk to cause irAEs requiring the use of corticosteroids and other immunosuppressive agents [5]. For instance, pembrolizumab exhibited reduced infection risk relative to ipilimumab or nivolumab. In another study that included 167 patients with lung cancer treated with nivolumab as monotherapy, the frequency of infection was 19%, and pneumonia was the most common reported infectious syndrome [14]. The causative organisms include *Streptococcus pneumonia*, *Staphylococcus aureus*, and *Haemophilus influezae* followed by *influenza* A and B. In this study, two patients also developed VZV infection. Pulmonary aspergillosis occurred in one patient and esophageal candidiasis in another. Other sporadic case reports of opportunistic infections involved various vital organs that have been described in the settings of irAE treatment. This includes a case of *Aspergillus fumigatus*-related necrotizing skin infection in a patient with renal cell carcinoma treated with dual ICIs and relapsing autoimmune hepatitis [35].

As Adjuvants to Chemotherapy

To our knowledge, the only controlled study to date where authors have comprehensively investigated the risk of infection in patients with advanced lung cancer treated with ICIs combined with conventional chemotherapy (compared to patients treated with cytotoxic chemotherapy alone) reported the experience at The University of Texas MD Anderson Cancer Center [7]. In this study, the authors found that ICIs-based anticancer regimen was not associated with an increased risk of overall infection compared to the control group; however, there were numerically fewer infections in the ICIs group (15% in the ICIs group versus 22% in the conventional chemotherapy group with P = 0.1) [7]. It is notable that in this study the incidence of irAEs was low and was largely explained by pembrolizumab combined with conventional chemotherapy as opposed to the use of various other ICIs with a higher propensity to cause irAEs. Larger studies are needed to determine if therapy with ICIs alone is associated with fewer infections than conventional chemotherapy and the relative contribution that conventional chemotherapy has on PD and PD-L pathway relative to infection.

Overlap Between Clinical Presentation of Infection and Immune Adverse Events

The potential overlap between infection and immune-related adverse symptoms remains a clinical challenge that may be encountered in any patients receiving ICIs. For example, pulmonary symptoms and presence of infiltrates on chest imaging could be secondary to immune-related pneumonitis or infection and it is often difficult to differentiate between the two conditions based on clinical grounds alone. The same applies to gastrointestinal symptoms as these could be secondary to ICIs-mediated disease or infectious colitis. Another possibility clinicians may face is that both conditions coexist. Therefore, rigorous and comprehensive diagnostic workup and evaluation are required in such clinical settings [34]. In the study by Fujita and colleagues, it is noteworthy that 11 patients with pneumonia were diagnosed based on the clinical ground alone as no pathogens were identified, but in these cases postobstructive pneumonia or ICIs-induced pneumonitis could not be ruled out [14]. In certain settings, judicious use of antimicrobials may be indicated while waiting for the infectious disease workup (Table 8.3) to be completed.

Organ-Specific Considerations

Pneumonitis

Immune-mediated pneumonitis is less frequent than other irAEs, but it is the most severe irAE associated with ICIs therapies with a mean duration of onset of approximately 3 months. Autoimmune pneumonitis accounts for 35% of deaths secondary

Table 8.3 Empiric antibiotic regimens

Organ-specific consideration	Diagnostic approach and initial antimicrobial recommendations	
Pneumonitis Grade 2 of lung toxicities or higher; grade 1 with no improvement after holding checkpoint inhibitors	Assess for immunosuppression. Obtain respiratory NAAT panel (that includes SARS-CoV-2), sputum Gram stain and culture, T spot. Imaging studies. Bronchioalveolar lavage and serological testing for endemic fungi indicated for severe cases, immunosuppressed, or those not responding to corticosteroids/ immunosuppression. Consider empiric antibiotic therapy based on the severity of clinical presentation, potential pathogens, level of care, acquisition and local epidemiology, and antimicrobial susceptibility patterns.	
	Outpatient Amoxicillin/clavulanic acid or cefuroxime PLUS macrolide or doxycycline, or levofloxacin until cultures results.	**Inpatient** Beta-lactam + macrolide, or levofloxacin. Consider anti-MRSA and anti-pseudomonal coverage in the presence of risk factors.
Colitis	NAAT for enteropathogens including *C. difficile* with reflex EIA for toxin A and B, calprotectin, lactoferrin. Empirical antibiotic therapy is not indicated prior to infectious disease workup, unless the patient has megacolon, bowel perforation, and is at risk for sepsis.	
Meningoencephalitis	Assess for immunosuppression. Brain imaging with contrast and CSF examination indicated including opening pressure. CSF should be sent for protein, glucose, NAAT meningoencephalitis panel, gram stain and culture, AFB smear and culture, fungi smear and culture, cryptococcal antigen. Patients with any grade toxicity should be treated empirically with intravenous acyclovir and antibacterial therapy (cefepime plus vancomycin +/− ampicillin if adults >50 years of age or immunosuppressed) until CSF results are available.	

[a] Consider risk/benefit for use of empiric antimicrobial agents as their use may compromise antitumor effects of ICIs
NAAT nucleic acid amplification test

to PD-1/PD-L1 blockade [30]. The relative contribution that infection has on mortality is unknown. Since this is a modifiable condition and the treatment of infection is substantially different than irAE, it is of vital importance to exclude the possibility of infection in patients receiving ICIs and presenting with pulmonary symptoms such as dry cough, dyspnea, and pulmonary infiltrates seen on the imaging studies. Per the ASCO clinical practice guideline, the management of pneumonitis is based on the extent of parenchymal involvement and respiratory status [30]. The use of high-dose corticosteroids and/or TNF-alpha inhibitors such as infliximab can lead to the development of opportunistic infections. For grade 2 and above pulmonary irAEs, infectious diseases workup may include a nasopharyngeal swab for common respiratory pathogens, including the novel SARS-CoV-2, sputum, urine EIA tests for *Legionella* and pneumococcus, and blood cultures with antimicrobial sensitivity testing when cultures are found to be positive. Results from screening tests for LTBI

and endemic fungi if done prior to ICIs therapy should be reviewed and if indicated based on clinical features and imaging studies should be repeated. For those cases where the diagnosis remains uncertain, and respiratory status permits, bronchoscopy with bronchoalveolar lavage (BAL) is warranted and empirical antibacterial therapy may be considered while awaiting BAL results (Table 8.3) [33]. Additional considerations include ruling out *Pneumocystis jirovecii* pneumonia or other opportunistic infections in patients with relapsing pneumonitis that have been exposed to corticosteroids or other immunosuppressive agents.

Colitis

Autoimmune colitis is one of the most well-known immune-mediated adverse events in patients treated with ICIs. Infectious colitis should be in the differential diagnosis in any patients presenting with symptoms of nausea, vomiting, diarrhea, and abdominal pain with or without fever in the setting of ongoing immunotherapy (Table 8.3). Inhibition of CTLA-4 is associated with higher rates of colitis than the use of PD1 or PD-L1 inhibitors and the effect can be additive, for example, when ipilimumab and nivolumab are used in combination. A recommended workup includes measuring systemic [C-reactive protein (CRP)] and intestinal (lactoferrin, calprotectin) inflammatory markers, testing for *Clostridioides difficile* using a two-step diagnostic algorithm of that includes an initial screening with a sensitive test such as nucleic acid amplification test (NAAT) for toxin A and B or an EIA for glutamate dehydrogenase (GDH) followed by a confirmatory specific test for toxin A and B by EIA, and multiplexed nucleic acid amplification tests (NAAT) for enteropathogens including viral, bacterial, and protozoa. Studies for ova and parasites should be considered in the appropriate setting (*Strongyloides* in the southern USA and Latin America) [30]. For colitis that is grade 2 and above, a colonoscopy with intestinal mucosa biopsies should be considered to rule out CMV infection. Campylobacteriosis has been recently reported in five patients following immunosuppression therapies for ICIs-mediated colitis [36]. In addition, cytomegalovirus infection has been reported in five patients with refractory ICIs (ipilimumab)-mediated colitis treated with corticosteroids and infliximab. CMV infection was documented either by CMV viremia by PCR or colonic histopathological examination [37]. Another patient with ICIs colitis developed CMV hepatitis [38]. CMV infection should be suspected in patients receiving ICIs therapy presenting with an acute abdomen due to hollow viscus perforation. The negative predictive value of multiplexed NAAT is high and therefore can be used to exclude the major enteropathogens and withhold empiric antibiotics, the exception being fecal NAAT for CMV which lacks sensitivity in this setting. Similarly, serum PCR testing for CMV cannot be used to rule out CMV colitis.

In addition to adversely impacting the antineoplastic efficacy of ICIs, the use of antibiotics particularly those with anti-anaerobic activity in patients receiving ICIs is associated with not only a higher frequency of immune colitis but also severe and refractory colitis that often requires intensification of immunosuppressive therapy and hospitalization [39].

Following an acute episode of enterocolitis due to invasive and noninvasive agents, a subset of patients develops postinfectious irritable bowel syndrome (PI-IBS). PI-IBS is characterized by persisting GI symptoms, most commonly diarrhea that is associated with microscopic colitis, resulting in immunological dysregulation and increased intestinal permeability and motility [40]. Further down in the spectrum of postinfectious bowel disease complications following enterocolitis due to *C. difficile* or invasive enteropathogens is a smaller subgroup of patients that are predisposed to developing inflammatory bowel disease (IBD) [41]. While IBD can exacerbate with the use of ICIs, it remains unknown if a history of infectious enterocolitis or PI-IBS predisposes to ICIs-related immune colitis or can predispose patients with gastrointestinal irAEs to have refractory disease. It is also unknown if ICIs and/or the treatment of irAE predisposes to gastrointestinal infections. Two studies have examined the association of *C. difficile*-associated diarrhea (CDAD) in patients receiving ICIs [5, 42]. One study done with five patients who developed CDAD while receiving immunosuppression for ICIs suggested that CDAD may occur as a superimposed infectious process and could be responsible for persistent symptoms. Of note in this study, four out of five patients were not exposed to antibiotics prior to the onset of CDAD [42]. Clinicians should be mindful of the possible coexistence of both CDAD and autoimmune colitis despite the absence of recent antibiotic use. Differentiating the relative contribution that *C. difficile* has on patients with diarrhea undergoing treatment with ICIs can be difficult given the high frequency of *C. difficile* colonization in cancer patients. Thus, we recommend the use of a two-step diagnostic approach as outlined above for patients with symptoms that are compatible with CDAD [43]. For patients with inconclusive results or failing therapy for CDAD, colonoscopy with colonic biopsies should be pursued. Future studies are necessary to elucidate the direct impact or the association between ICIs-mediated colitis and enteropathogens including CDAD.

Encephalitis

Nervous system irAEs are rare and occur approximately in 1% of patients receiving ICIs. As is the case for colitis, CNS autoimmune manifestations are more common following the use of anti-CTLA4 combined with anti-PD1/PD-L1 agents, where the frequency increases to 3%[30]. Given that cancer, immunosuppression, and advanced age are risk factors for CNS infection, an infectious etiology should be excluded in any patients who developed clinical symptoms suggestive of meningoencephalitis (Table 8.3). Some preclinical studies have suggested that PD-L1 blockers may be associated with worrisome outcomes following *Listeria* infections and, therefore, CNS infections secondary to *Listeria* should be considered in the context of ICIs therapy [44]. A recent case series and review of literature described the spectrum of symptoms and disease severity of ICIs-induced aseptic meningitis and encephalitis [45]. A key aspect common to almost all cases of encephalitis was the presence of concurrent findings suggestive of meningitis. To ensure early diagnosis, prompt, and appropriate management, a meticulous medical history, review of patient's cancer and immunosuppression medication history, and clinical

examination are of paramount importance. It is noteworthy that both meningeal enhancement in the case of aseptic meningitis and parenchymal enhancement in the case of encephalitis is commonly seen on brain MRIs [45] of patients with CNS irAE. Although none of the reported cases had a pathogen identified, most had received empiric antimicrobial therapy including antibacterial and acyclovir prior to undergoing a lumbar puncture for CSF examination. Nevertheless, we recommend that a diagnostic lumbar puncture be performed for all patients with suspected meningitis or meningoencephalitis with the following CSF studies done: measurement of opening pressure, cell count and differential, chemistry (protein and glucose), multiplexed NAAT with a panel that includes at least probes for herpes simplex, varicella zoster, enterovirus, and cytomegalovirus, and bacterial agents such as pneumococcus, meningococcus, and *Listeria* – a Gram stain, a cryptococcal antigen, as well as reflex cultures for bacterial, fungal, and acid-fast bacilli, and finally, cytology [30]. In addition, for patients with hematological malignancies, additional infections such as human herpesvirus 6, progressive multifocal leukoencephalopathy (JC virus), adenovirus, and Epstein–Barr virus should be considered. The typical CSF profile seen in patients with ICIs-related meningoencephalitis is characterized by lymphocytic pleocytosis, elevated protein level, and normal glucose levels with negative viral and bacterial cultures/NAATs [45]. Another systematic review described 82 patients presented with encephalitis presumed to be induced by ICIs after excluding other differential diagnoses such as toxic and metabolic encephalopathy, in addition to infectious causes [46].

Sepsis

The term sepsis first appeared in antiquity in poems by Homer and it is defined as a life-threatening multisystem dysfunction caused by a dysregulated host response to infection [47, 48]. Despite the advances in understanding the immunopathology of sepsis and introduction of timely antibiotics, no definitive therapies exist to treat this condition effectively. During the initial stages of sepsis, there is a constellation of excessive inflammation mediated by the release of pro-inflammatory mediators following recognition of pathogen-associated molecular patterns (PAMPs). Whereas in later stages, sepsis may result in immune suppression state involving both the adaptive and innate immune systems via the release of anti-inflammatory cytokines, immune cells apoptosis, exhaustion of T cells, and expansion of regulatory T cells (Treg). In addition, there is increased expression and upregulation of PD-1/PD-L1 and CTLA-4 axis on T cells and may further predispose the host for a “second hit” following onset of sepsis [49]. Importantly, numerous preclinical studies have demonstrated that blocking the inhibitory effect of immune checkpoints by using ICIs, improve innate and adaptive immune cell function and enhance host resistance to infection and subsequently improve survival and this merits further investigation in sepsis [50]. An ex vivo model conducted by obtaining blood samples from 43 septic and 15 nonseptic critically ill patients showed the increase of expression of PD-1 on CD8-T cells and demonstrated that blockade of the PD-1/PD-L1 pathway decreases

cellular apoptosis and improves immune cell function in septic patients [51]. A single case study of an immunosuppressed patient with extensive life-threatening abdominal mucormycosis infection refractory to conventional therapy was treated successfully with combined treatment of nivolumab (anti-PD-1 antibodies) plus Interferon γ (INFγ) [52]. Combination ICIs have been proposed as adjuvant treatment for septic and vulnerable patients [53]. Given the lack of well-controlled studies evaluating ICIs in sepsis, recent phase 1b, placebo-controlled, randomized cohort study was launched evaluating the blockade of PD-1/PD-L1 pathway in sepsis, and the intervention was well tolerated with no evidence of drug-induced cytokine storm or hypercytokinemia and showed evidence of immune cell function restoration over 28 days [54]. All in all, data regarding the use of ICIs in sepsis are still scarce and limited. Studying ICIs in patients with cancer and sepsis remains challenging given the variety of causal pathogens, their tropism for distinct organs, and variation in the host immune response due to underlying diseases such as diabetes, tumor type, and host gene polymorphisms in effector proteins that mediate innate and acquired immune responses.

Since adrenal crisis can masquerade as sepsis and presents with severe dehydration, hypotension, and shock that can sometimes be refractory to volume repletion and vasopressors, primary or secondary immune-related adrenal insufficiency (AI) should be considered in patients with suspected sepsis [55]. AI requires an early recognition and cortisol replacement and, if untreated, can be associated with life-threatening condition [55, 56].

Mucositis

Oral involvement following immune checkpoint inhibitors therapies is not uncommon and can include xerostomia, dysgeusia, and lichenoid reaction and together constitute approximately 10% of all irAEs [57, 58]. However, oral mucositis is mainly seen after conventional chemotherapy but has been sporadically reported with immunotherapy primarily with anti-PD-1 blockade [57, 59–62]. It is important to maintain a high level of awareness to exclude an infectious process such as oropharyngeal candidiasis or herpetic stomatitis, particularly in patients receiving conventional chemotherapy. Of note, mucositis and oral mucosal ulcerations can predispose to bacterial or fungal translocation (predominantly *Candida*) into the bloodstream, particularly in the settings of concomitant neutropenia.

Infections that Can Trigger ICIs Toxicity

Given the strong association between microbiome composition, dysbiosis, irAE, and ICIs response to therapy, there is a potential risk that inflammation and activation of the immune system secondary to an infectious process in a patient receiving ICIs can cause irAE, an example being the immune reconstitution leading to

reactivation of *Mtb* infection. However, to date there is no conclusive evidence that patients with chronic, latent viral infections have an increased risk of irAE [63]. Of interest though is a recent clinical study conducted by Hutchinson and colleagues showing that a subset of patients predisposed to immune-related hepatitis following ICIs therapy have a chronic expansion of effector memory CD4+ T cells. Additionally, the CD4+ T-cell expansion was more pronounced in patients with high titers of antibodies to CMV and hypothesized that the expanded CD4+ T cells could be responsible for immune-related hepatitis in patients receiving ICIs. Furthermore, they also describe four patients who were given prophylactic valganciclovir during ICIs therapy and remained hepatitis-free. Therefore, the authors concluded that CMV may play an important role in the development of hepatitis after immunotherapy in a specific subset of patients with melanoma [64]. Of note, other pathogens and commensals have been implicated in the expansion of immune cell subsets following immunotherapy and can shape clinical responses and irAEs following anticancer therapy.

Extrapolating from inflammatory bowel disease (IBD), dysbiosis has been implicated in the pathogenesis of IBD in genetically predisposed hosts [65]. Studies have showed that butyrate-producing bacteria play an important role in the gut homeostasis and reduced prevalence of these bacteria is associated with active IBD [65, 66]. Numerous microorganisms have been implicated in the pathogenesis of IBD and relapses including *Mycoplasma* spp., *Mycobacterium* spp., and *Salmonella* spp. [67]. Interestingly, a recent paper showed that *Escherichia coli* pathobionts [adherent invasive *E. coli* (AIEC) and diffusely adherent *E. coli* (DAEC)] are linked to IBD pathophysiology [68]. Therefore, several microorganisms may play a role in the pathogenesis of immune-related colitis in the setting of immune-enhancing therapies (ICIs).

Infection with SARS-CoV-2 in Patients Receiving ICIs

The novel Coronavirus Disease 2019, also known as COVID-19, secondary to SARS-CoV-2, is associated with a high mortality in patients with cancer (13%), particularly in those with hematological malignancies (17%) compared to 1% in the general population [69, 70]. The impact of SARS-CoV-2 on cancer patients receiving ICIs is poorly understood. In some patients, ICIs may have beneficial effects presumably by improving the host immune response to early stages of infection and avoid progression to a lower respiratory tract infection. There are concerns that an enhanced inflammatory response secondary to ICIs effect on interferon pathway signaling can result in respiratory distress, lung toxicity, and interstitial pneumonitis [71, 72]. However, data is continually evolving and is sometimes conflicting. A recent retrospective study by Robilotti and colleagues that evaluated 423 patients with cancer and symptomatic COVID-19 infection demonstrated that advanced age (>65 years) and treatment with immune checkpoint inhibitors were independent risk factors for hospitalization and severe disease and those receiving chemotherapy were not at higher risk for severe disease [73]. In another study of a subset of 102

patients with lung cancer treated with PD-1 blockade and after adjusting for smoking status, immune checkpoint inhibitor therapy was not associated with increased risk of severe COVID-19 [74]. A subsequent study by Mehta and colleagues evaluated 218 patients with cancer and showed that ICIs were not associated with increased mortality [75]. Major limitations of these studies include heterogeneity in patient populations in terms of underlying malignancies, lack of control groups, differences in standard of care due to saturation of medical facilities early in the pandemic, variable use of corticosteroid therapy to treat severe COVID-19, use of monoclonal antibodies to prevent COVID-19, use of hyperimmune serum, and access to remdesivir, among others. Nevertheless, during the current pandemic distinguishing between COVID-19 and immune pneumonitis is sometimes difficult as illustrated by a recent case of 65-year-old patient with head and neck cancer treated with anti-PD-L1 blockade. The patient had evidence of resolving COVID-19 pneumonia based on chest imaging and positive IgG antibodies against severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). After started receiving immunotherapy, the patient developed pneumonitis and the authors speculated that previous COVID-19 pneumonia may have primed the immune system and facilitated the development of irAEs [76].

Vaccination of Patients Receiving ICIs

Immune checkpoint inhibitors have become a main part of the therapeutic arsenal against cancer. However, to date, there are no standard recommendations for guiding the best practice of routine vaccinations during ICIs treatment. Also, little is known about the interactions between vaccination and the potential increase risk of irAEs secondary to ICIs treatment. To date, there are no clinical studies available assessing the long-term safety, tolerance, and efficacy of vaccination including COVID-19 vaccines for patients treated with ICIs. One study by Waissengrin and colleagues showed that BNT122b2 mRNA COVID-19 vaccine in patients with cancer treated with ICIs is safe and well tolerated without an increased risk for irAEs during the short-term follow-up period [77]. A study conducted by Weber and colleagues that evaluated the immunogenicity of tetanus, influenza, and pneumococcal vaccines in patients with melanoma treated with ipilimumab observed enhancement of T-cell-mediated and humoral immunity to all three vaccines at week 7 relative to immune status at baseline [78]. In another prospective safety and efficacy observational study of 28 patients who were treated with anti-PD-1 blockade that concurrently received quadrivalent inactivated influenza vaccine, no grade 3/4 irAEs were noted [79]. Furthermore, a separate prospective study published in 2018 evaluated the frequency and severity of irAEs in patients with lung cancer treated with nivolumab that received trivalent-inactivated influenza vaccine. In this study, the rate of all grade irAEs was not significantly greater in the vaccinated group compared to the nonvaccinated group whether the vaccine was administered before ICIs or between biweekly nivolumab infusion [80]. In

more informative and larger prospective trial, Chong and colleagues studied the new onset of irAEs in 370 patients on ICIs who received inactivated flu vaccine over three consecutive seasons [81]. In this study, there were no increases in the occurrence or severity of irAEs and the authors encouraged influenza vaccination in patients on ICIs [81]. All in all, the best evidence-based practice of vaccination and ICIs therapy is mainly confined to inactivated influenza vaccines that appeared to be safe and efficacious.

As with other patients with cancer, immunization for indicated inactivated vaccines is more likely to be efficacious if administered ≥2 weeks prior to initiation of chemotherapy. We recommend annual seasonal immunization for influenza for patients receiving ICIs preferably starting ≥2 weeks prior to initiation of ICIs.

For patients that are immunosuppressed, have hematological malignancies, and are undergoing HSCT, live vaccines are contraindicated regardless of concomitant ICIs therapy. Likewise, in patients with solid tumors on ICIs and receiving conventional chemotherapy or immunosuppression the use of live vaccines is also contraindicated. The use of live vaccines in patients with solid tumors who are not receiving conventional chemotherapy, who are not immunosuppressed, and for whom ICIs are contemplated is a gray area due to the potential use of future immunosuppression that could lead to vaccine-related illness and therefore should be avoided if immunosuppression is considered possible within ≤4 weeks. Large, prospective studies evaluating the immunogenicity, reactogenicity, safety, and efficacy of other vaccines are of utmost importance.

Knowledge Gaps and Other Areas of Uncertainty (Table 8.4)

Adjuvant Use of ICIs to Treat Infection

The availability of immune checkpoint inhibitors has ignited enthusiasm for their use as adjunctive immunotherapies to treat indolent or chronic viral infections in an attempt to reverse the host immune-paralysis state. Pembrolizumab or nivolumab has been used in the treatment of progressive multifocal leukoencephalopathy (PML) [82, 83]. ICIs have been evaluated as an adjunct to highly active antiretroviral therapy in HIV-1 infection in an attempt to achieve a cure since HIV-1-infected T cells express PD-1 and this correlates with HIV persistence and immunotherapy can reverse this immunotolerance state [84]. The first clinical trial using ICIs (BMS-936559) appeared to enhance HIV-1-specific immunity in a subset of participants [85]. In addition, initial studies indicated that ICIs are safe and well tolerated in chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. Of note, cure of HBV infection has not been achieved in contrast to HCV infection in the era of direct antiviral therapies [84]. Hence, future studies should elucidate if overcoming the CD8 T-cell exhaustion using ICIs can achieve long-term viral suppression in patients with chronic HBV infection [84, 86].

Table 8.4 Knowledge gaps and suggested approaches

Areas of uncertainty	Key questions	Proposed approaches
Role of microbiome	What is the impact of the gut microbiome on the rate and types of irAEs? What is the role of respiratory or oral microbiome in ICIs–pneumonitis and infections rate?	Detailed documentation of microbiome signatures prior to, during, and post-ICIs therapy and in the setting of specific irAEs or infections Multidisciplinary trials including translational and clinical studies
Fecal transfer to enhance ICIs' clinical effects	Is fecal transfer safe in patients with solid tumors and hematological malignancies receiving ICIs?	Experimental studies are needed to ensure the safety and tolerability of such procedure, especially in neutropenic hosts
Impact of prior or active infection on irAEs	Does active or prior infection (including COVID-19) increase the risk of specific irAEs?	Focusing studies on reporting irAEs in patients with infection and validate specific observation in preclinical studies
Impact of ICIs on infections	Do ICIs alter or change the natural history of specific infections, in particular latent, chronic or refractory infections? Do ICIs prevent the occurrence of new infections?	Meticulous documentation of each infection arises during or following ICIs therapy and reporting the severity Clinical trials are ongoing for major ID syndromes (sepsis, HIV, etc.)
Impact of CMV serostatus on irAEs	Does CMV-positive serostatus increase the risk of autoimmune hepatitis or other irAEs following ICIs therapy?	Comparing the incidence of irAEs in patients receiving ICIs based on negative or positive CMV serostatus
Impact of adjuvant chemotherapy	Can adjuvant cytotoxic chemotherapy reduce the rates of irAEs and without affecting the clinical benefits of ICIs?	Detailed documentation in clinical trials of irAEs' rate, infections, immunosuppressive use
Antifungal prophylaxis	Do patients with irAEs treated with prolonged and high dose of corticosteroids require anti-mold prophylaxis?	Reporting mold infections in patients treated with ICIs and had irAEs requiring immunosuppressive
Antibacterial prophylaxis	Do patients with ICIs-related neutropenia or secondary to adjuvant chemotherapy necessitate antibacterial prophylaxis?	Documenting the rate of bacterial infections in the setting of neutropenia during ICIs therapy and assessing the clinical benefits of ICIs after antibacterial use

Biomarkers That Can Help Differentiate irAEs from Infection

Differentiating infection from immune checkpoints inhibitor-related toxicities can be challenging and complex. From the clinician's perspective, the onset of new symptoms or signs during ICIs therapy falls into three categories that include irAEs, infection, or tumor progression and require a different approach. Thus, there is a need for biomarkers that not only predict the efficacy of ICIs therapy but can also

aid in distinguishing between infection and irAEs. The onset of irAEs is often unpredictable as they may occur early after ICIs initiation or late during therapy [87]. A study conducted by Kim and colleagues characterized the lymphocytes in bronchoalveolar lavage (BAL) fluid and peripheral blood from patients with acute myeloid leukemia/myelodysplastic syndrome (AML/MDS) with pulmonary symptoms after receiving ICIs-based treatment. In this study, BAL T cells in the ICIs group were clonally expanded, and BAL IFNγ+ CD8+ T cells and Th17/Th1 cells were enriched in the ICIs group, but could not reach definitive conclusions differentiating between ICIs–pneumonia versus ICIs–pneumonitis [88]. Another study showed that baseline circulating IL-17 in patients with melanoma treated with ipilimumab was significantly associated with the development of severe diarrhea and colitis rather than therapeutic clinical outcome [89]. A retrospective study of 167 patients treated with anti-PD-1 noticed that patients with absolute lymphocyte count >2000 cells per mL at baseline and at 1 month into therapy more commonly developed grade ≥2 irAEs [90]. In addition, an increase in peripheral eosinophil counts during ICIs correlates with ≥2 irAEs [90]. In such a clinical scenario, patients receiving immunosuppression for the treatment of irAEs due to ICIs with elevated eosinophils should be evaluated for strongyloidiasis [5]. Further work is required to identify soluble biomarkers in the blood, BAL, and stools that can differentiate between irAEs and infectious process.

Tailoring Immunosuppression to Least Dose Effective

Objective Markers of Net Immunosuppression

IrAE management requires immunosuppression with either corticosteroids as monotherapy or combined with other immune- modulators/−suppressive agents. As much as controlling irAEs is critical, the ideal approach should be tailored to short duration and least dose possible as affecting the T-lymphocytes function would negatively impact ICIs' clinical efficacy. However, a retrospective study performed by Reid and colleagues revealed first that the presence of irAEs was associated with tumor response [91]. In this study, the authors suggested that immunosuppressive agents should not be precluded from the management of irAEs as progression-free survival remains comparable to those who received immunomodulators or corticosteroids alone. Extrapolating from clinical experience in recipients with organ transplant, few studies address adjustment of immunosuppression during active infections. The successful post-transplant course relies on optimal management of immunosuppression intertwined with antimicrobial prophylaxis [92]. The risk for infection in cancer patients with irAEs is likely a constellation of factors consisting of exposures to potential pathogens, hosts, intensity, and types of immunosuppressive agents. Therefore, having some objective measures for the host's immune state is required to assess the infectious risk and implement a preventive measure. Similarly, to solid-organ transplant (SOT) recipients, the "net state of

immunosuppression" is a conceptual framework design to assess the infectious risk at individual scale and takes into consideration the immunosuppressive regimen, host preexisting comorbidities such as diabetes mellitus, renal failure, surgery, and malnutrition [92, 93].

The Need for Antimicrobial and Microbiome Stewardship

The key challenge in patients receiving ICIs with irAEs is the absence of standardized guidance for tailoring immunosuppression and assessing infection risk. Clinical judgment on a case-by-case basis remains the best approach. Apart from the established guidance on PJP prophylaxis in patients treated with prolonged high-dose corticosteroid, the role of antibacterial, antifungal, and/or antiviral prophylaxis in patients receiving immune checkpoint blocking agents requires further evaluation. Importantly, additional studies focused on unlocking further the power hidden within the microbiome as it may not only influence and enhance the clinical efficacy of checkpoint inhibitors but also reduce the risk of infections.

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Chapter 9
Nephrology (Kidney)

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Abstract Immune checkpoint inhibition (ICI) has been very effective in cancer treatment and has changed the treatment paradigm for many cancers. ICIs act by releasing the natural regulators of the immune system, leading to overall immune activation and stimulation of the immune system against antigens in tumors. The inhibitors target cytotoxic T-lymphocyte-associated antigen-4, programmed cell death protein 1, and programmed death ligand-1. These accentuated antitumor effects are associated with off-target side effects, so maximizing the antitumor effects ICI while preventing the off-target effects is challenging. The term immune-related adverse event (irAE) was coined to denote a toxic effect associated with ICI that can involve any organ in the body, including the kidneys. Although the incidence rates for renal irAEs are reported to be only 1–5%, the decline in kidney function associated with ICI would impact survival and eligibility for further clinical trials. Therefore, appreciation of close monitoring of kidney function to preserve and optimize it during ICI has grown. In this chapter, we present the incidence of renal irAEs of, risk factors for, clinicopathologic features of, treatment strategies for, challenges associated with, and a proposed algorithm for diagnosis and management of renal irAEs.

Keywords irAE · ICI · Nephritis · Vasculitis · Kidney transplant · Infliximab

Chapter debriefing: Power point video presentation is provided at the end of the chapter.

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Abbreviations

AKI	Acute kidney injury
ATIN	Acute tubulointerstitial nephritis
ATN	Acute tubular necrosis
GN	Glomerulonephritis
ICI	Immune checkpoint inhibition
irAE	Immune-related adverse event
CTLA-4	Cytotoxic T-lymphocyte antigen-4
PD-1	Programmed cell death protein 1
PD-L1	Programmed ligand-1
Ab.	Antibody
MHC	Major histocompatibility complex
TCR	T-Cell receptor
Na	Sodium
Ca	Calcium
PO4	Phosphorus
SIADH	Syndrome of inappropriate antidiuretic hormone secretion

Introduction

Multiple studies have reported acute kidney injury (AKI) in association with the use of immune checkpoint inhibition (ICI) for cancer therapy, which is particularly concerning in patients with solitary kidney, renal cell carcinoma, or pre-existing chronic kidney disease [1]. The incidence of ICI-associated AKI is uncertain, although it is reported to occur in 1.4–16.5% of patients on ICI therapy with median times of AKI diagnosis ranging from 1 to 3 months after ICI exposure [2–6]. However, authors have reported ICI-associated AKI as early as 2 weeks after initiation of therapy and months after cessation of it [5]. In two recent studies in which the attribution of AKI to ICI was carefully adjudicated, the overall incidence rate for AKI was 16.5–17.0%, among which only 3.0–4.2% attributed to ICI therapy [2, 4]. Nevertheless, these studies were all retrospective, with various definitions of AKI.

In this review, we will discuss the incidence of ICI-associated renal adverse events, particularly electrolyte disturbances and acute kidney injury in patients with native kidneys and kidney allograft, the most common reported kidney pathologies identified in these patients, the risk factors and predictors to develop the observed toxicity, the current treatment strategies and their challenges, and finally a proposed algorithm for diagnosis and management of renal irAEs.

Incidence and Risk Factors

To evaluate AKI in patients receiving ICI, we recommend using Kidney Disease Improving Global Outcomes consensus criteria, which define AKI as any of the following: increase in serum creatinine level of at least 0.3 mg/dL within 48 hours; increase in serum creatinine level to at least 1.5 times above baseline, which is known or presumed to occur within the prior 7 days; and urine volume less than 0.5 mL/kg/hour for 6 hours. In addition, AKI can be classified into three stages as follows: stage 1, increase in serum creatinine level of at least 0.3 mg/dL or 1.5–1.9 times the reference value; stage 2, 2.0–2.9 times the reference serum creatinine value; and stage 3, at least 3.0 times the serum creatinine reference value, increase in serum creatinine level to at least 4.0 mg/dL, or initiation of renal replacement therapy [7]. Several published national, international, multicenter, and single-center studies have evaluated the incidence of AKI using the Kidney Disease Improving Global Outcomes criteria but with several variations, such as defining ICI-induced AKI as a 50% increase in the serum creatine level from baseline, a twofold or greater increase in serum creatinine level, and the need for dialysis [2–5]. As far as the incidence of AKI in patients with different types of cancer, authors have reported no differences, but in a recent retrospective cohort of 1664 melanoma patients, researchers concluded that the incidence rate for stage 1 AKI was only 3.49% and was decreased by half when attributed directly to ICI [6]. In a single-center study by Seethapathy et al. that involved 1016 patients, 82 patients (8%) had sustained AKI, defined as a serum creatinine level that remained at least 1.5 times greater than the baseline for at least 3 days. Forty-seven percent of these patients had stage 1 AKI, 37% had stage 2 AKI, and 16% had stage 3 AKI, and only 3% needed dialysis [2].

In several studies, researchers sought to evaluate predictors of AKI after ICI exposure, and combined use of anti-cytotoxic T-lymphocyte-associated antigen-4 and anti-programmed cell death protein 1/programmed death ligand-1 agents was an independent predictor of AKI, which is evident in other immune-related adverse events (irAEs) [3, 6, 8]. Some authors have reported decreased baseline estimated glomerular filtration rates associated with AKI, but this association was not consistent in all studies [2, 3, 6]. Therefore, ICI should not be withheld from patients with impaired kidney function or chronic kidney disease, particularly given the low incidence of AKI in these patients. In addition, extrarenal irAEs are reported to be independent predictors of AKI, and in a multivariable analysis, the presence of a concomitant irAE was associated with reduced likelihood of complete kidney recovery [3, 4].

Use of nonsteroidal anti-inflammatory drugs and proton pump inhibitors has been associated with increased risk of acute interstitial nephritis, which appears to be the predominant ICI-related form of kidney injury [3, 9–11]. Investigators have studied several comorbidities in patients with ICI-associated AKI, and based on our

literature review, diabetes mellitus, heart failure, liver cirrhosis, chronic obstructive pulmonary disease, and hypertension are considered possible risk factors for AKI. Furthermore, in one of these studies, hypertension was found to be an independent predictor of ICI-induced AKI in multivariable analysis [2–4]. We summarize our proposed approach for evaluation and treatment of AKI in patients on ICI therapy based on etiology, AKI severity, and kidney pathology in the algorithm included at the end of this chapter.

Clinical Characteristics of Renal Adverse Events

Renal adverse effects of ICI have varied presentations, including electrolyte disturbances, acute tubulointerstitial nephritis (ATIN), acute tubular necrosis (ATN), vasculitis, and glomerulonephritis (GN). We discuss below the spectrum of these pathologies and their management based on the limited evidence at hand.

Electrolyte and Acid-Base Disturbances

In the US Food and Drug Administration Adverse Event Reporting System database, about half of the reported ICI-associated adverse events are electrolyte disturbances [12]. In a meta-analysis of 44 clinical trials, hypophosphatemia and hyponatremia were the most common electrolyte disturbances, with pooled incidence rates of 1.3% and 1.2%, respectively [13]. These electrolyte disturbances were mild, with only 29% being grade 3 or higher according to the Common Terminology Criteria for Adverse Events [13]. Also, of these reported electrolyte disturbances, only hypocalcemia was strongly associated with use of ICI despite a relatively low incidence rate of 1%. Grade ≥ 3 hyponatremia was attributed to syndrome of inappropriate antidiuretic hormone secretion, hemodynamic disturbances, terminal illness, and less commonly associated endocrinopathy [14]. Interestingly hypercalcemia was reported as well in association with ICI use, and four distinct causes were observed, endocrine disease related, sarcoid-like granuloma, humoral hypercalcemia, and rapid progressive disease (Fig. 9.1) [15]. Additionally, authors have reported metabolic acidosis with ICI use and attributed it to interstitial inflammation with possible subsequent alterations in tubular intercalated cells (i.e., H + -ATPase or Cl-/HCO3-) that manifest as renal tubular acidosis [16]. Treatment of electrolyte disturbances typically consists of providing supportive care with repletion of electrolytes and treating the underlying etiology.

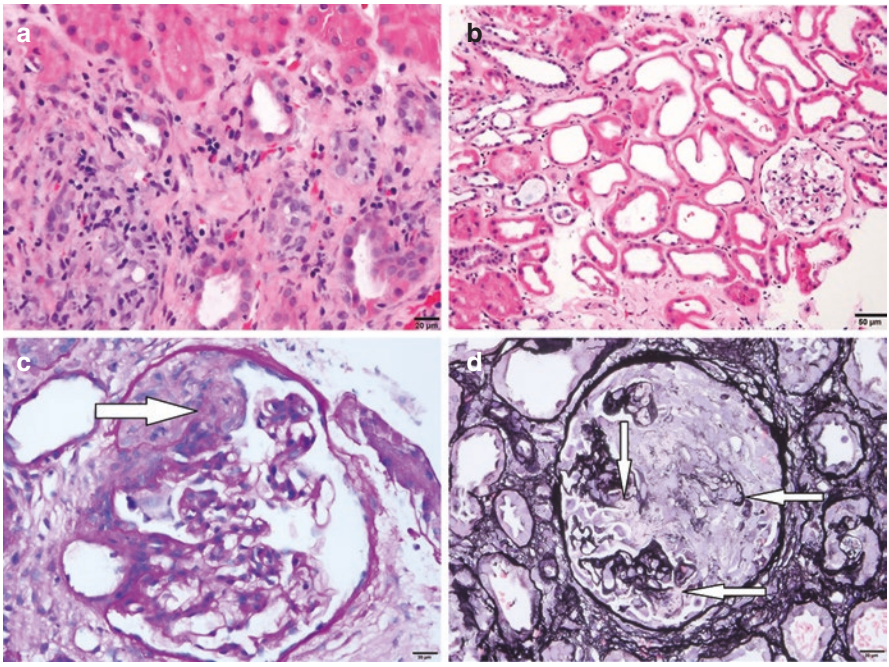


Fig. 9.1 Histological findings of common kidney pathologies associated with ICI acute kidney injury. (**a**) Interstitial inflammation with eosinophils and lymphocytes with focal tubulitis suggestive of acute interstitial nephritis (H&E, 40×). (**b**) Normal-appearing glomerulus with ectatic proximal tubules suggestive of acute tubular injury (H&E, 20×). (**c**) Segmental glomerular basement membrane break (arrow) observed in patient with renal vasculitis (PAS, 40×). (**d**) Silver stain highlighting glomerular basement membrane breaks observed in patient with renal vasculitis (arrows, 40×). (Courtesy of Dr. William Glass and Dr. Amanda Tchakarov, University of Texas, McGovern Medical School, Department of Pathology and Laboratory Medicine)

Renal Pathologies Associated with irAEs

ATIN

Histologically, in patients with ATIN, patchy interstitial edema is expected, with lymphocyte and macrophage infiltrates and possible granuloma formation with or without associated acute tubular injury (Fig. 9.1a).

ATIN is the most common reported kidney pathology in patients with AKI associated with ICI [10]. ATIN can be the dominant pathology or coexist with glomerular pathologies. In a single-center study of 16 cancer patients given ICI and developed AKI, 14 patients had ATIN, with 9 of these patients having concurrent

glomerulopathy and 5 having ATIN only [9]. Patients with suspected ATIN often present with sterile pyuria, subnephrotic-range proteinuria, or eosinophilia similar to drug-induced ATIN. However, these findings are neither sensitive nor specific to confirm or exclude ICI-induced ATIN [3, 9, 11]. In other studies, researchers suggested performing early, prompt diagnosis of ATIN with a kidney biopsy, when possible, to prevent immune-mediated inflammation resulting in the development of interstitial fibrosis and subsequent irreversible kidney damage. Progression to chronic kidney disease and end-stage kidney disease requiring dialysis are common sequelae of ATIN [17, 18]. Although ICI induction of ATIN progressing to end-stage kidney disease is rare, preserving kidney function in cancer patients is critical because elevated creatinine levels would limit their ability to receive further cancer treatment.

Current guidelines vary with regard to treatment of ICI-induced ATIN. However, glucocorticoid-based therapy along with discontinuation of the potential offending medication represents the mainstay of ICI-associated ATIN management. Data on the duration of glucocorticoid-based treatment, optimal glucocorticoid dose, treatment of relapsed ATIN, and re-challenge of ICI in the setting of ATIN are lacking. Studies demonstrated that not all patients with ATIN experience complete recovery kidney function to baseline (<50%) [3]. In addition, authors reported that relapse of ATIN is a challenge and associated with worse kidney prognosis than patients who experienced no relapse [19]. In a multicenter study, re-challenge of an immune checkpoint inhibitor was attempted in 31 (22%) patients at a median of 1.8 months (interquartile range, 1.2–11.0 months) after diagnosis of ICI-AKI. Thirty-nine percent of the patients were receiving concomitant steroids at the time of re-challenge, with 23% having repeat AKI with a shorter latency period than then initial ICI-AKI.

With these challenges, and to avoid steroid-induced suppression of active T cells targeting tumor cells, recent studies demonstrated that decreasing steroid treatment to 3 weeks was equally effective compared to the standard 4–6 weeks of steroid therapy in treating ICI-induced ATIN [20, 21]. In a recent single-center study, researchers compared rapid taper of prednisone (tapering from 60 mg to 10 mg within 3 weeks) in a small cohort of 13 patients with ICI-induced nephritis with 6 weeks of prednisone therapy (standard of care) in a control group of 14 patients. They concluded that the two groups did not differ significantly with regard to time to kidney recovery [20]. Interest in steroid-sparing agents in the field of irAEs has grown over the past few years, and a recent study by our group demonstrated for the first time durable response to treatment with infliximab without prolonged steroid exposure in cases of relapsed ICI-ATIN [21]. This study included ten patients with ICI-ATIN who received glucocorticoids for a median of 3.5 weeks (range, 1.0–8.0 weeks) for the initial ATIN episode who had ATIN relapse within 4 weeks after initial glucocorticoid therapy. Eighty percent of them had complete or partial renal recovery with infliximab-based therapy. Further basic research and clinical trials are needed to elucidate the mechanism by which ATIN is induced by ICI and to evaluate the clinical benefits of biologics to further optimize renal care in patients with ICI-ATIN while continuing life-saving cancer therapies. Please refer to the algorithm for our proposed approach for treatment of ICI-associated ATIN.

Proposed Mechanisms of ATIN

ATIN is a well-described etiology for AKI and commonly associated with use of certain medications (e.g., antibiotics, proton pump inhibitors, nonsteroidal anti-inflammatory drugs), autoimmune diseases (e.g., lupus, sarcoidosis), and systemic bacterial and fungal infections [22]. The proposed mechanism of medication-induced ATIN is an immune response trigged by either exogenous antigens processed by renal tubular cells or endogenous nephritogenic antigens [11, 23, 24]. ICI may lower the threshold for activation of drug-specific T lymphocytes and cross-reactive T lymphocytes to renal tissue-associated epitopes. Chemokines are important in tumors, where they are responsible for differentiation, activation, and migration of immune cells. Nevertheless, these cytokines are implicated to have a role in off-site tissue injury (irAEs), as authors have reported that patients with irAEs have upregulation of various cytokines, such as CXCL9, CXCL10, CXCL11, and CXCL13. With respect to kidney irAEs, this upregulation can be associated with direct tubular injury in addition to increased immune infiltration, leading to the development of fibrosis, and subsequently progress to chronic kidney disease if interstitial inflammation continues over months (Fig. 9.2) [25]. Therefore, the duration of kidney injury and degree of pre-existing renal fibrosis may be most predictive of renal response to treatment with glucocorticoids as reported in cases of non-ICI-induced kidney injury [18, 32–35]. Additional cytokines that may be involved in the pathogenesis of ICI-ATIN include tumor necrosis factor-α and interleukin-9, as prior studies demonstrated that elevated urinary levels of them were independently predictive of drug-induced ATIN [36, 37]. Measuring cytokine levels when possible may be helpful; however, the variability in reporting of cytokines levels may be difficult due to their inherent short half-lives. In cases of ICI-ATIN or cytokine-mediated ATIN, if cytokine levels are elevated, this may support the use of biologics in patients who have relapsed after steroid tapering.

ATN

Histologically, patients with ATN have dilated proximal tubules along with vacuolization and loss of brush border (Fig. 9.1b). ATN is one of the most common etiologies for AKI in hospitalized patients with active infections or receiving nephrotoxic medication(s). In a study involving 12 patients given pembrolizumab who underwent diagnostic kidney biopsy, ATN was the most common etiology for AKI, 6 patients were found to have ATN and 5 with ATIN [38]. In a different case series, six patients with AKI from possible ICI-associated ATN, treatment with steroids resulted in three out of five patients having full kidney recovery [39]. Of note, antibiotic, intravenous contrast, and cardiovascular risk factors were more common in patients who had ICI-associated ATN than in those who had ATIN [38, 39]. While more research is needed, one postulated mechanism of ATN in patients with ICI-induced kidney injury may be a result of direct cytokine-induced tubular injury

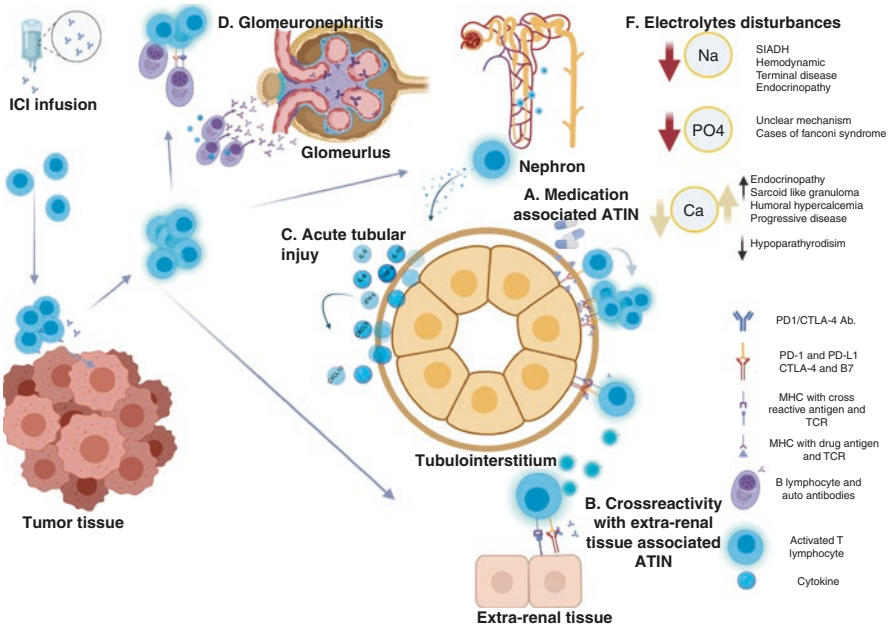


Fig. 9.2 Most common ICI-associated kidney IrAEs with the proposed mechanism and etiology. (**A**) ATIN, ICI may cause loss of immune tolerance to drugs and lower the threshold for activation of drug-specific T lymphocytes. (**B**) Another proposed mechanism is the cross-reaction of ICI-activated T lymphocyte with endogenous renal tissue-associated epitopes. (**C**) [23–25]. ATI, cytokines secreted directly by activated T cells or immune cells that may be associated with off-site tissue injury (irAEs) resulting in direct tubular injury and immune cell infiltration in the kidneys. Proposed cytokines include IL-6, IL-9, IL-10, TNF-α, interferon gamma, CXCL9, CXCL10, CXCL11, and CXCL13. (**D**). Pauci-immune GN and other GN, the mechanism is poorly understood and possibly related to regulatory T-cell suppression by ICI, increasing the risk for antibody-mediated autoimmune diseases including glomerulonephritis. In addition, the upregulation of certain cytokines, by activated T lymphocytes, like interferon gamma and interleukin-12, and CXCL9 and CXCL10 has been associated with antineutrophil cytoplasmic antibody vasculitis and IgA vasculitis, respectively [26–30]. (**F**) Electrolyte disturbances, Syndrome of inappropriate antidiuretic hormone secretion, hemodynamic disturbances, terminal illness, and less commonly ICI-associated endocrinopathy are the main observed etiologies for ICI associated with hyponatremia. Endocrine diseases, sarcoid-like granuloma, humoral hypercalcemia, and rapid progressive disease are the four distinct etiologies of hypercalcemia in patients receiving ICI. Hypophosphatemia, while the underlying mechanism is unclear, a subset of patients had Fanconi syndrome with proximal tubular injury. Hypocalcemia, the etiology is likely multifactorial, including autoimmune hypoparathyroidism [13–15, 31]. This figure was developed using biorender.com

(Fig. 9.2). Therefore, use of steroids and biologics may help prevent cytokine injury and further inflammatory cell migration to renal tissue.

GN

GN is a rare renal pathology induced by ICI and associated with significant patient morbidity and mortality. However, increasing use/indication of ICI has been accompanied by recognizing that ATIN is not the only ICI-associated renal pathology.

Kidney biopsies are necessary for GN diagnosis to tailor treatment as steroid therapy alone is insufficient to treat GN [9, 40]. This recommendation is a departure from some of the current guidelines for management of renal IrAEs that suggest forgoing kidney biopsy or discourage reflex kidney biopsy until corticosteroid-based treatment is attempted [41]. In a recent meta-analysis of de novo glomerular diseases after ICI exposure, pauci-immune GN and renal vasculitis accounted for 27% of glomerular disease cases, followed by minimal change disease (20%) and C3GN (11%). 41% of the patients had concomitant ATIN [42]. The median time to glomerular disease diagnosis after starting ICI was 93 days (interquartile range, 44–212 days). ICI was discontinued in 88% of the patients, and nearly all of them received corticosteroids (98%), with 31% and 42% of the patients having complete and partial recovery from AKI, respectively. Approximately 19% of the patients underwent dialysis, and of these dialysis cases, approximately one third died. Please refer to the algorithm for our recommended approach for treatment of ICI-associated GN.

Re-Challenge of ICI in GN Cases

The data on ICI re-challenge in GN cases are very limited. In one study four patients with GN were re-challenged: one with C3 glomerulonephritis (who had recurrence upon re-challenge), one with renal vasculitis (who had progression to end-stage renal disease), and two with minimal change disease (one had recurrence of minimal change disease upon ICI re-challenge) [42]. In another case report, reactivation of biopsy-proven primary membranous nephropathy (anti-phospholipase A2 receptor-positive) was diagnosed following nivolumab treatment of malignant pleural mesothelioma. In this case, the patient was treated with steroids and rituximab and achieved complete renal recovery and continued ICI therapy with cancer remission [43]. Reactivation of GN after ICI exposure has been rarely reported, and in this situation, treatment of membranous and continued ICI therapy was successful.

Proposed Mechanisms of Glomerular Diseases and Vasculitis

In the meta-analysis of ICI-associated GN described above, vasculitis was the most common type of GN, and data on its management are limited, with some studies using only corticosteroids and others using corticosteroids with rituximab and plasmapheresis [40, 44]. Histologically, glomeruli will exhibit segmental breaks in the glomerular basement membrane along with crescent formation, periglomerular inflammation, and fibrinoid necrosis of small arteries in patients with vasculitis (Fig. 9.1c, d). The mechanism of vasculitis associated with ICI remains poorly understood. Among the speculated mechanisms involve ICI-induced regulatory T-cell suppression, thereby increasing the risk for antibody-mediated autoimmune diseases, and upregulation of interferon-γ and interleukin-12. Upregulation of these two aforementioned cytokines has been associated with increased B-lymphocyte interaction with expanded T-lymphocyte populations and development of antineutrophil cytoplasmic antibody vasculitis [26–30]. Additionally, authors reported that

ICIs upregulate CXCL9 and CXCL10, which facilitate T-cell recruitment and have been associated with tissue injury in patients with IgA vasculitis [45, 46].

In our experience, we recommend treatment with rituximab opposed to other cytotoxic therapies in cases of GN and (non-crescentic) vasculitis. Rituximab, a monoclonal anti-CD20 antibody, disrupts pathogenic B-lymphocyte interaction with cytotoxic T lymphocytes, reduces chemokine production, and limits endothelial injury which, to date, has not been shown to inhibit the antineoplastic effects of ICI therapy [47, 48]. In a small cohort of five patients diagnosed with ICI-induced renal vasculitis, treatment with rituximab resulted in partial to complete renal recovery and no renal relapses [40]. Please refer to our recommended approach for treatment of ICI-associated GN.

ICI Use in Solid Organ Transplant Recipients

Recipients of organ transplants have a higher risk of malignancy development compared to the general population [49]. In particular, this risk in kidney transplant recipients is estimated to be at least twofold higher [50]. Furthermore, cancer is considered one of the leading causes of morbidity and mortality in this population [50]. Immunosuppressive therapy is essential to prevent allograft rejection. However, this can be a double-edged sword in cancer patients with history of solid organ transplants given the detrimental immunosuppressive effects to cancer treatment.

In 2014, Lipson et al. described the first case of successful melanoma treatment with an immune checkpoint inhibitor (ipilimumab) in two kidney allograft recipients who were receiving low-dose immunosuppressants [51]. However, multiple studies since then reported kidney allograft rejection associated with ICI usage [52, 53]. In a study based on single-center experience and literature review describing the experience of ICI therapy in 39 cancer patients (10 patients from the cancer center and 29 patients from the literature review) who received solid organ transplants that also included a literature review, 23 patients were kidney allograft recipients who initiated ICI therapy approximately 9 years after transplantation (range, 0.93–32.00 years) [54]. Eleven of the 23 patients were diagnosed with allograft rejection around 21 days after receiving ICI (range, 19.3–22.8 days). Eighty-one percent of the patients with rejection had graft loss, and 46% died. The rates of allograft rejection were similar in those who underwent anti-cytotoxic T-lymphocyte-associated antigen-4 and anti-programmed cell death protein 1 therapy [54]. Interestingly, authors of multicenter study observed a similar rejection rate, to the study described above, of 42% in a recent study of 69 kidney allograft recipients with cancer histories who underwent ICI [55]. Notably, in this study receiving triple-agent immunosuppressant medications and a mammalian target of rapamycin inhibitor was associated with lower risk of allograft.

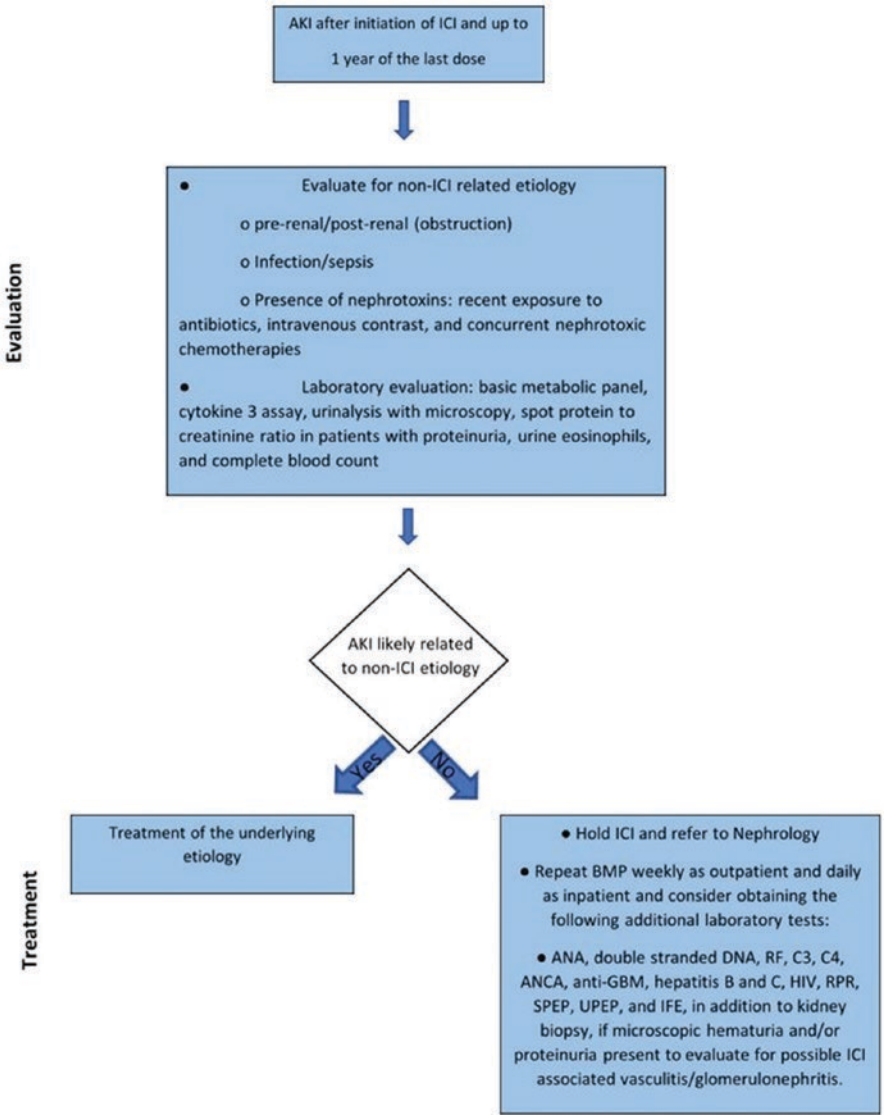
The proposed mechanism of ICI-associated graft rejection is attributed to the inhibition of programmed death ligand-1. This ligand induces regulatory T cells,

which limits effector T-lymphocyte function and expansion and prevents autoimmunity, allowing for allograft tolerance. Previous studies showed that programmed cell death protein 1 and programmed death ligand-1 are upregulated in T cells and allograft cells, respectively, which can hinder allospecific lymphocyte activation and proliferation; thus, blockade of these ligands decreases tolerance and likely leads to allograft rejection [56, 57].

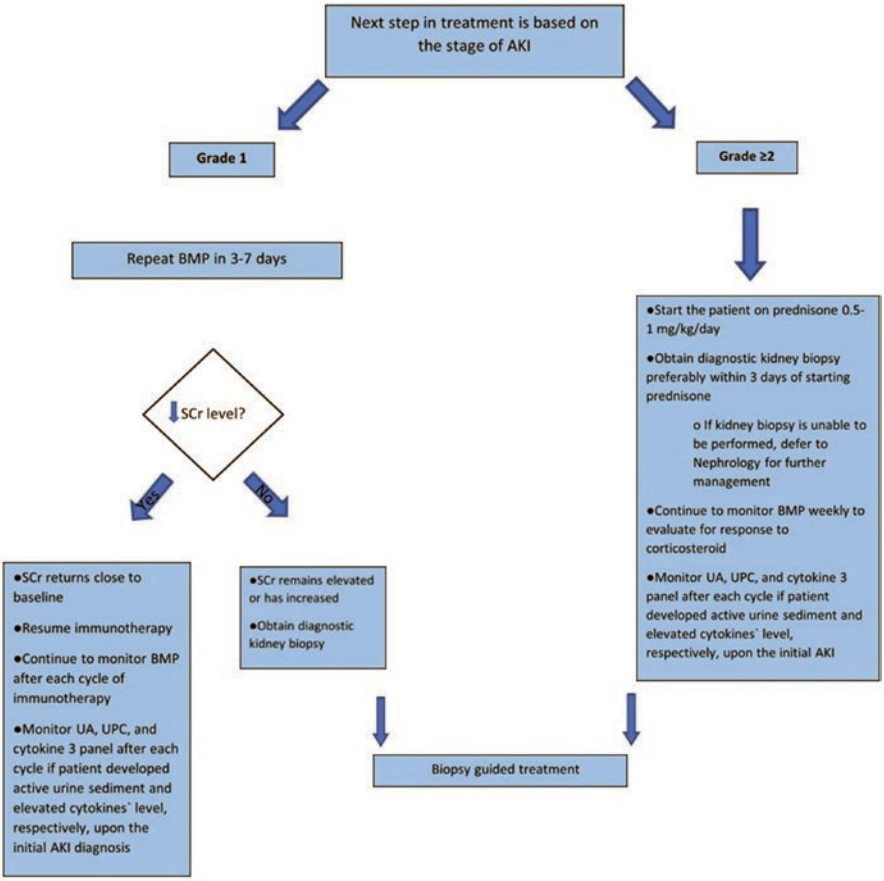
Given the high risk of kidney allograft rejection, subsequent graft loss, and ICI treatment discontinuation among cancer patients, a multidisciplinary approach to delivering optimal cancer and transplant care is essential, and establishing a national registry of cancer patients who receive solid organ transplants and ICI therapy in prospective multicenter studies is needed to help identify patients who are at risk for allograft rejection and introduce a guided approach to optimizing immunosuppressive regimens prior to and during ICI [58].

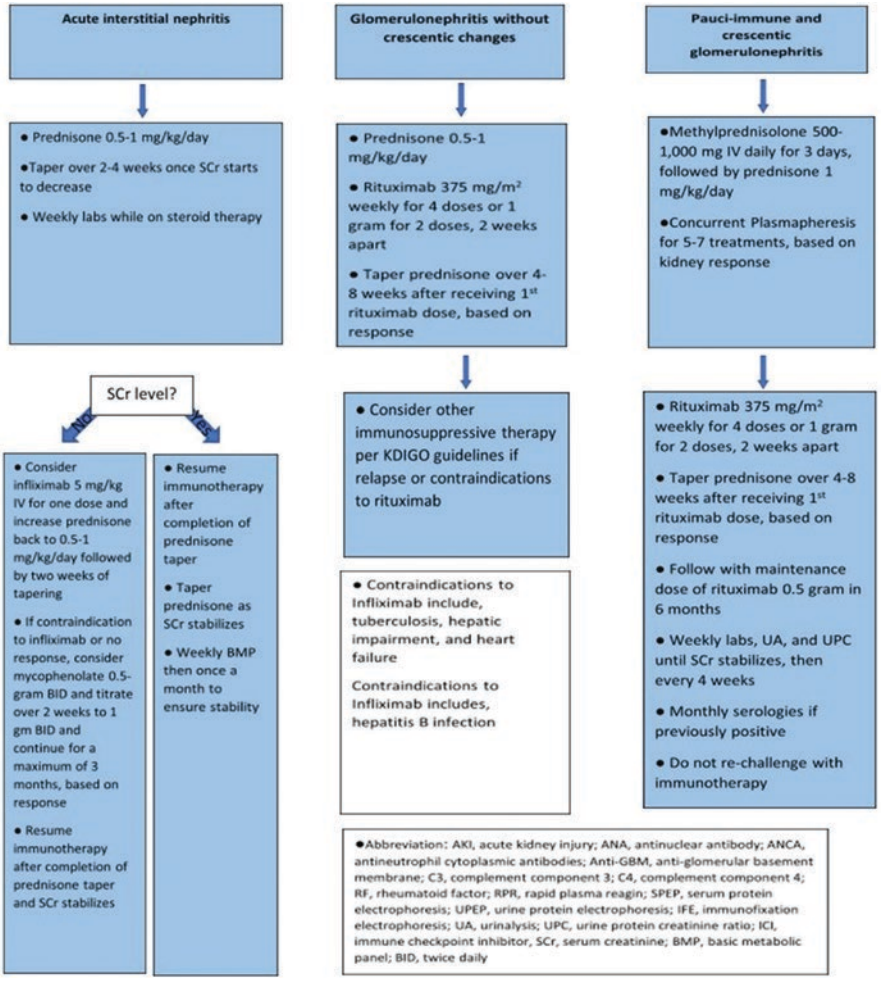
Long-Term Complications and Follow-Up

With supportive care and appropriate renal treatment, the majority of patients who experience ICI-related AKI are expected to have renal recovery. In a multicenter study >80% of patients with ICI-AKI will have complete or partial kidney recovery irrespective of the severity of renal injury [3]. Out of 13 patients who required dialysis, kidney recovery occurred in 6 (46%; 4 with partial and 2 with complete recovery). To date pathologic characteristics of ATIN such as presence/severity of granulomatous, tissue eosinophilia, interstitial fibrosis, and glomerulosclerosis were not found to impact kidney prognosis [3]. In regard to overall prognosis, the impact of AKI has been evaluated in a few studies. A recent single-center study demonstrated that a single AKI episode was an independent risk factor for mortality in a cohort of 759 patients exposed to ICI [5]. However, ICI-associated AKI ICI-AKI has not always been associated with increased risk of mortality [4, 59]. This was further demonstrated in the melanoma cohort study by Abdelrahim et al. [6]. Nonetheless, failure to recover from AKI was an independent predictor of increased mortality in cancer patients [3]. Therefore, re-challenge with ICI has been predominantly limited to patients with partial or complete kidney recovery after ICI related AKI. The recurrence was observed in 23% of re-challenged patients, with a shorter period of relapse with re-challenge of ICI than with/in the initial AIN [3]; however, data on outcomes in patients who undergo re-challenge of ICI after ATIN are limited. To decrease the risk of IrAE recurrence, re-challenge with immunosuppression as a secondary prevention has been suggested, especially if ICI is the only effective anticancer option. This requires close follow-up by multidisciplinary team with careful evaluation to balance the risk and benefits for each patient, and its effectiveness should be evaluated as well in a well-designed prospective randomized study [60].



Proposed algorithm for evaluation and management of patients with suspected ICI-associated acute kidney injury. Adapted from https://www.mdanderson.org/content/dam/mdanderson/documents/for-physicians/algorithms/clinical-management/clin-management-nephritis-web-algorithm.pdf


Next step in treatment is based on the stage of AKI
Grade 1
Grade ≥2
Repeat BMP in 3-7 days
•Start the patient on prednisone 0.5-1 mg/kg/day
•Obtain diagnostic kidney biopsy preferably within 3 days of starting prednisone
o If kidney biopsy is unable to be performed, defer to Nephrology for further management
•Continue to monitor BMP weekly to evaluate for response to corticosteroid
•Monitor UA, UPC, and cytokine 3 panel after each cycle if patient developed active urine sediment and elevated cytokines` level, respectively, upon the initial AKI
SCr level?
Yes
No
•SCr returns close to baseline
•Resume immunotherapy
•Continue to monitor BMP after each cycle of immunotherapy
•Monitor UA, UPC, and cytokine 3 panel after each cycle if patient developed active urine sediment and elevated cytokines` level, respectively, upon the initial AKI diagnosis
•SCr remains elevated or has increased
•Obtain diagnostic kidney biopsy
Biopsy guided treatment



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Chapter 10
Neurology

Sudhakar Tummala

Abstract Immune checkpoint blockade by antibodies has revolutionized oncological care in recent years moving from investigative protocols to frontline therapy. Increased use in multiple cancers leads to greater recognition of immunotoxicity across multiple disciplines. Providers including neurologists need to recognize the central and peripheral nervous system inflammatory autoimmune conditions, as these therapies unleash unrestrained T cells [1]. Compared to the classic inflammatory conditions, these tend to be different with marked variability in clinical presentation, disease course, and response to therapy. Our continued identification of the various clinical manifestations, refining clinical examination and advancing radiological and laboratory and tissue biomarkers, will continue to advance our understanding and better treatment of these toxicities. This chapter highlights the heterogeneous variable clinical presentations along the neural axis, principles of treatment, and therapies available to treat.

Keywords Immune checkpoint inhibitors · Neurologic immune-related adverse events (n-irAEs) · Encephalitis · Meningitis · Cranial neuropathies · Myositis · Myasthenia gravis · Cranial neuropathies · Inflammatory neuropathies · Central nervous system · Peripheral nervous system · Guillain-Barré syndrome · Subacute and chronic inflammatory neuropathy · Tumor-infiltrating lymphocytes · Leptomeningeal disease · Total plasma exchange · Lumbar puncture

Chapter debriefing: Power point video presentation is provided at the end of the chapter.

Supplementary Information The online version contains supplementary material available at [https://doi.org/10.1007/978-3-031-00241-0_10].

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Abbreviations

CNS	central nervous system
FAERS	United States Food and Drug Administration Adverse Event Reporting System
GBS	Guillain-Barré syndrome
ICI	Immune checkpoint inhibitors
LMD	Leptomeningeal disease
LP	Lumbar puncture
n-irAEs	Neurologic immune-related adverse events
PNS	Peripheral nervous system
SIDP, CIDP	Subacute and chronic inflammatory neuropathy
TILs	Tumor-infiltrating lymphocytes
TPE	Total plasma exchange

Epidemiology

Initial approval of immune checkpoint inhibitor by the FDA started with ipilimumab in 2011 that blocks cytotoxic T lymphocyte-associated protein 4 (CTLA-4). Additional agents targeting other immune checkpoints leading to approval are programmed cell death protein 1 (PD-1, nivolumab, pembrolizumab, cemiplimab) and programmed cell death ligand 1 (PD-L1, atezolizumab, avelumab, durvalumab). In a recent review looking at FAERS (United States Food and Drug Administration Adverse Event Reporting System) database, from Jan 2014 to Dec 2019, the neurologic toxicity is 7.2% out of total ICI adverse events [1]. The frequency of ICI neurotoxicity remains rare compared to other organ toxicities and recognized to be at 1% among multiple reviews [2]. The possibility of permanent neurological dysfunction and rare fatal nature of this toxicity needs to be recognized.

Dual or sequential checkpoint inhibitor use has also come to the forefront and is used frequently. Risk of n-irAEs and fatal outcomes appears higher on dual ICI use [1]. Anti-CTLA-4 is more frequently associated with meningitis, and encephalitis. Anti-PD-1/PD-L1 is more frequently associated with myositis and myasthenic syndromes and less common in meningitis, encephalitis, and GBS. Anti-PD-1 is relatively more associated with myositis and myasthenia overlap syndrome compared to CTLA-4 and PD-L1. Mortality appears higher in myasthenic syndromes. Cancer-specific neurotoxicity and population-specific neurotoxicity likely exist and need further data as more prospective information is gathered. Melanoma was more frequent among other cancers in patients with peripheral neuropathies [2].

In most published studies (individual cases, case series, literature review), n-irAEs are usually observed within the first 4 months of therapy. Cases very early after one dose and late after many months to beyond a year have been reported as well, including few cases reported after cessation of immunotherapy.

Uncovering of prior existing autoimmune or flare-up of prior existing conditions can occur with potential mortality [3, 4]. With quiescent and well-controlled underlying autoimmune condition, ICI could be tried under very close observation or with potential use of biologics like tocilizumab given the favorable known oncological responses to ICI.

Clinical Characteristics

Immune-related adverse effects need to be recognized from the traditional chemotherapy neurotoxicity (platins, taxanes). Examples of traditional neurotoxicity include noninflammatory toxic axonal peripheral neuropathy (CIPN-chemotherapy-induced peripheral neuropathy), leukoencephalopathy with white matter changes, and PRESS (posterior reversible encephalopathy syndrome) [5].

Central nervous system n-irAEs include encephalitis, meningitis, CNS demyelinating diseases including flare-up of underlying multiple sclerosis, neuromyelitis spectra and transverse myelitis, cranial neuropathies, CNS vasculitis, opsoclonus-myoclonus, and cerebellar syndromes. Both nonlimbic and limbic autoimmune encephalitides occur with nonlimbic presentation roughly twice as common as limbic autoimmune encephalitis [6]. In this large collection series of 54 patients, common symptoms and signs are altered mental status, focal CNS deficits, psychiatric symptoms, seizures, autonomic dysfunction, working memory deficits, ataxia, and dyskinesias. The presence of antibodies to intracellular antigens (anti-Ma2, anti-Hu, anti-GAD, anti-Ri) was a significant predictor for lack of improvement after first-line immunosuppressive therapy. Antibodies against cell surface antigens (NMDA, CASPR2) are much less frequent with better response to first-line therapy. Lack of good responses in intracellular antigen patients in contrast to better outcomes in cell surface antigen cases is similar to non-ICI-triggered patients as well. Identification of novel new paraneoplastic antibodies in cancer patients who have received ICI along with patients who did not receive ICI argues in favor of paraneoplastic autoimmune pathogenesis [7]. Novel new PDE10A paraneoplastic antibody was identified in seven patients with movement disorders of which six had cancer and two received ICI [8].

Peripheral nervous system n-irAEs include inflammatory neuropathies, myasthenic syndromes, myositis [9], and gastrointestinal pseudo-obstruction. Neuropathies include Guillain-Barré syndrome (GBS), Guillain-Barré syndrome variants, and subacute and chronic forms (SIDP, CIDP) as well. These inflammatory neuropathies in comparison with the CIPN present in acute to subacute fashion and in non-length-dependent fashion (descending fashion, asymmetric ascending, sensory neuronopathy, focal cervical, thoracic, lumbosacral radiculitis, cranial neuropathies). In comparison with the traditional Guillain-Barré, with cyto-albumino dissociation where there is generally increased protein but no WBC in the CSF, ICI-related inflammatory neuropathies could have abnormal CSF with increased WBC [10]. Guillain-Barré variants like Miller-Fisher and axonal predominant neuropathies are also seen. Workup (EMG, LP) and management (TPE, IVIG) are

generally the same as traditional idiopathic disease except steroids are used concomitantly given the T cell responses.

There are distinct myositis, myasthenia gravis, and myocarditis syndromes (3 Ms) with the possibility of occurring simultaneously in an individual patient. Workup and management are based on the presentation and recommended to include all three clinical entities. Clinicians need to recognize ocular myositis associated with ICI [11]. Bulbar muscle weakness can occur with dysarthria, dysphagia, and the need for tube feeds. Diaphragm muscle weakness can occur with need for early noninvasive ventilation. Myositis presentations could mimic myasthenia gravis and could be hard to differentiate from the predominant pathology (isolated myasthenia vs isolated myositis or combination) [12]. Isolated myasthenia requires the use of pyridostigmine, and judicious use of steroids as higher dose of steroids could push a mild to moderate myasthenic patient into crisis. Myasthenia patient with myositis in contrast would be requiring higher-dose steroids. 3 M presentation could be acute to subacute, with patients requiring ICU care from onset. With the necrotizing myopathy as described in many published cases, there could be permanent muscle loss resulting in fixed muscle weakness as a sequela. Muscle loss could be early during the initial inflammatory response. Early intervention and multimodal immunosuppressive strategy might be needed to mitigate the inflammatory response and limit the degree of muscle loss. Monitoring of respiratory functions with vital capacity and NIF and ABG for PCO_2 retention are needed with earlier use of BiPAP [13]. Earlier use of BiPAP could prevent the need for ventilatory support in some patients. Cardiology consultation and cardiac work are needed with cardiac MRI, echocardiogram, and troponin I to differentiate from myositis given that troponin T can be elevated in myositis. Early speech therapy and swallowing evaluation are recommended. Few patients could require permanent tube feeds.

Multifocal involvement of both CNS and PNS can occur in few patients.

Evaluation

Differential diagnosis: Immunotherapy-related neuroimaging changes (called iRANO) [14] could be challenging and require advanced tumor neuroimaging (cerebral blood flow studies along with PET scan). This is especially challenging in patients with cranial or spinal metastasis who have undergone prior surgical and/or radiological treatment [15]. Tumor recurrence along the neuroaxis, including leptomeningeal disease (LMD), should be undertaken with neuroimaging and CSF analysis if safe to perform lumbar puncture. Cranial neuropathies from ICI-related inflammation can be challenging as these are common clinical manifestations of LMD. Infectious workup, including reactivation of indolent viruses (HHV-6), is recommended for CNS conditions. Workup for concomitant organ toxicity especially endocrine (thyroid, adrenal) and cardiac needs to be considered given that these also affect the nervous system (myopathy from hypothyroidism, adrenal

insufficiency, stroke from cardiac arrhythmia). Coexisting organ toxicity needs multidisciplinary coordinated care. Examples are ICI pneumonitis and ICI myasthenia/myositis and ICI rheumatological manifestations like polymyalgia rheumatica, fasciitis, and ICI neuromuscular weakness. ICI vasculitis would need multidisciplinary approach for a thorough investigation and treatment decisions given the possibility of multivessel vasculitis and multiorgan involvement [16, 17].

Clinical stratification is recommended for grading the pathological process and guiding treatments. Oncology societies have published management guidelines based on clinical grades. These include the American Society of Clinical Oncology (ASCO) [18] and National Comprehensive Cancer Network (NCCN) [19]. Myasthenia gravis clinical grades like MGFA could be reliably applied. Grade 1 toxicities require close clinical and lab monitoring, though grades 2–4 often warrant discontinuation of immunotherapy, along with immunosuppression.

Algorithms listed detail the needed evaluation and treatment of altered mental status (Fig. 10.1) and weakness (Fig. 10.6). ICI CNS immunotoxicity causes altered mental status from aseptic meningitis, autoimmune encephalitis, demyelinating lesion, and central nervous system vasculitis (Figs. 10.2, 10.3, 10.4, 10.5, and 10.6). Seizures need to be managed in a timely fashion. There is a reported increased occurrence of status epilepticus in brain metastasis patients treated with ICI [18]. Appropriate CNS imaging and EEG tests for nonconvulsive status epilepticus are recommended. ICI PNS immunotoxicity causes weakness due to nerve root/

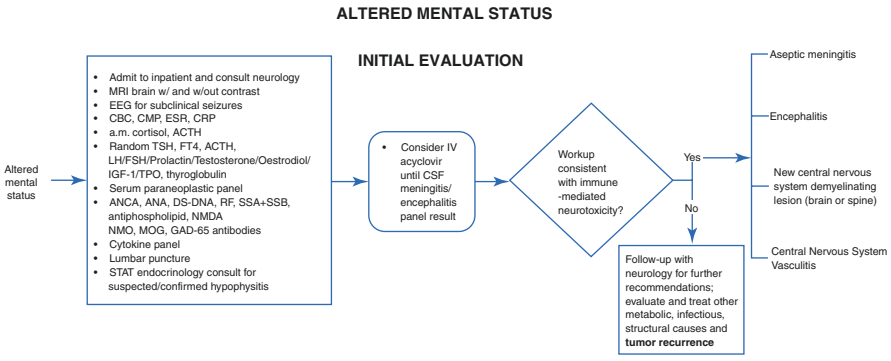

Fig. 10.1 Management algorithm for altered mental status. Lumbar puncture, CSF studies: measure opening pressure, cell count, protein, glucose, Gram stain, culture, PCR for HSV, HHV-6, meningitis/encephalitis panel, cytology, flow cytometry, autoimmune encephalopathy and CSF paraneoplastic panels, CSF kappa light chains, *or* oligoclonal bands. Aseptic meningitis symptoms include headache, photophobia, and neck stiffness, with or without fever; mental status may be normal (distinguishes from encephalitis); LP, abnormal; cytology may show reactive lymphocytes or histiocytes. Encephalitis symptoms include altered mental status, headaches, seizure, focal weakness, and speech abnormality; LP, abnormal; cytology may show reactive lymphocytes or histiocytes. Central nervous system vasculitis presentations vary, including altered mental status, stroke without clear risk factor, or other unexplained neurologic deficits, often in the setting of nonspecific constitutional symptoms, after excluding other possible diagnoses. Workup may reveal small and medium blood vessels and cerebral abnormalities on vascular imaging or brain biopsy. LP usually shows nonspecific protein elevation and lymphocytic-predominant pleocytosis

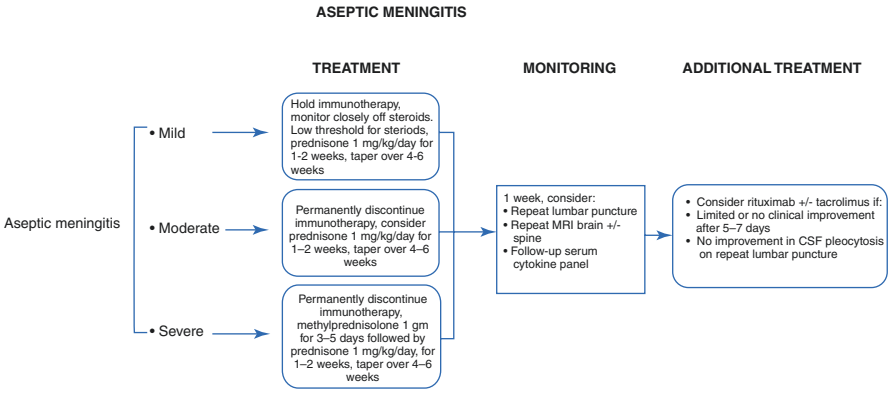

Fig. 10.2 Management algorithm for aseptic meningitis. Symptoms include headache, photophobia, and neck stiffness, with or without fever; mental status may be normal (distinguishes from encephalitis); LP may show pleocytosis, normal glucose, normal Gram stain, and culture; cytology may show reactive lymphocytes or histiocytes. Mild (CTCAE grade 1): asymptomatic or mild symptoms. Moderate (CTCAE grade 2): limiting age-appropriate instrumental ADL. Severe (CTCAE grade 3): severe or medically significant but not immediately life-threatening; disabling; limiting self-care ADL. Lumbar puncture CSF studies: measure opening pressure, cell count, protein, glucose, Gram stain, culture, PCR for HSV, meningitis/encephalitis panel, cytology, flow cytometry, autoimmune encephalopathy and CSF paraneoplastic panels, CSF kappa light chains, *or* oligoclonal bands

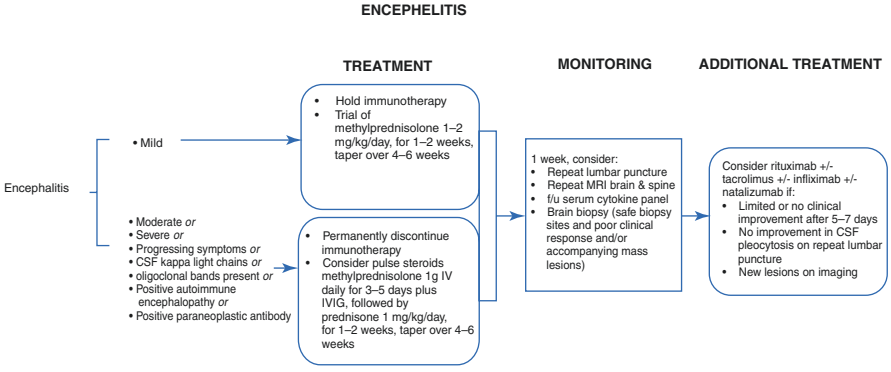

Fig. 10.3 Management algorithm for encephalitis. Symptoms include confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality; LP may show elevated WBC with lymphocytic predominance and/or elevated protein; MRI may reveal T2/FLAIR changes typical of autoimmune encephalopathies or limbic encephalitis or may be normal. Mild (CTCAE grade 1): asymptomatic or mild symptoms. Moderate (CTCAE grade 2): limiting age-appropriate instrumental ADL. Severe (CTCAE grade 3): severe or medically significant but not immediately life-threatening; disabling; limiting self-care ADL Lumbar puncture CSF studies: measure opening pressure, cell count, protein, glucose, Gram stain, culture, PCR for HSV, meningitis/encephalitis panel, cytology, flow cytometry, autoimmune encephalopathy and CSF paraneoplastic panels, CSF kappa light chains, *or* oligoclonal bands

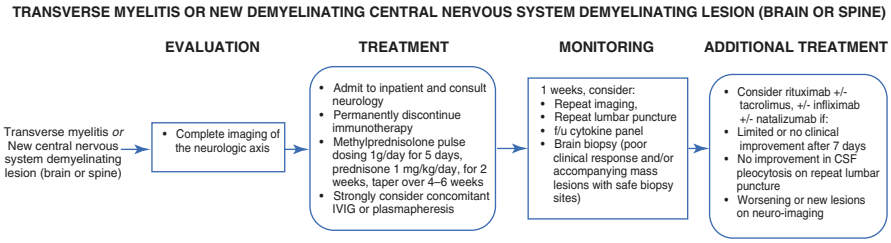

Fig. 10.4 Management algorithm for transverse myelitis. Acute or subacute weakness or sensory changes bilaterally often with bowel/bladder dysfunction. May develop increased deep tendon reflexes later in disease course New brain or spine lesion to be differentiated from metastatic lesions. Might need additional studies (LP if safe to do, PET, ABTI-advance brain tumor imaging). Biopsy might be needed

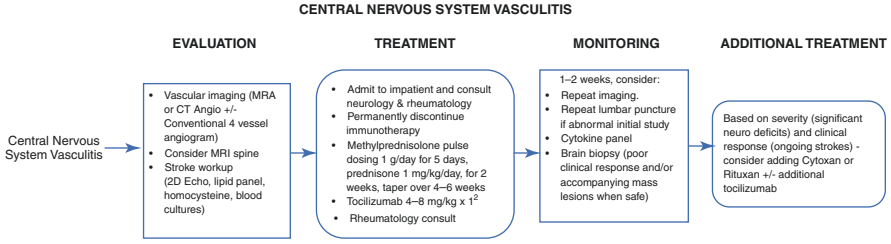

Fig. 10.5 Management algorithm for central nervous system vasculitis. Clinical presentations vary, including headache, altered mental status, neurologic deficits, and multiple strokes in different vascular distribution. LP may show nonspecific protein elevation and lymphocytic-predominant pleocytosis. Tocilizumab – do not initiate if ANC is <2000/mm^3, if platelets are <100,000 mm^3, or if ALT or AST is >1.5 times ULN. Further dosing based on clinical response q monthly

peripheral nerve inflammation and varying presentations, myasthenia gravis, and myositis (Figs. 10.7, 10.8, 10.9 and 10.10). Figure legends explain the clinical syndromes and clinical stratification.

Myositis and myasthenia gravis with or without myositis can clinically look similar with eye lid ptosis, opthalmoplegia causing double vision bulbar weakness (swallowing and speech difficulty) and breathing difficulty due to diaphragm weakness [11, 12]. Differentiating isolated myasthenia gravis and myasthenia graivs with accompanying myositis from isolated myositis is important in regards to management and overall course. It is possible to push patient with isolated myasthenia into myasthenic crisis needing intubation with the use of high dose steroids (100 mg prednisone or equivalent) unless total plasma exchange is concomitantly done. Proposed algorithm that is in part is based on resources available at local facility could be helpful in differentiating the 3 entities (Fig. 10.10). It is also important to recognize the possibility of fixed muscle weakness from myositis given the necrotizing process to limit prolonged immune suppression.

The needed workup is detailed in the algorithms. Important evaluation includes lumbar puncture with CSF analysis for routine studies, oligoclonal bands,

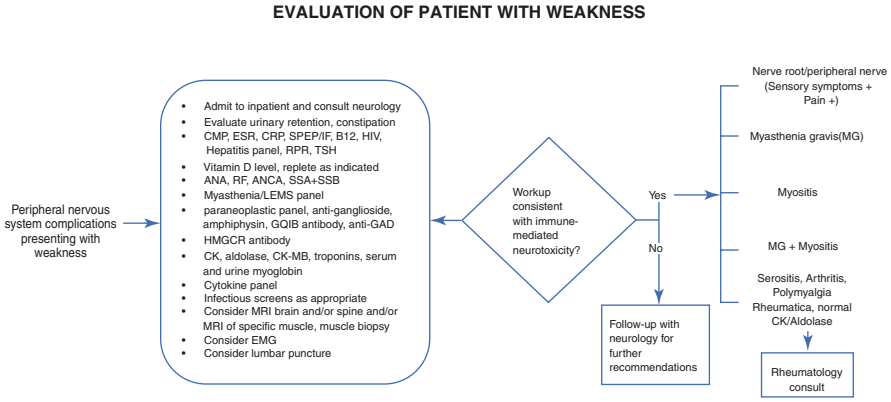

Fig. 10.6 Management algorithm for weakness. Lumbar puncture CSF studies include cell count, protein, glucose, viral PCRs, cytology, flow cytometry, CSF paraneoplastic panel, CSF kappa light chains, or oligoclonal bands. Weakness can present as asymmetric or symmetric sensory-motor deficit. Sensory deficit may be painful or painless paresthesia or autonomic dysfunction. Hypo- or areflexia. Isolated sensory deficit or sensory plus lower motor neuron deficit. Includes Guillain-Barré syndrome and variants (AMAN, acute motor axonal neuropathy; AMSAN, axonal motor sensory acute neuropathy; pharyngo-cervical-brachial variant-Miller-Fisher syndrome). Pharyngo-cervical-brachial variant-progressive or fluctuating muscle weakness, generally proximal to distal. May have bulbar involvement and/or respiratory muscle weakness. May occur with myositis and myocarditis. Miller-Fisher syndrome (MFS) variant of GBS has overlapping symptoms (ophthalmoplegia and ascending weakness). Rheumatological conditions could mimic weakness and generally with normal CK and aldolase

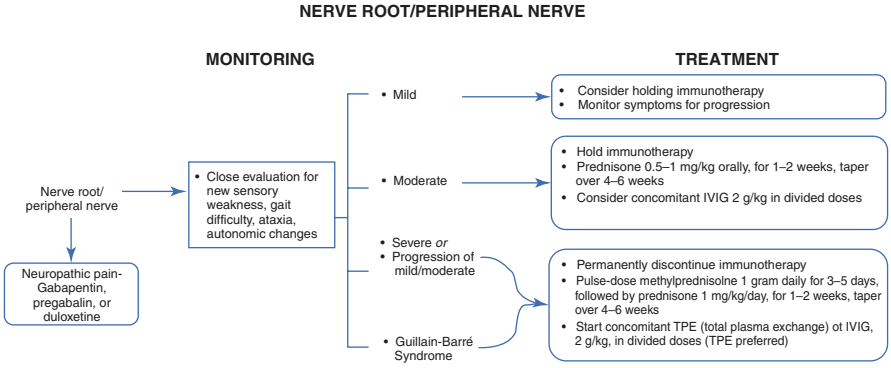

Fig. 10.7 Management algorithm for nerve root and peripheral nerve inflammation. Mild: no interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate. Moderate: some interference with ADLs, symptoms concerning to patient (e.g., pain but no weakness or gait limitation). Severe: limiting self-care and aids warranted, weakness limiting walking or respiratory problems (e.g., leg weakness, foot drop, rapidly ascending sensory changes). Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. May involve extremities, facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves. Often starts with pain in the lower back and thighs. Cerebrospinal fluid (CSF) typically has elevated protein and often elevated white blood cell (WBC) count; even though this is not typically seen in classical GBS, cytology and flow cytometry should be sent with any CSF sample

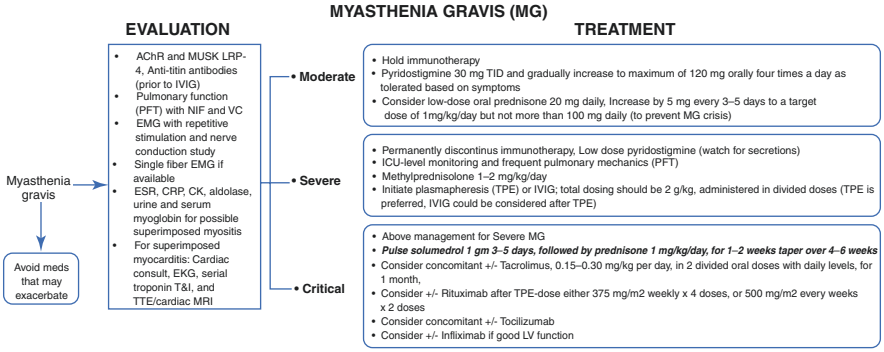

Fig. 10.8 Management algorithm for myasthenia gravis: progressive or fluctuating muscle weakness, generally proximal to distal. May have bulbar involvement (i.e., ptosis, extra-ocular movement abnormalities resulting in double vision, dysphagia, facial muscle weakness) and/or respiratory muscle weakness. May occur with myositis and myocarditis. Respiratory symptoms may require evaluation to rule out pneumonitis. Miller-Fisher variant of Guillain-Barré syndrome (GBS) has overlapping symptoms (ophthalmoplegia and ascending weakness). Moderate (MGFA severity class I), ocular symptoms only, and (MGFA severity class II): ocular symptoms +mild generalized weakness. Severe: Weakness limiting self-care, weakness limiting walking, any new-onset dysphagia, facial weakness, respiratory muscle weakness (VC < 30 cc/kg), or rapidly progressive symptoms or MGFA severity classes III–IV, moderate to severe generalized weakness to myasthenic crisis. *Critical parameters for severe MG*: Respiratory insufficiency (VC < 15 cc/kg) or significant bulbar symptoms or concomitant myositis (CK > 250) or concomitant myocarditis. Steroid taper based on clinical response, compared to idiopathic MG – ICI MG could consider taper over a few months

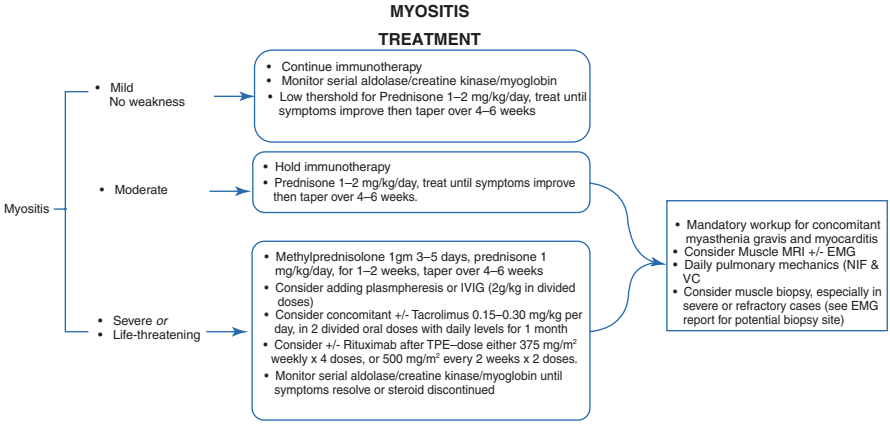

Fig. 10.9 Management algorithm for myositis. Myositis is a disorder characterized by inflammation and/or weakness involving the skeletal muscles. It may accompany symptoms of myalgias, or a marked discomfort sensation originating from a muscle or group of muscles. CK, aldolase, and myoglobin are elevated. Moderate weakness associated with weakness limiting instrumental ADL. Severe weakness limiting self-care ADLs. Myositis can present with ptosis and bulbar and respiratory (diaphragm) weakness and should be considered severe needing steroid + the above additional therapy

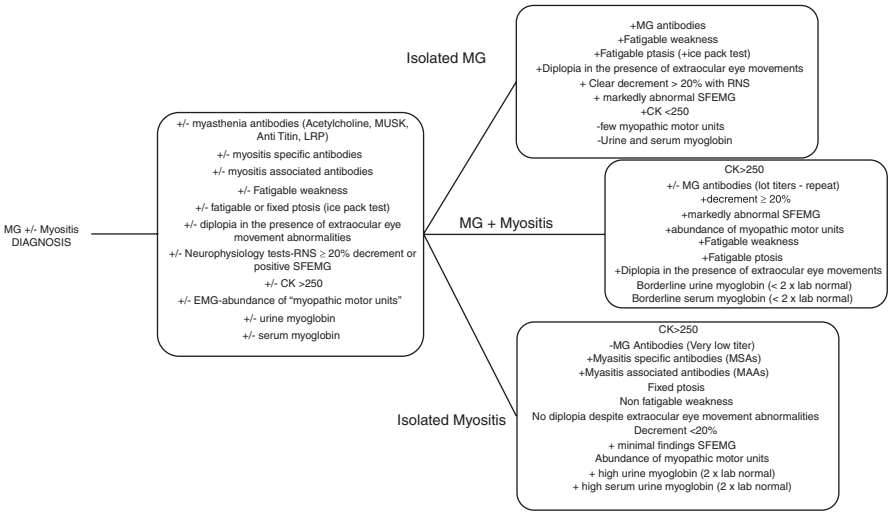

Fig. 10.10 Diagnostic algorithm for differentiating myositis and myasthenia or combination. MG – myasthenia gravis

paraneoplastic antibodies, and CSF cytology, with recommended flow cytometry as well given the generally seen increased white cells. CSF analysis is needed for both central nervous system toxicity and peripheral nervous system toxicity affecting the nerve roots, and inflammatory conditions of the nerves. Infections need to be ruled out appropriately, and with meningitis encephalitis PCR-based panel, Gram stain, cultures, and viral PCR are highly recommended (Fig. 10.11). An increase in isolated CSF WBC, with or without increased oligoclonal bands, with or without identified paraneoplastic antibodies, is a possibility and should be considered a marker of CNS or PNS inflammation in the presence of negative cytology and negative infection.

Paraneoplastic antibodies could be detected in serum and/or CSF and are recommended to be screened in both. It is possible to have negative antibodies on initial commercial lab testing and be positive on more specialized cell-based immunofluorescence evaluation [19, 20]. As detection of antibodies takes time, and the inflammatory process can be rapidly evolving, finding such as increased CSF WBC and/or oligoclonal bands could give enough information regarding CNS inflammation in the absence of infection.

Disease tempo can be evolving over weeks or months. In some patients it could be dramatic with rapid-onset encephalitis or rapid-onset necrotizing myopathic process. Initial assessment and stratification along with the very close monitoring of the disease course could guide the immunosuppressive agents chosen and degree of immunosuppression/immune modulation as shown in the algorithms.

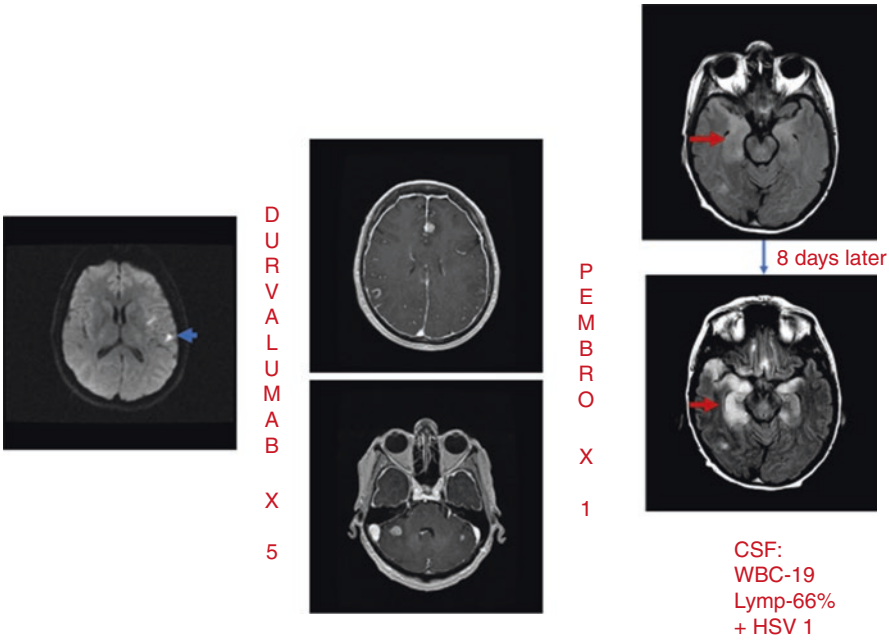

Fig. 10.11 Non-small cell carcinoma patient with atrial fibrillation (resulting in stroke – image 1 arrow). Patient received durvalumab for progressive tumor × 5 cycles. Patient also developed brain metastasis and completed whole brain radiation followed by pembrolizumab one cycle after which presented with mental status changes. Workup showed HSV encephalitis (image 3 arrows). Differential diagnosis includes ICI limbic encephalitis

Treatment Principles

The disease process in each individual patient is an important aspect in guiding management. The degree of inflammation causing organ dysfunction and response to immunosuppression could result in the following patterns: monophasic, monophasic with recrudesce, remitting and relapsing (incomplete recovery with relapsing at later date), initial monophasic with later recurrence, and refractory persistent patterns could be seen (Fig. 10.12). Defining this trajectory helps in guiding initial steroid dose and taper and need for additional immunosuppressive agents at onset or within short time frame from onset (1–2 weeks). Given the T cell-mediated process, permanent deficit from loss of neuronal tissue is a possibility and favors an early multimodal aggressive immunosuppressive strategy. Early aggressive intervention could facilitate early weaning of steroids and stopping unnecessary immunosuppression. Cerebellar inflammation could result in permanent deficits as inflammation resolves along with improvement in CSF inflammatory indices and resolution of MRI contrast enhancement with

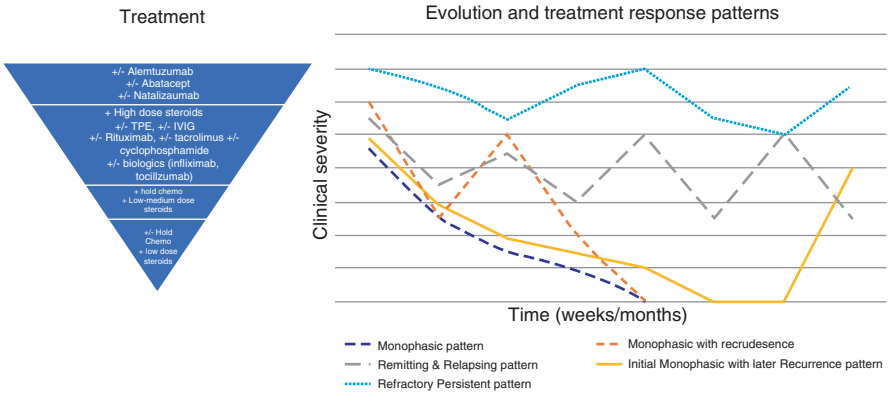

Fig. 10.12 Disease patterns. Y-axis, severity; X-axis, time in weeks/months. CNS and most PNS toxicities generally could resolve in a month. Pyramid highlights the escalating multimodal treatment regimen along with high-dose steroids in higher-grade neurotoxicity compared to holding ICI and low-medium dose steroids in lower grades

subsequent cerebellar atrophy. Resolution of inflammatory myositis could also result in permanent deficits rather than ongoing inflammation (atrophy of extra-ocular muscles, fixed ptosis, need for permanent tube feeds). Necrotizing myopathy could result in loss of muscle with permanent weakness, not necessarily needing more immunosuppressive agents as serum CK, aldolase, and myoglobin levels taper off. Most central nervous inflammatory conditions tend to follow a monophasic pattern favoring steroid taper over 3–4-week time frame. It is also possible of having a recrudescence of the inflammatory process needing reintroduction of higher-dose immunosuppression. Should a rarer prolonged persistent inflammation pattern trajectory be seen, earlier initiation of additional immunosuppressive agents could be done which could also be steroid-sparing agents. Close monitoring is recommended in the proposed algorithms with serial clinical, radiological, and laboratory follow-up. Initiating total plasma exchange 5–6 sessions along with daily steroids is a reasonable initial strategy to mitigate inflammatory process rapidly and limit the loss of neuronal tissue and muscle loss from necrotizing myopathy. Some conditions like neuromyelitis optica could argue for biological agents given recent approval like IL-6 antagonists [21].

Earlier introduction of steroid-sparing agents is detailed in the algorithms. This mitigates the steroid side effects and aggressive earlier suppression of inflammation to limit neuronal and muscle tissue loss. The possibility of converting other disease patterns to a monophasic pattern exists. Earlier tapering of immunosuppressive agents would limit the degree of immunosuppression, with preservation of TILs (tumor-infiltrating lymphocytes) to maintain tumor-killing capabilities [22]. Limiting exposure of immunosuppression will prevent infections. Fulminant bacterial, fungal, and viral infections have been reported. PJP prophylaxis is recommended while on steroids. Baseline hepatitis panel on admission is recommended as rituximab could reactivate hepatitis B and IVIG use could result in false-positive

hepatitis serology if obtained after infusing IVIG per ASCO guidelines. Vitamin D level optimization is recommended to mitigate steroid side effects and probable anti-inflammatory activities [23].

Predominantly antibody-mediated conditions like myasthenia gravis would need antibody-mitigating strategies like plasma exchange, IVIG, and B cell therapies like rituximab. While antibodies help in the diagnosis of T cell-mediated process or conditions with intracellular antigen targets, the titers do not reflect the clinical severity. Most ICI immunotoxicity pathogenesis is a T cell-predominant process needing the use of steroids and agents like tacrolimus and cyclophosphamide. Rationale for and use of biologics like tocilizumab, infliximab, anti-integrin blockers, and JAK inhibitors is discussed recently [24]. Agents chosen should be effective for rapid amelioration of inflammation, for example, steroids or JAK inhibitor ruxolitinib in comparison with mycophenolate. Initial use of multimodal therapies at onset or early in the process based on clinical severity and tempo (disease evolution) could limit the duration of steroids and attenuate the inflammatory process rapidly and maintain the immunotoxicity in a monophasic pattern. Given the rapid inflammatory process leading to tissue loss, the above rationale could also limit some of the permanent neurological dysfunction [25]. This is contrary to a stepwise approach generally taken for managing idiopathic autoimmune conditions. Despite predominant T cell-mediated process, mitigating B lymphocytes with use of B cell-mediated therapies attenuates the inflammatory process [26]. Initial use of TPE along with steroids is an effective strategy for faster mitigation of inflammation. Medications that can be dosed during TPE like tacrolimus whose levels could be followed can be added as well. Agents like rituximab and biologics are given after completion of TPE. The need for chronic immunosuppression beyond few initial rituximab doses or 4–6 weeks of tacrolimus and steroids beyond 4–8 weeks to be assessed on an individual basis depends on evidence for ongoing persistent inflammation and degree of ongoing organ dysfunction.

Treatment decisions need to be discussed with patients and their families including the side effects, especially infections. Balancing between persevering tumor-fighting lymphocytes and mitigating organ inflammation argues toward early aggressive intervention and weaning in a short timely fashion, generally like in a month's time frame. As we gain knowledge, experience, and accumulate a shared provider wisdom, we must balance between paternalism and patient's autonomy. Providers equipoise between a range of therapeutic options to mitigate the inflammation. Defining the endpoints clearly with patients and that stability first followed by improvement over time are the goals. Lack of randomized prospective trials and rationale for aggressive early multiple immunosuppressive therapies makes this much a shared decision-making (SDM) process [27]. Providers balance between off-target organ immunotoxicity by aggressive early anti-inflammatory strategies while preserving tumor-fighting lymphocytes. Every patient's off-target neurological dysfunction remains unique. Close clinical observation and stratification, along with careful selection of immunosuppressive strategies, could lead to better outcomes (Fig. 10.12).

Long-Term Complication and Follow-Up

As illustrated in the treatment principles and above algorithms, patients need very close monitoring with the initial presentation to recognize the disease tempo and need for additional immunomodulatory/immunosuppressive agents. Following resolution of inflammatory process, there is rare occurrence of relapse after some time interval or possible much rarer inflammation along the different part of the neuroaxis. There is mortality associated with these inflammatory conditions with reported 28% in myasthenic syndromes and 21% in encephalitis [2]. Compared to native myasthenia gravis, ICI-triggered demyelinating disorders and myasthenia gravis tend to remit rather than persist needing prolonged immunosuppression. Trial of immunosuppressive wean is recommended given the unknown course with close clinical follow-up [7]. Uncovering of prior existing autoimmune condition might need a longer immunosuppressive regimen which becomes apparent following the initial or subsequent wean. It is recommended to try nonsteroidal, non-T cell agents if feasible to preserve TILs. Rechallenge in patients with higher grades and residual inflammation is not recommended [28]. Lower grades and close observation for 2–8 weeks after resolution or stabilization of inflammation could be considered prior to ICI reinstitution as oncologists balance between tumor management and immunotoxicity. Prolonged antitumor response after immunotoxicity is noted in many cancers [29]. Multiorgan toxicity could also favor prolonged oncological response [30].

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Chapter 11
Ophthalmology (Eye)

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Abstract Ophthalmic immune-related adverse events occur at a lower frequency than other immune-related adverse events, in part due to the immune privilege of the eye. Their severity can range from mild and not requiring specific treatment to severe, requiring discontinuation of the medication as well as management with systemic immunosuppressive medications. The spectrum of events can involve all structures of the eyes, with keratoconjunctivitis sicca and uveitis being the two most common ocular manifestations. This chapter will review the epidemiology, clinical presentations, evaluation, management, and prognosis for patients with ophthalmic adverse events of immune checkpoint inhibition.

Keywords Ophthalmic · Conjunctivitis · Keratitis · Episcleritis · Scleritis · Thyroid eye disease · Uveitis · Vasculitis · Retinal detachment · Optic neuropathy · Orbital inflammation · Giant cell arteritis · Myasthenia gravis

Chapter debriefing: Power point video presentation is provided at the end of the chapter.

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Abbreviations

ADLs	Activities of daily living
ARMD	Age-related macular degeneration
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte antigen 4
FAERS	FDA's Adverse Event Reporting System
FDA	Food and Drug Administration
GCA	Giant cell arteritis
ICIs	Immune checkpoint inhibitors
IRAEs	Immune-related adverse events
MG	Myasthenia gravis
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
NAION	Non-arteritic anterior ischemic optic neuropathy
NSAID	Nonsteroidal anti-inflammatory drug
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
IRIS	Intelligent Research in Sight
SITC	Society for Immunotherapy of Cancer
TED	Thyroid eye disease
VEGF	Vascular endothelial growth factor
VKH	Vogt-Koyanagi-Harada

Introduction

Immune checkpoint inhibitors (ICIs) are novel immunotherapy agents used in the treatment of metastatic melanoma and other solid tumors. ICIs can produce immune-related adverse events (IRAEs), specific adverse events that relate to activation of the immune system, thus manifesting similarly to autoimmune diseases, including ocular inflammation. Ophthalmic toxicities of immunotherapies present unique challenges to clinicians caring for oncology patients. Differentiating the symptoms and signs of the cancer from these side effects of immunotherapy can be difficult. This chapter reviews the epidemiology, mechanism, clinical presentations, evaluation, management, and prognosis for patients who develop ophthalmic adverse events of immune checkpoint inhibition (i.e., ICIs IRAEs).

Epidemiology

The unique features of ocular immune privilege have been well described in the literature, with multiple mechanisms postulated including the presence of the blood-retina barrier, lack of direct lymphatic drainage source, and increased conversion of T cells into regulatory T cells and other mechanisms to decrease inflammatory T cell activity [1, 2]. Antigens in the eye may not result in an immune response where they would in other parts of the body [1]. This is thought to be a contributing factor to the lower prevalence of ocular toxicities associated with immune checkpoint inhibitors (ICIs), compared to other system toxicities, with some reports estimating the prevalence of ICIs-associated ocular toxicities to be only ~1% [2, 3]. Among four randomized controlled studies comparing ICIs and control groups, an estimated all-grade pooled analysis odds ratio estimate of 3.40 for ocular toxicities was obtained [4]. Indeed, reports of ocular toxicities in major trials are often limited as they are both less frequent and rarely grade 3 or greater [5]. Clinical presentation of ocular toxicity is typically seen within weeks of onset of the medication; however, delayed presentations of up to a year after medication onset may also occur [2].

Fang et al. quantified the risk of ocular adverse events with ICIs reported to the Food and Drug Administration (FDA) [6] using disproportionality analysis of data from US FDA's Adverse Events Reporting System (FAERS) database 2003–2018, data from pharmaceutical manufacturers, healthcare providers, consumers in the USA, and post-marketing clinical trial reports from US and non-US studies. All cases of uveitis, dry eye syndrome, ocular myasthenia, and eye inflammation reported occurred with the use of the following ICIs: atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, nivolumab, and pembrolizumab. The reported odds ratios (RORs) and corresponding 95% confidence intervals (CIs) were computed for all drugs as a group or as individual agents. 113 ocular adverse events were identified. Nivolumab had the highest number of IRAE (N = 68) and had the highest association with ocular myasthenia [ROR = 22.82, 95% CI (7.18–72.50)] followed by pembrolizumab [ROR = 20.17, 95% CI (2.80–145.20)]. Among all ICIs approved in North America, atezolizumab had the highest association with eye inflammation [ROR = 18.89, 95% CI (6.07–58.81)], and ipilimumab had the highest association with uveitis [ROR = 10.54, 95% CI (7.30–15.22)] [6].

Mechanism of IRAEs

The normal immune system involves mechanisms for self-tolerance in order to avoid autoimmunity. Costimulatory molecules exist on cells and counteract the immune system activating signals to avoid activation of the immune system in response to self-antigens. Typical T cell activation requires multiple stimulatory signals – first between a major histocompatibility complex (MHC) and T cell receptor, as well as a B7/CD28 complex. Cytotoxic T lymphocyte antigen 4 (CTLA-4) is responsible for inhibition of T cell activation when bound to B7, a self-tolerance mechanism, and binds with higher affinity than CD28 – when CTLA 4 is present, the T cell is likely to stay naïve. Ipilimumab, a CTLA-4 monoclonal antibody, preferentially binds to the CTLA-4 site, stopping the inhibitory signal, and allowing activation of the T cell to then further activate the immune response [7].

Programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) are two other ligands for which ICIs have been developed. These are expressed on many different cell types, not just T cells, and PD-L1 can be found on tumor cells as an immune escape mechanism. The binding of PD-1 to PD-L1 results in inhibition of the T cell. Monoclonal antibodies to either PD-1 (pembrolizumab, nivolumab, cemiplimab) or PD-L1 (atezolizumab, durvalumab, avelumab) will interrupt this binding, thus decreasing the inhibition of T cells, and allowing a stronger immune response [7].

IRAEs from these medications occur when the ICIs acts on antigen-presenting cells expressing self-antigens, or self-cells. This will result in activation of the T cells and upregulation of the immune response, and an inflammatory response in the relevant structure [7].

Clinical Characteristics

Ophthalmic IRAEs range from mild to sight-threatening, with dry eye syndrome and uveitis being the most common. Interestingly, cases of a Vogt-Koyanagi-Harada (VKH)-like syndrome have also been described [8–10]. In addition, orbital inflammatory syndromes, thyroid eye disease, and myasthenia gravis have all been reported with ICIs [11–15]. These and other less common/less severe manifestations are also described below.

Conjunctiva/Cornea

Keratoconjunctivitis

Keratoconjunctivitis refers to inflammation of the conjunctiva and superficial cornea. The most common form is keratoconjunctivitis sicca, more commonly known as dry eye syndrome. It is estimated to have a prevalence of up to 33% in the general

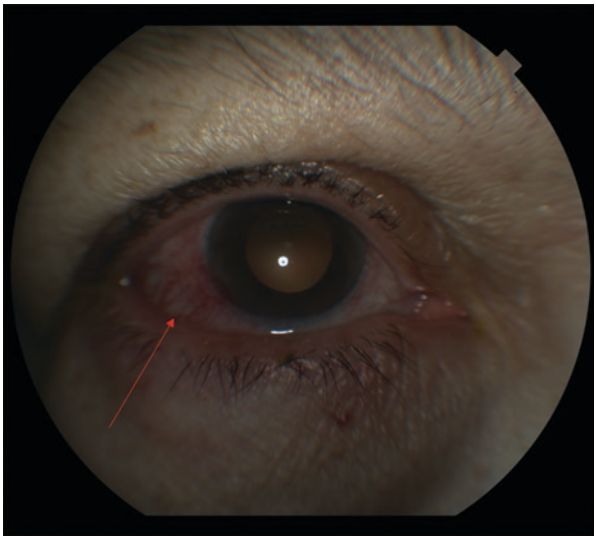

Fig. 11.1 Photo of the right eye, showing conjunctival injection consistent with keratoconjunctivitis (arrow), in this case after durvalumab use

population, more in females than males, and associated with other autoimmune diseases [16].

Keratoconjunctivitis sicca (dry eye syndrome) is one of the two most common ocular toxicities of ICIs [4, 12, 17]. Patients typically present with painful or irritated red eyes, a grit-like sensation and increased tearing. There may be associated light sensitivity; symptoms are typically worse at the end of the day and with prolonged screen use and improved with lubrication of the eyes (artificial tears, washing out eyes) and rest. An example is seen in Fig. 11.1. Dry weather exacerbates the symptoms. The prevalence of dry eye syndrome in large American populations has been estimated at ~5% [18]. Other forms of keratoconjunctivitis including superior limbic keratoconjunctivitis and vernal keratoconjunctivitis are not commonly reported with ICIs use. Keratoconjunctivitis sicca has been associated with ipilimumab, nivolumab, pembrolizumab, and durvalumab [17, 19, 20].

Peripheral Ulcerative Keratitis

Keratitis refers to inflammation involving the cornea – an example is shown in Fig. 11.2. In the general population, it may be associated with systemic autoimmune conditions and is commonly associated with scleritis. Patients typically present with pain, photophobia, and blurred vision, and may be noted on examination to have cloudiness of the cornea. Of the reported cases of peripheral ulcerative keratitis (nine in a recent analysis of the Federal Drug Association Adverse Event Reporting System), most have occurred in association with nivolumab, although there are isolated reports of association with ipilimumab, pembrolizumab, atezolizumab, and durvalumab [17, 21].

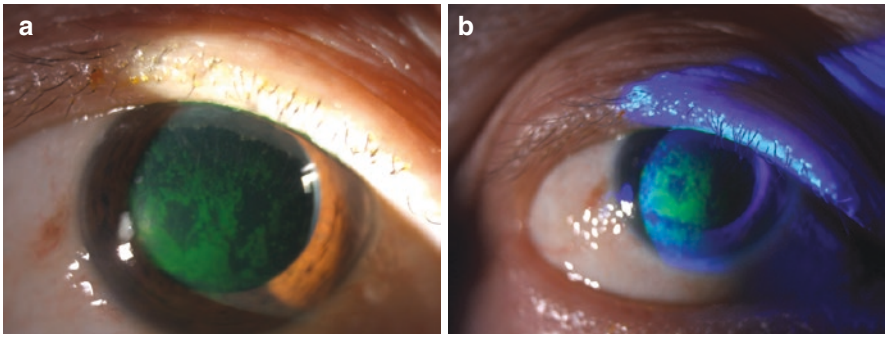

Fig. 11.2 Slit lamp examination after fluorescein staining showing keratitis with normal light filter (**a**) and cobalt blue filter (**b**). The abnormal area is green, which represents defects in the corneal barrier that allow the fluorescein dye to contact the alkaline interstitial fluid

Sclera and Episclera

Episcleritis

Episcleritis, or inflammation of the episcleral layer of the eye, typically presents as an irritated, red, and watering eye. Patients do not have vision loss. Episcleritis may be associated with anterior uveitis. Manifestations of isolated episcleritis in the literature are extremely rare and a corresponding association with uveitis is much more common but has occurred with ipilimumab [17]. Furthermore, it is thought that uveitis/episcleritis is more highly correlated with the presence of colitis as another ICIs toxicity [22].

Scleritis

The division between anterior and posterior scleritis lies at the level of the insertion of the recti muscles. Patients typically present with more severe eye pain, worse with eye movements. While scleritis has been reported in association with other ocular toxicities in patients on ICIs, there are no reports in the literature of isolated scleritis with ICIs use [22].

Uvea (Choroid, Ciliary Body, Iris)

Uveitis

Uveitis can refer to inflammation involving the iris, ciliary body, and/or the choroid. In the general population, uveitis is commonly associated with systemic autoimmune conditions; a similar mechanism of susceptibility to immune dysregulation has been proposed to explain the high frequency of uveitis among ICIs-associated ocular toxicities [23]. Uveitis is thought to occur in up to 1% of patients on ICIs and is

commonly listed as a side effect on the product information of many medications [23]. Of note, there have not been any case reports of uveitis occurring with avelumab and cemiplimab, although this may relate to lack of real-world experience given their relatively recent approval and more narrow range of clinical indications [23].

The clinical presentation of uveitis differs depending on which uveal structures are involved. With iritis (also known as anterior uveitis), patients typically present with a painful red eye, either unilaterally or bilaterally, loss of vision, and photophobia. The anterior segment inflammation manifests as conjunctival, episcleral, or scleral injection and anterior chamber cell and flare that can be detected on slit lamp biomicroscope. Intermediate and posterior uveitides are less likely to have pain or a red eye, and typically present with blurred vision and a perception of floaters in the eye with vitreous cells. Posterior uveitis can involve the retina, retinal pigment epithelium, choroid, and sclera. Panuveitis will present with a combination of these symptoms, depending on the severity of the inflammation in each area.

Uveitis associated with meningeal involvement can occur after ICIs producing a VKH-like syndrome. VKH is characterized by bilateral posterior uveitis or panuveitis, aseptic meningitis, and features of vitiligo, poliosis, alopecia, and hearing loss or tinnitus. Pathologically, VKH is an autoimmune disease targeting melanocytes, which are more prevalent in the uvea, ears, and the meninges [12]. ICIs have been noted to cause a VKH-like syndrome seen in both patients treated for melanoma and non-melanomatous malignancy [8–10]. It is documented as a risk in the product inserts of all the ICIs. While most patients develop VKH-like syndrome while on the ICIs, in one patient, onset of the VKH-like symptoms only started 2 months after completion of the course of ipilimumab [8].

The occurrence of uveitis with ICIs in retrospective reviews may be as high as 38% with anterior uveitis, 25% posterior uveitis, and 34% panuveitis [23]. Intermediate uveitis was extremely rare (0.01%) [23]. Dow et al. reported a comprehensive literature review utilizing MEDLINE/PubMed, Cochrane, and Web of Science databases. One hundred and twenty-six (126) cases of ICIs IRAE were reported in the literature prior to January 31, 2020, of anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis from 67 reports in the literature. Patients typically developed uveitis at a median of 9 weeks after initiation of ICIs, and 83.6% of cases occurred within 6 months. Most patients recovered to within one line of baseline vision after topical, local, and/or systemic steroid treatment and cessation or reduction of dosing of the ICIs [23].

A retrospective analysis of patients within the American Academy of Ophthalmology Intelligent Research in Sight (IRIS) reviewed patients with ocular IRAE within 1 year of commencing ICIs [24]. Of 3123 patients who had been treated with ICIs, 112 were identified to have ocular IRAE (3.6%). Among patients with a previous uveitis diagnosis, up to 51% of patients had a recurrence while on ICIs [24]. Of the ICIs, ipilimumab was found to have the highest association with uveitis, and all patients in this retrospective review developed uveitis within 20 days of drug initiation, with an incidence of 8.2% [24]. Combination ipilimumab and nivolumab therapy had a slightly lower frequency (5.56%), and other immunotherapy agents were reported as 2–3% [24]. In other reviews, atezolizumab was found

to have a statistically significant association with posterior uveitis compared to the other ICIs [23]. Patients on avelumab and cemiplimab have not to date been noted to develop uveitis; however, this finding should be interpreted with caution given the lack of clinical experience with these medications [23].

In a small subgroup analysis, the incidence of uveitis in all drug forms was also noted to be higher in African-American patients, although larger studies would be required to confirm this association (6/62 patients developed uveitis) [24].

Choroidal Neovascularization

Choroidal neovascularization occurs when there is loss of integrity of Bruch's membrane, causing growth of blood vessels from the choroid into the subretinal space. Patients typically present with painless vision loss, and altered perception, including metamorphopsia (seeing straight lines as wavy), macropsia (images appear larger than they are), or micropsia (images appear smaller than they are), because of impaired transmission of the visual image. Most cases of choroidal neovascularization in the general population are related to age-related macular degeneration (ARMD), although inflammatory causes can be implicated as well. To date, only one case of ipilimumab-associated choroidal neovascularization has been noted, in a patient who also had ARMD for 14 years and had received 1 year of ipilimumab treatment [25].

Retina/Optic Nerve

Cystoid Macular Edema

The macula is responsible for the highest acuity vision, and thus disruption from edema as occurs in cystoid macular edema primarily causes decline in visual acuity, with associated misperceptions in vision from distorted photoreceptors including metamorphopsia (seeing straight lines as wavy) and micropsia/macropsia (seeing objects as smaller/larger than they are, respectively). Macular edema is most commonly seen as a complication of poorly controlled diabetes mellitus. Cystoid macular edema has been reported in multiple cases of ICIs-associated toxicity. In some occasion it may present in conjunction with or as a manifestation of other findings, such as retinal vasculitis [26, 27]. It has been reported in nivolumab [20].

Retinal Vasculitis

Retinal vasculitis can involve both central and peripheral arteries and veins supplying the retina. It has a similar association with autoimmune diseases as previously described, as well as can have idiopathic manifestations. Retinal vasculitis has been reported in multiple ICIs, including pembrolizumab, often with other manifestations including cystoid macular edema and sometimes uveitis as described above [26–29].

Retinal Detachment

Retinal detachments result in the separation of the retina from the retinal pigment epithelium of the eye. The clinical relevance is that the retinal blood supply comes from the choroid and is lost in a retinal detachment, leading to relative ischemia of the photoreceptors. In the case of serous retinal detachments, accumulation of subretinal fluid, frequently around the macula, results in decreased visual acuity. An example of optical coherence tomography findings of serous retinal detachment is seen in Fig. 11.2. Patients typically present with painless decreased vision and distortions in their vision including metamorphopsia. Serous retinal detachments are the most common forms of retinal detachment associated with ICIs, although still only noted in isolated case reports. Some patients with serous retinal detachments may have other risk factors for detachment, including medications or the presence of choroidal metastases [30, 31]. Retinal detachments have been reported in nivolumab, as well as combination nivolumab/ipilimumab [20].

Optic Neuropathy

There are many different etiologies for optic nerve pathologies. Optic neuritis refers to inflammation of the optic nerve – patients typically present with pain and loss of visual acuity, with pain on eye movements, and desaturation of color (dyschromatopsia). The most common cause of optic neuritis is multiple sclerosis. Magnetic resonance imaging (MRI) is typically abnormal, and visual prognosis is variable depending on the underlying etiology [32].

Non-arteritic anterior ischemic optic neuropathy (NAION) is a disease of sudden ischemia to the optic nerve via damage to its arterial supply – patients typically present with sudden onset painless loss of vision in one eye that typically does not progress, and with variable recovery. It is thought to be associated with typical stroke risk factors, as well as hypercoagulability, a risk factor of malignancy. MRI is typically normal, or later shows T2 hyperintensity consistent with previous optic nerve damage only, but no signs of active inflammation.

There have been 23 cases of ICIs-associated optic neuritis reported in the literature, including 18 episodes (11 eyes) from a single series [33]. Of note in this series, the patients on multiple ICIs were more likely to have earlier onset optic neuritis with a median of 4 cycles, while patients on single-agent therapy had more delayed onset of episodes, with 1 patient having an episode after 95 cycles [33]. ICIs-associated optic neuritis was also associated with painless loss of vision in 90% of cases, dyschromatopsia in only 67% of cases, and bilateral involvement in 64% of patients, which are all atypical features of "classical" optic neuritis [33]. Magnetic resonance imaging (MRI) is abnormal in up to 92% of cases of typical optic neuritis; however, in this series, only 40% of patients who had MRI did not have any MRI abnormalities [32, 33]. The presence of uveitis in some cases is also atypical. Together, this suggests a possible difference in the underlying pathophysiology of ICIs-associated optic neuritis that is yet to be understood, or potentially that some cases might have had NAION or other causes of optic neuropathy, and definitions of

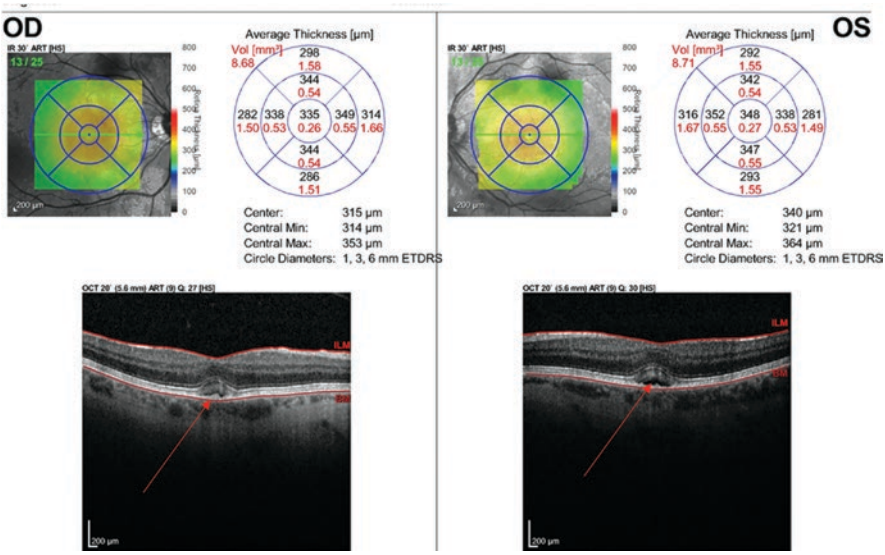

Fig. 11.3 Optical coherence tomography of the macula showing serous retinal detachment in both eyes, in this instance from pembrolizumab (arrows marking the area of serous elevation at the macula)

ICIs-associated optic neuritis differ in the literature, making this distinction even more challenging [33–35]. Most cases of optic neuritis have been associated with ipilimumab, but cases of nivolumab, pembrolizumab, and atezolizumab have also been reported [35]. An example of optical coherence tomography findings of optic neuropathy is seen in Fig. 11.3.

Orbital Inflammation

Orbital Inflammatory Syndrome

Orbital inflammatory syndrome refers to a spectrum of inflammatory diseases within the orbit, orbital apex, and the cavernous sinus. It encompasses orbital myositis and the eponymously named Tolosa-Hunt syndrome (cavernous sinus). MRI will typically show enhancement in the affected location. Manifestations vary depending on anatomic location affected and can involve features of optic neuropathy (decreased visual acuity, color vision abnormalities), eye pain, diplopia, and proptosis. It is commonly considered idiopathic but is also associated with many autoimmune conditions. Orbital inflammatory syndromes have been described in isolated reports with multiple ICIs, including ipilimumab, nivolumab, and pembrolizumab [17, 35].

Thyroid Eye Disease

Thyroid eye disease (TED) is an antibody-mediated disease that causes extraocular muscle enlargement without tendon enlargement from activation of orbital fibroblasts, with patients typically presenting with proptosis (eyes bulge), diplopia, and eye pain. It is not hormonally mediated and can occur in patients with hyperthyroidism, euthyroid, or hypothyroidism. Baseline thyroid function tests- typically thyroid-stimulating hormone levels - are recommended in all patients prior to commencing ICIs [12, 36].

A meta-analysis of genetic polymorphisms has found an association between the CTLA-4 + 49A/G and TED, which could reflect a possible mechanism via which this disease is more prevalent in ICIs, especially those targeting CTLA-4 [37]. Cases of TED have been associated with ipilimumab, pembrolizumab, as well as nivolumab [35].

Giant Cell Arteritis

Giant cell arteritis (GCA) is a large vessel vasculitis that can affect multiple large arteries including the aorta and temporal arteries. In temporal arteritis, there are typical manifestations with temporal artery tenderness, jaw claudication, and vision loss (either transient or permanent), and there may also be other manifestations where other large vessels are involved, including ischemic stroke. There have been limited cases of GCA post ICIs associated with ipilimumab, nivolumab, and pembrolizumab, including some that are biopsy proven [17, 35, 38].

Myasthenia Gravis

Ocular myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction. It is a systemic disease which typically presents with variable weakness and fatigue involving one or multiple systems. Some patients have ocular MG, while others have ocular manifestations of generalized MG, both of which typically present as painless and variable diplopia, ptosis, and/or ophthalmoplegia. Patients with initial presentation of ocular MG symptoms only will have ~53% risk of progression to generalized MG within 2 years [39]. Diagnosis can be made with testing for antibodies which include acetylcholine receptor antibodies, anti-muscle specific kinase, anti-titin antibodies, or neurophysiological testing (repetitive nerve conduction studies, single-fiber electromyogram).

Most cases of ICIs-associated MG in the literature have both ocular and systemic manifestations. Large series of ICIs-associated generalized myasthenia gravis have noted an approximate prevalence of 0.24%, although this figure includes patients who had known myasthenia gravis and a flare of their disease on ICIs [15].Most cases in this series and in the literature are associated with PD-1 antibodies [15, 35]. In the series,

ptosis was seen in 75% of patients, and diplopia in 42% high prevalence of ocular symptoms, reflecting the importance of noting visual symptoms in this more serious disease [15]. Median time to symptom onset was 29 days, although the longest case was noted 3 months after the last dose of ICIs [35]. ICIs associated with MG include ipilimumab, pembrolizumab, nivolumab, atezolizumab, and durvalumab [15, 17].

Evaluation

Most ophthalmological presentations involve symptoms of either blurred vision, vision loss, eye pain/irritation, diplopia, or a red eye. Clarifying the time course, severity, previous history, and specifically ICIs use will also assist in the differential diagnosis. Ophthalmic IRAEs from treatments may appear indistinguishable from the direct effects of the cancer itself or its indirect complications. Recognition and differentiation of these complications is crucial to the proper care and treatment of the patient.

Basic ophthalmological examination by the ophthalmologist can involve checking the visual acuity in each eye separately with a Snellen chart (easily printable off the Internet); color vision (red saturation can be assessed with a small red object, or online color vision tests); assessment of pupils for symmetry, size, and reactivity; and assessment of eye movements. Checking the visual fields by confrontation may also identify field defects. If the patient reports diplopia, covering each eye individually can help with triaging it to a neurological pathology or an ophthalmological pathology – in a neurological pathology, covering either eye will result in resolution of the diplopia, whereas in an ophthalmological pathology, when the abnormal eye is uncovered, the diplopia will persist (if both eyes are abnormal, covering won't change the diplopia at all).

The following are red flags for urgent ophthalmology evaluation:

- Sudden onset vision loss
- Acute painful red eye
- Diplopia, especially if acute onset
- Significant eye pain
- New anisocoria (unequal pupils)
- Ophthalmoplegia
- Sudden sensitivity to light (photophobia)

However, given that patients with malignancy and who are on ICIs are immunosuppressed, and therefore at high risk of atypical and more severe infection presentations, as well as ocular toxicities from ICIs and possibly other medications, a formal ophthalmology review would be recommended for all patients with new ophthalmic symptoms.

The overall grading system of the Common Terminology Criteria for Adverse Events (CTCAE) Version 5, published by the US Department of Health and Human Services, has four grades for patients with ocular toxicity from medications [40]:

Grade 1: Mild toxicity (patients may be asymptomatic, but have clinically detectable findings).

Grade 2: Moderately symptomatic, which may interfere with ADLs and with visual acuity of 20/40 or better (or loss of 3 lines or fewer from baseline).
Grade 3: Decrease in vision (worse than 20/40, or more than 3 lines decreased from baseline, but better than 20/200), limiting activities of daily living, severe pain, and visual field defects.
Grade 4: Visual acuity equivalent to or worse than 20/200.

These are further described in Table 11.1, the CTCAE scale (Version 5) [40]. Of note however, there are many ICIs ocular toxicities with symptoms not well

Table 11.1 Modified table from the Common Terminology Criteria for Adverse Events, grading different ophthalmic complications by severity [40]

Diagnosis	Grade 1	Grade 2	Grade 3	Grade 4
Dry eye (keratoconjunctivitis sicca)	Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL	–
Orbital inflammation[a]	Asymptomatic; clinical or diagnostic observations only Mild eye pain	Unilateral ocular muscle paresis without double vision Moderate pain, may limit ADLs	Bilateral paresis or unilateral paresis causing double vision in peripheral gaze, but not in central gaze Severe pain, limiting self-care ADLs	Bilateral paresis requiring head turning to see beyond central 60 degrees or double vision in central gaze
Keratitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); corneal ulcer; limiting self-care ADL	Perforation; best corrected visual acuity of 20/200 or worse in the affected eye

(continued)

Table 11.1 (continued)

Diagnosis	Grade 1	Grade 2	Grade 3	Grade 4
Optic neuritis[a]	Asymptomatic; clinical or diagnostic observations only	Moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye
Retinal tear/ detachment[a]	Retinal tear, treatment not indicated	No retinal detachment and treatment indicated	Macular sparing rhegmatogenous detachment	Macula-off rhegmatogenous retinal detachment
Retinal vascular disorder	–	Retinal vascular disorder without neovascularization	Retinal vascular disorder with neovascularization	–
Retinopathy	Asymptomatic; clinical or diagnostic observations only	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye
Scleral disorder (episcleritis/ scleritis)[a]	No change in vision from baseline	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye
Uveitis	Anterior uveitis with trace cells	Anterior uveitis with 1+ or 2+ cells	Anterior uveitis with 3+ or greater cells; intermediate posterior or panuveitis	Best corrected visual acuity of 20/200 or worse in the affected eye

ADL activities of daily living

[a] Diagnosis or grading slightly modified to reflect ICIs ocular toxicities

described in the scale, including ocular myasthenia gravis, non-arteritic anterior ischemic optic neuropathy, retinal artery/vein occlusions, choroidal neovascularization, and retinal vasculitis.

Treatment Algorithm

There are currently no formal treatment recommendations for most ocular toxicities from ICIs. The Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group has suggested general guidelines for management of immune-related adverse events by grade – grade 1 events do not warrant corticosteroid administration or cessation of ICIs [36]. Grade 2 events might warrant a temporary suspension of ICIs and initiation of systemic corticosteroids (either intravenous or oral) once symptoms have improved to grade 1 frequency. Grade 3 events would warrant consideration of suspension of ICIs and cessation if symptoms haven't resolved within 4–6 weeks, as well as systemic steroids. Grade 4 events warrant discontinuation of ICIs and management with systemic steroids. Specific recommendations are only made for uveitis (graded by the uveal structures affected and visual acuity) and episcleritis (graded by visual acuity, which should not be impaired in episcleritis and might suggest an alternative diagnosis) [36].

Antoun et al. proposed in 2016 an algorithm for treatment of ocular toxicity where manifestations in the anterior eye (anterior uveitis/episcleritis/anterior scleritis/peripheral ulcerative keratitis) should be initially treated with topical steroids, and most will resolve [12]. Those that do not resolve should be treated with systemic steroids and the ICIs stopped. For those patients with choroidal neovascularization, treatment should consist of anti-vascular endothelial growth factor injections, and cessation of the ICIs. In all other patients (orbital inflammation, intermediate/posterior uveitis, and VKH-like syndrome), cessation of ICIs and treatment with systemic steroids are recommended.

Further reviews of patient outcomes post ICIs, ICIs cessation, and systemic steroid usage since this algorithm was proposed suggest that a more nuanced approach to treatment might be beneficial. In general, a risk/benefit analysis is required to ascertain the severity of the toxicity, in comparison with the benefit of the ICIs, available alternative malignancy treatments, as well as the long-term prognosis of the patient. Ocular adverse effects also rarely occur in isolation, and typically systemic adverse effects will also occur, making the decision to alter therapy likely to be multifactorial, and not always solely based on the specific ocular pathology [2]. Specifically, there has been an association with ICIs-associated colitis and episcleritis/uveitis, such that the severity of the colitis may necessitate cessation of the drug and systemic corticosteroid administration, even where the ocular symptoms would not [13]. Naing et al. more report that the development of toxicity-specific guidelines is in part impaired by lack of standardized reporting – they recommend redefining the CTCAE definitions to be diagnosis specific, which would then allow better reporting in the literature [41]. This better analysis of the reported cases would eventually allow management guidelines to change from being expert opinion based as they primarily currently are and allow them to become evidence based [41].

The accepted treatments for the ocular condition when occurring separate to ICIs administration are typically also considered for the respective ICIs-associated toxicity as well. Table 11.2 summarizes the clinical symptoms, evaluation, and standard treatment for ophthalmic IRAEs:

- Keratoconjunctivitis sicca (dry eye syndrome): Treatment typically involves artificial tears or ointments, and topical cyclosporine. If these are unsuccessful, consider punctual plugs, or autologous tears.

Table 11.2 Clinical symptoms, findings on evaluation, and recommended treatment options for the ophthalmic manifestations of IRAE

Disease condition	Clinical symptoms	Evaluation	Treatment
Keratoconjunctivitis sicca	Painful/irritated red eyes Increased tearing Grit-like sensation Light sensitivity	Mildly decreased visual acuity, improving with trial of lubricating eye drops/ blinking Conjunctival injection Excessive tearing/ decreased link rate	Reduce environmental triggers Topical lubricating eye drops/cyclosporine Punctal closure Autologous tears
Peripheral ulcerative keratitis	Pain, blurred vision, photophobia	Decreased visual acuity, corneal cloudiness/thinning/ ulcers – Best seen on slit lamp examination	Topical lubricating eye drops Consider antibacterial eye drops to prevent superinfection Punctal closure Consider topical/systemic steroids based on severity of symptoms
Episcleritis	Irritated, red, watering eye	Normal visual acuity Episcleral inflammation seen best on slit lamp examination	Depending on severity, consider medication discontinuation or systemic steroids
Scleritis	Red eye, severe eye pain, pain on eye movements	Scleral inflammation, best seen on slit lamp examination	Depending on severity, consider medication discontinuation or systemic steroids
Uveitis	Painful red eye, photophobia, blurred vision, floaters	Decreased visual acuity Conjunctival, episcleral, or scleral injection Inflammation of the anterior chamber, or vitreous, only seen on slit lamp examination	Depending on severity, consider medication discontinuation, topical or systemic steroids
Vogt-Koyanagi-Harada syndrome	Uveitis symptoms as above, plus features of meningitis, vitiligo, poliosis, alopecia, hearing loss or tinnitus	Uveitis features as above. Neck stiffness, photophobia, vitiligo, poliosis, alopecia	Consider discontinuation of medication and treatment with systemic steroids
Choroidal neovascularization	Vision loss, altered visual perceptions (metamorphopsia, macropsia, micropsia)	Decreased visual acuity, abnormalities on Amsler grid testing Neovascularization best seen on dilated fundus examination	Consider used of anti-vascular endothelial growth factor (VEGF) medications

Table 11.2 (continued)

Disease condition	Clinical symptoms	Evaluation	Treatment
Cystoid macular edema	Vision loss, altered visual perceptions (metamorphopsia, macropsia, micropsia)	Decreased visual acuity, abnormalities on Amsler grid testing Macular edema, best seen on dilated fundus examination	Depending on severity, consider medication discontinuation, topical or systemic steroids
Retinal detachment	Vision loss, altered visual perceptions (metamorphopsia, macropsia, micropsia)	Decreased visual acuity, abnormalities on Amsler grid testing Retinal detachment, best seen on dilated fundus examination	Typically can continue medication and monitor
Optic neuropathy	Vision loss, potentially associated with pain, dyschromatopsia, pain on eye movements	Decreased visual acuity, decreased color vision, relative afferent pupillary defect, may have optic disc edema (best seen on dilated fundus examination)	Medication is typically ceased, and high-dose corticosteroids commenced
Orbital inflammatory syndrome	Eye pain, diplopia, proptosis, features of optic neuropathy (see above)	Features of optic neuropathy (see above), cranial nerve palsies, proptosis	Medication is typically ceased, and high-dose corticosteroids commenced. Other immunosuppressive agents (methotrexate, plasmapheresis, mycophenolate, intravenous immunoglobulin) may be given depending on response
Thyroid eye disease	Eye pain, diplopia, proptosis	Restricted eye movements, proptosis	Medication is typically ceased, and high-dose corticosteroids commenced
Giant cell arteritis	Vision loss, jaw claudication, temporal artery pain, systemic myalgias, fatigue, weight loss	Decreased visual acuity, relative afferent pupillary defect, optic disc edema (best seen on dilated fundus examination) Temporal artery tenderness	Medication is typically ceased, and high-dose corticosteroids commenced
Myasthenia gravis	Variable diplopia, ptosis, restricted eye movements Systemic fatigue/ weakness	Restricted eye movements, ptosis, which may be fatiguable	Pyridostigmine for symptomatic treatment, combined with systemic corticosteroids, intravenous immunoglobulin, or plasmapheresis

- Peripheral ulcerative keratitis: Treatment typically involves promotion of reepithelialization of the ulcerated lesion – this may include artificial tears, punctual plugs, and consideration of bandage contact lenses.
- In one patient with ipilimumab-associated peripheral ulcerative keratitis, initial trial of systemic antiviral/antibiotic ointments was unsuccessful, and the patient was treated with topical prednisolone drops, with resolution in 4 weeks [13].
- Uveitis:

  The strongest literature base exists for uveitis, as it is one of the more common manifestations of ocular toxicity. In a review of the literature, it was noted that of the patients who developed uveitis, 63% of patients had their ICIs suspended or discontinued and in 93%, this was done without initiating other uveitis-specific therapies [23]. The number of patients who restarted their ICIs was low (12), but of those, 58.3% had a recurrence of uveitis [23]. Other treatments that were utilized included steroids, typically topical steroids (72%) and most commonly for anterior uveitis [23]. On occasions, cycloplegic and nonsteroidal eye drops were also administered [4, 23]. 20% of patients received intra−/periocular steroid injections (these patients tended to have the poorest visual acuity at presentation) [23]. 53.2% of patients were given systemic steroids, either intravenous or oral methylprednisolone or prednisone. Median time to symptom control was reported at 30 days, but some patients had ongoing symptoms after 1 year.

  In patients with VKH-like syndrome, systemic steroids have been used where there have been non-ocular manifestations as well. In the limited literature reports, there has been noted some steroid dependence, with symptoms recurring/worsening when steroids have been weaned [10]. The package inserts of all the ICIs note VKH as a serious complication and recommend consideration of systemic steroids [42–48].
- Choroidal neovascularization: Standard treatment includes the use of antivascular endothelial growth factor (VEGF) medications, designed to decrease the proliferation of the choroidal vessels. In the one patient reported in the literature, he received 20 months of these medications at 2 monthly intervals. His ipilimumab was initially continued, but subsequently stopped due to other systemic toxicities [25].
- Retinal detachment: Management is typically conservative – the subretinal fluid is typically reabsorbed, and patients have improved symptoms. If there is an associated condition, this should be managed accordingly. In the literature, patients were conservatively managed, and their ICIs continued [31].
- Optic neuropathy: Standard treatment for optic neuritis includes the use of high-dose corticosteroids, often followed by a rapid taper over a few weeks. 10 out of 11 patients in the largest review of ICIs-induced optic neuritis were treated with corticosteroids, and had their ICIs ceased. Of the 16 eyes with poor visual acuity at onset of presentation, posttreatment vision improved, stabilized, and deteriorated in 12, 2, and 2 patients, respectively [33]. Management of NAION typically involves management of cardiovascular figures, and consideration of antiplatelet therapy (Fig. 11.4).

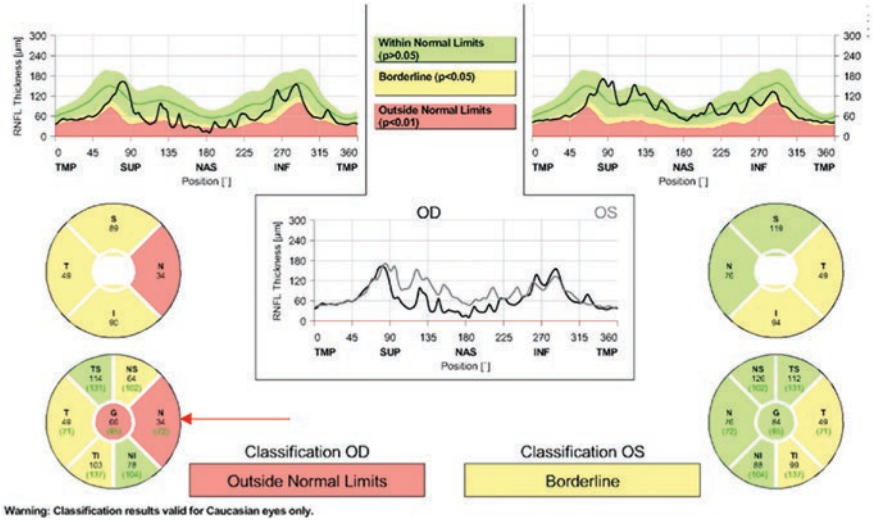

Fig. 11.4 Optical coherence tomography of the optic disc showing thinning of the retinal nerve fiber layer in the right eye greater than the left eye, consistent with optic neuropathy in both eyes. The thinning is greatest in the right eye nasal portion of the optic disc (arrow). This patient was on a combination of nivolumab and ipilimumab therapy

- Orbital inflammatory syndrome: Standard treatment involves steroids to suppress the inflammation and treatment of the underlying cause if identified. In patients with ICIs-associated orbital inflammatory syndrome, most patients required systemic corticosteroids, and then ongoing additional therapies, including intravenous immunoglobulin, methotrexate, plasmapheresis, and mycophenolate [35].
- Thyroid eye disease: Standard treatment of TED can involve nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, other immunosuppressive agents, or teprotumumab, a recently approved monoclonal antibody against insulin-like growth factor 1. Treatment depends on the severity of symptoms and will typically involve starting with the generally most tolerated medications (i.e., NSAIDs). Within the literature, most patients with ICIs-associated TED were treated with systemic corticosteroids, although in this subgroup of patients, the risk/benefit profile of NSAIDs might be different, if they are also on anticoagulation/antiplatelets, or have renal impairment, or other contraindications to NSAID use [35].
- Giant cell arteritis: Standard treatment for suspected GCA involves urgent commencement of high-dose corticosteroids. Given the significant morbidity associated with giant cell arteritis in the general population, all patients in the literature have been treated with systemic corticosteroids when this diagnosis was suspected/confirmed in association with ICIs [38].
- Myasthenia gravis: Standard treatment for myasthenia gravis is composed of acetylcholinesterase inhibitors (e.g., pyridostigmine) which are shorter lasting and aim to maximize the amount of acetylcholine available for use in the neuro-

muscular junction, as well as immunosuppressive therapies (mycophenolate, azathioprine, intravenous immunoglobulin, plasmapheresis – steroids may be considered in the short term, but conventionally there is a hypothesis that high-dose steroids may paradoxically worsen myasthenia gravis). These two treatments domains are similar to what has been offered to patients with ICIs-associated myasthenia gravis, although the longer-term immunosuppressive agents are more frequently intravenous medication (corticosteroids, intravenous immunoglobulin, plasmapheresis). It should be noted that given the multisystem involvement in myasthenia gravis, it is more likely the other system manifestations that would prompt discontinuation or suspension.

A review of 65 patients with ICIs-associated myasthenia gravis from a single center noted that 94% of them were treated with steroids, 51% acetylcholinesterase inhibitors, 48% plasmapheresis, and 44% intravenous immunoglobulin [15]. Illness severity in this cohort given the generalized manifestations was marked, with 96% requiring hospitalization, and 19% requiring invasive ventilation [15]. Thus while the ocular manifestations in isolation if mild may not require systemic treatment or discontinuation of the ICIs, other manifestations may.

Long-Term Complication and Follow-Up

Because of the relative infrequency of these toxicities, overall long-term complications are unknown. Some authors advocate routine ophthalmological examination every 4–6 months due to the possibility of ocular toxicities; however, given that treatment is not typically recommended for asymptomatic patients, this may not be of additional yield to the patient [49].

Prognosis

The rarity of ocular toxicities in ICIs has meant that little data is available on the long-term prognosis. To the best of our knowledge, the only study to date is related to uveitis; in a small subgroup in a retrospective analysis, 7 of the 12 patients who restarted their ICIs after an episode of uveitis (58.3%), had a recurrent uveitis episode [23].

Summary

In summary, clinicians should be aware of the ocular IRAE of ICIs. Early recognition and treatment are critical to avoid potentially vision-threatening complications. In addition, unusual presentations of ICIs-related IRAE include VKH-like syndromes, ocular myasthenia, and autoimmune thyroid eye disease.

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Chapter 12
Pancreas and Gallbladder

Anusha Shirwaikar Thomas, Hao Chi Zhang, Yinghong Wang, and Suresh T. Chari

Abstract Immune checkpoint blockade offers a revolutionary oncologic treatment strategy by modulating the T-cell pathway in order to enhance and enable immune-mediated antitumor responses. However, blockade of certain checkpoints, namely CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), PD-1 (programmed cell death protein 1), and PD-L1 (programmed cell death-ligand 1), can lead to enhancement of normal immunity, which may inadvertently cause immune-related adverse events (irAEs) primarily due to the dampening of normal protective immune tolerance [1].

Immune checkpoint inhibitor-mediated pancreas and gallbladder injuries are infrequent. The most common manifestation of the effects on the pancreas is asymptomatic elevation of pancreatic enzymes. In symptomatic cases, clinical presentations and management may resemble that of acute pancreatitis and cholecystitis. The role of steroid therapy in the management of these toxicities is yet to be elucidated. Long-term complications, albeit rare, are associated with better overall survival in this group of patients.

Keywords Immune checkpoint inhibitors · Immunotherapy · Pancreatitis · Cholecystitis · Gastrointestinal adverse events

Chapter debriefing: Power point video presentation is provided at the end of the chapter.

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Abbreviations

AIP	Autoimmune pancreatitis
CD	Crohn's disease
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
IBD	Inflammatory bowel disease
ICICC	Immune checkpoint inhibitor-mediated cholecystitis
ICI-PI	Immune checkpoint inhibitor-mediated pancreas injury
IrAEs	Immune-related adverse events
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death-ligand 1
UC	Ulcerative colitis
ULN	Upper limit of normal

Immune Checkpoint Inhibitor-Mediated Pancreas Injury (ICI-PI)

Definition and Background

Knowledge of the biological and physiopathological aspects of ICI-PI is limited. To date, only one case report has described ICI-PI histologically in a patient with advanced primary renal carcinoma and metastasis to the pancreas who developed type 1 diabetes mellitus after combination CTLA-4 and PD 1 blockade therapy. The patient underwent a pancreatic resection, and an immunohistochemical analysis performed on non-tumoral pancreas tissue revealed T-lymphocyte infiltration of the pancreatic islets, 15 times higher than a control group of 7 patients with normal glucose tolerance with similar resection [2, 3]. Although a case like this may suggest that the mechanisms underlying ICI-PI might be similar to those of other irAEs, further studies are warranted given the lack of available data. Therefore, it is suggested that ICI-PI is defined as a disorder characterized by inflammation of the pancreas as an outcome of nonspecific inflammatory T-cell-mediated immune response triggered by checkpoint inhibition for advanced malignancies. ICI-PI could also manifest in pancreatic endocrine insufficiency, i.e., type 1 DM, a rare irAE predominantly associated with PD-1 blockade that occurs secondary to autoreactive T cells that target the islet β-cells which will be addressed in detail separately.

Grading and Severity

The CTCAE is routinely employed to grade the severity of immune checkpoint inhibitor-mediated pancreatitis and lipase elevation [4]. As depicted in Table 12.1, grade 3 and higher toxicity is associated with >2× upper limit of normal (ULN) pancreas enzyme (lipase) elevation and/or severe clinical presentation necessitating medical intervention.

The National Comprehensive Cancer Network (NCCN) [5] has two separate grading systems to categorize asymptomatic pancreatic enzyme elevation and pancreatitis as is shown in Tables 12.2 and 12.3.

The Atlanta criteria [6] are routinely employed for diagnosis of acute pancreatitis which is made when two of the following three criteria are met: (i) acute onset of severe, persistent epigastric pain, often radiating to the back, (ii) lipase enzyme elevation (≥3× upper limit of normal), and (iii) findings of acute pancreatitis on abdominal imaging. Disease severity is primarily based on the presence of organ failure (OF) which is assessed by modified Marshall scoring system and local or systemic complications [6, 7]. While these sets of criteria, albeit variable, overlap, a universal, validated, standardized criterion for diagnosis and scaling severity is lacking.

Table 12.1 Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

CTCAE grade	1	2	3	4	5
Pancreatitis	NA	Enzyme elevation *or* radiologic findings	Severe pain, vomiting, medical intervention indicated (analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death
Lipase elevation	>1.5× ULN	1.5–2.0× ULN >2.0–5.0× ULN & asymptomatic	>2.0–5.0× ULN with symptoms >5.0× ULN & asymptomatic	>5.0× ULN with signs/symptoms	

Table 12.2 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

Table 12.3 National Comprehensive Cancer Network grading of immune checkpoint inhibitor-associated 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

Epidemiology and Risk Factors

The pathophysiologic mechanisms for the variable presentations have not been elucidated. ICI-PI is relatively rare and occurs in association with other immune-related adverse events. Among different ICI classes, the reported incidence of ICI-induced pancreatic injury ranges from is 0.6% to 4% [8–11]. As described above, this irAE can have variable presentations from a mere asymptomatic elevation in pancreatic enzymes, i.e., an incidental finding detected during routine monitoring through expectations in the treatment protocol [12], estimated to have an incidence of 2.7%, to clinically significant pancreatic injury in the form of true pancreatitis which bears a slightly lower incidence of 1.9% [11]. One study involving patients with melanoma demonstrated a 43.7% incidence of elevations in serum lipase and/or amylase of grade 3–4 magnitude without symptomatic pancreatitis, compared to an incidence of 1.7% with symptomatic pancreatitis.

As pertains to risk factors for this form of immune-mediated injury, the type of checkpoint inhibition, patient demographics, and underlying cancer are implicated in conferring an increased risk. Prior retrospective analyses have shown a male preponderance for this disease entity with a median age of greater than or equal to 60 years [13]. A meta-analysis that systematically assessed the incidence of lipase elevation and pancreatitis according to the Common Terminology Criteria for Adverse Events (CTCAE) across 33 trials with over 7000 patients suggests that CTLA-4 inhibition and/or combination ICI therapy significantly increases the risk of this adverse event. Similarly, the group demonstrated lipase elevation and grade 2 pancreatitis to be higher in patients with melanoma when compared to nonmelanoma cancers [11]. The mechanism of the differential pancreas toxicity based on cancer being treated is unclear.

Clinical Presentation and Management

ICI-PI often occurs approximately 3–4 months after initiation of immunotherapy. However, this irAE has been reported to occur as early as a median of 2 weeks after starting ICI therapy as seen in a retrospective analysis of 148 patients who received PD-1 blockade therapy and developed asymptomatic pancreatic enzyme elevation.

ICI-PI is a diagnosis of exclusion. The clinician should explore a differential diagnosis of other etiologies of pancreatitis (i.e., alcohol consumption, hypertriglyceridemia, biliary causes, autoimmune pancreatitis, pancreatic cystic lesions, pancreatic diseases related to genetic predisposition, and metastatic disease to the pancreas).

The clinical presentation ranges from the incidental finding of elevation of the serum pancreatic enzymes on routine bloodwork in the absence of symptoms to

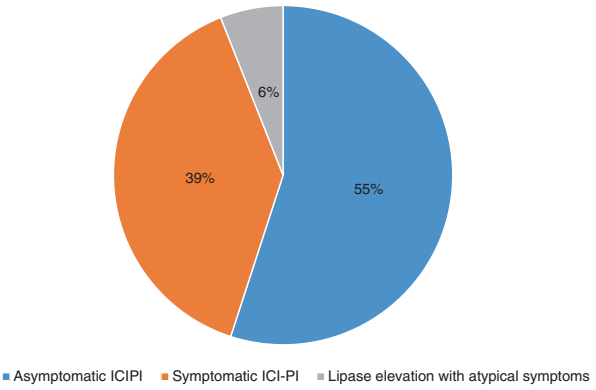

Fig. 12.1 Distribution of type of clinical presentation of ICI-PI. Note that 11% and 25% of patients with asymptomatic ICI-PI and symptomatic ICI-PI respectively had imaging evidence of pancreatic injury [15]

symptoms of acute pancreatitis including abdominal pain, nausea, and emesis [10]. As previously mentioned, the literature demonstrates that patients tend to present as the former (Fig. 12.1). However, clarity on the relevance of an asymptomatic elevation of pancreatic enzymes in patients treated with ICIs in the absence of clinical pancreatitis is lacking. Is a subtle inflammation present or absent in the former? Other considerations for the same may include T-cell-mediated inflammation in other organs that may produce this enzyme, pancreatic metastasis, renal failure, etc… that need to be evaluated. Can the patient eventually progress from being asymptomatic to symptomatic and vice versa? What predisposes one to each subtype of clinical presentation? In the absence of established histologic and imaging evidence, the answers to these questions are yet to be elucidated.

Long-term pancreatic exocrine insufficiency has been observed in pancreatic injury secondary to this irAE, though this risk appears to be much lower than other causes [10]. It is important to closely monitor for diabetes with hemoglobin A1c testing every 3 months for up to 6 months after the adverse event. Similarly, clinical evaluation, stool studies, and imaging may be indicated to monitor for exocrine insufficiency. Data is limited in terms of radiologic patterns and imaging features as pertains to this immune-related adverse event. In a recent systematic description of imaging features of immune checkpoint inhibitor-associated pancreatitis among 25 patients, Das et al. report 2 distinct radiologic patterns: (1) an acute interstitial pancreatitis pattern characterized by focal or diffuse pancreatic enlargement, peripancreatic fat stranding, and heterogeneous enhancement and (2) mass-like autoimmune pancreatitis pattern. A mixed pattern was rarely observed in this study cohort [14].

An important clinical dilemma is how to optimally manage the group of patients who present with asymptomatic serum pancreatic enzyme elevation. Presently, continued surveillance of pancreatic enzyme levels and the decision to continue ICI treatment are at the discretion of the clinician. On the other hand, patients with this irAE that present with clinical features classical for pancreatitis are often managed similar to acute pancreatitis from other causes, i.e., supportively with aggressive intravenous fluid hydration and pain control in addition to holding ICI therapy.

The National Comprehensive Cancer Network (NCCN) [5] has proposed guidelines for the management of immune checkpoint inhibitor-related pancreatitis (Fig. 12.2). Limited guidance on the management of this irAE is offered in the

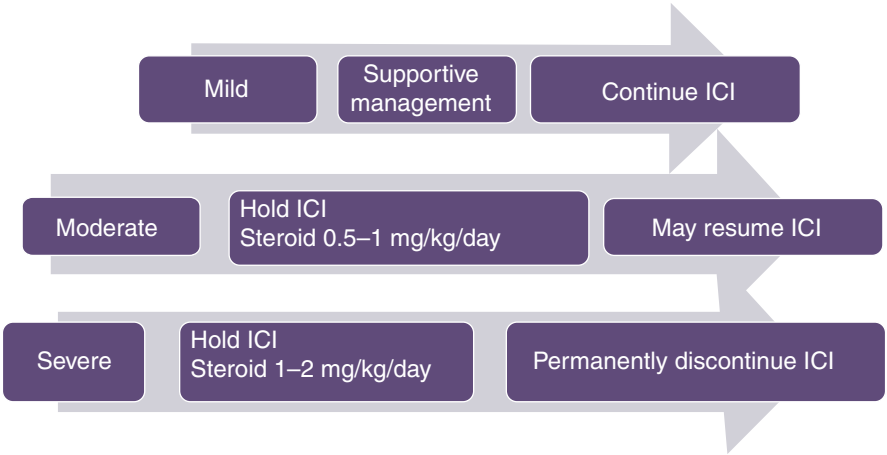

Fig. 12.2 NCCN guidelines 2019-Management of Immune Checkpoint Inhibitor-Related Toxicities, Ver 2 [5]

ASCO [16] and SITC [17] guidelines. No recommendations are offered in the ESMO guidelines [26, 27].

As has been depicted in Fig. 12.2, mild or grade 1 pancreatitis/asymptomatic pancreas enzyme elevation less than 3× ULN may be managed supportively, and immunotherapy may be continued. Grade 2 or moderate pancreatitis necessitates withholding immunotherapy and treatment with steroids at a dose of 0.5–1 mg/kg/d. Immunotherapy may be resumed when the adverse event lowers in severity to grade 1 or lower and steroids may be tapered off over 4–6 weeks. Grade 3 or higher severe pancreatitis is managed by permanently discontinuing immunotherapy and high-dose systemic corticosteroid therapy. We observe that existing recommendations offered in the current society guidelines do not advise interventions for asymptomatic pancreatic enzyme elevations, which questions the utility of grading enzyme elevation.

Interestingly, a retrospective analysis of 82 patients with ICI-PI showed no statistically significant differences in duration of symptoms or hospitalization with or without the use of immunosuppression, i.e., corticosteroids [10]. Therefore, the role of systemic steroids to treat ICI-PI has yet to be elucidated.

Albeit rare, complications secondary to steroid therapy have been reported such as one of severe pancreatitis secondary to avelumab monotherapy treated with high-dose corticosteroids that developed progressive morbid sequelae of pancreatic necrosis, bowel wall fistula formation, and liver abscess necessitating percutaneous drainage [18].

Overall Survival and Prognosis

Wang et al. demonstrated that varying clinical presentations or steroid use did not impact overall survival. The group also showed that resuming checkpoint inhibition and the presence of long-term pancreatic complications were associated with a significantly better overall survival in this group of patients [10].

Is ICI-PI a Third Type of Autoimmune Pancreatitis (AIP)?

Two forms of autoimmune pancreatitis (AIP), namely, type 1 and type 2 AIP, are well-described in literature. Type 1 AIP is the pancreatic manifestation of immunoglobulin G4-related disease. Type 2 AIP, a relatively uncommon disease, is a duct-centric pancreatic injury often associated with inflammatory bowel disease. ICI-PI, a third form of autoimmune pancreatic injury [19, 20] that we refer to as type 3 AIP, is a form of autoimmune injury [2] to the exocrine pancreas that is distinct from type 1 and type 2 AIP. We looked at these three types of autoimmune pancreatic injury by comparing clinical profiles of all three forms by retrospective analysis of data (Table 12.4) [21]. Similar to type 1 AIP, type 3 has a male preponderance and occurs often in the sixth decade of life. While jaundice is a common presentation of type 1 and 2 AIP, type 3 AIP most commonly presents with an asymptomatic elevation in lipase, and obstructive jaundice is rare. Similar to type 1 AIP, over half of the patients with type 3 AIP have immune-related other organ involvement. However, the organs affected and their presentations are distinctly different. While the pancreas is the most frequently involved organ in IgG4-related disease (type 1 AIP), type 3 AIP is infrequent among immune-related toxicities of ICI therapy. While the definition of steroid responsiveness may vary with each type, all three entities appear to improve with immunosuppression. Like type 1 AIP, type 3 AIP can also lead to long-term pancreatic endocrine and exocrine insufficiency, although the risk appears lower. Due to the asymptomatic presentation and lack of impact on clinical management, none of the patients with type 3 AIP had histological evaluation.

Table 12.4 Comparative analysis of three distinct types of autoimmune pancreatitis [21]

	Type 1 (n = 50)	Type 2 (n = 43)	Type 3 (n = 77)
Median age in years (IQR)	65 (53–72)	31(23–49)	60 (20–57)
Male N (%)	38 (76%)	23 (54%)	50 (65%)
Presentation:			
Pancreatitis	5 (10%)	25 (58.1)	30 (39%)
Jaundice	45 (90%)	13 (30.2)	1 (1.3%)
Asymptomatic lipase elevation N (%)	0	0	47 (61%)
Other organ involvement, N (%)	26 (52%)[A]	19 (44%)[B]	52 (68%)[C]
Steroid response	100% (21/21)[a]	100% (20/20)[a]	90% (9/11)[b]

IQR interquartile range

[A] Tumefactive presentation, bile duct, kidney, retroperitoneal fibrosis, lymph nodes; [B] IBD-UC [14], CD [3], indeterminate colitis [2]; [C] Inflammatory presentation, dermatitis, thyroiditis, colitis, pneumonitis, hepatitis

IBD inflammatory bowel disease, *UC* ulcerative colitis, *CD* Crohn's disease

[a] Defined by clinical/imaging/serologic response; [b] defined by decrease of lipase to <2 upper limit of normal; [c] heterogeneous enhancement of pancreas with peripancreatic fat stranding

Key points: ICI-PI
1. ICI-PI is a rare entity that has a male preponderance with median age of presentation of ≥60 years in association with other immune-related adverse events. The type of checkpoint inhibition and underlying cancer may pose as risk factors
2. ICI-PI may have variable clinical presentations and imaging patterns. It rarely may lead to long-term pancreatic endocrine and exocrine insufficiency
3. The management of this checkpoint inhibitor toxicity is similar to conventional pancreatitis. The role of systemic steroids remains to be clearly elucidated
4. Checkpoint inhibitor resumption and long-term pancreatic complications are associated with a better overall survival

Immune Checkpoint Inhibitor-Mediated Cholecystitis (ICICC)

Immune checkpoint inhibitor-mediated cholecystitis (ICICC) is an irAE that has been rarely observed and described. Its incidence is reported to be only 0.6%, higher than non-immunotherapy-associated cholecystitis (0.2%) [22]. The existing literature on this disease entity is limited. Acute cholecystitis with or without cholangitis has been reported in case studies and case series [23–25]. Based on retrospective analysis, similar to most other irAEs CTLA-4 blockade (vs. PD-1 or PD-L1 blockade) is associated with a higher risk. ICIC may present within 6 months of initiation of ICI with symptoms of fever, abdominal pain, nausea, and emesis. Management is similar to typical acute cholecystitis and includes intravenous hydration, antibiotics, and surgery/percutaneous drainage. Similar to ICI-PI, we presume that a subset of patients may be clinically asymptomatic. Complications are infrequent but include sepsis and perforation and often occur with combination immunotherapy. There is no conclusive evidence in literature on the role of steroids and management of this irAE. A retrospective study of 25 patients with ICIC demonstrated significantly better overall survival in the absence of steroid exposure and resumption of checkpoint inhibitors. The association between patients who develop ICI-related cholecystitis and patients who develop ICI-mediated bile duct injury (whether extrahepatic or intrahepatic) has not been observed or reported.

Key points: ICICC
1. ICICC is an infrequent irAE. The type of checkpoint inhibition, namely, CTLA-4 blockade, poses an increased risk for development of this event
2. Clinical presentation and management of this irAE are similar to cholecystitis from other causes. The role of systemic steroids is unclear
3. Immune checkpoint inhibitor resumption and long-term pancreatic complications are associated with a better overall survival

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Chapter 13
Pathology

Zongshan Lai, Yi Tat Tong, and Dongfeng Tan

Abstract Immune checkpoint inhibitors (ICIs) have gained more and more popularity as cancer treatment in recent years. These drugs have broad-spectrum activity and show effectiveness in more than 10 different types of cancers. They usually have favorable toxicity profiles compared to traditional treatment modalities, such as chemotherapy and radiotherapy.

However, ICIs are associated with a wide spectrum of organ toxicities termed immune-related adverse events. A timely diagnosis is paramount as early intervention may lead to partial or complete reversion from toxicity, whereas a delayed treatment could result in more severe toxicity, sometimes irreversible organ damage, or even death. Within the appropriate clinical context, a treating physician should maintain a high suspicion index. When appropriate, biopsy samples should be taken to be evaluated by an experienced pathologist. Moreover, clinical–pathological correlation is essential because oftentimes the degrees of clinical toxicity/symptoms are not necessarily matched to pathological findings. In this chapter, we aim to summarize the ICI-associated cytotoxic effects on organ systems from the pathological perspective.

Keywords Immune checkpoint inhibitors (ICIs) · PD-L1 · PD-1 · *Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)* · Drug-induced toxicity · Gastrointestinal (GI) · Heart · Liver · Cardiac muscle · Pancreas · Kidney · Skeletal muscle · Skin · Lung

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Abbreviations

AIH	Autoimmune hepatitis
AIN	Acute interstitial nephritis
AKI	Acute kidney injury
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
DAD	Diffuse alveolar damage
DIF	Direct immunofluorescence
EM	Erythema multiform
ICI	Immune checkpoint inhibitor
INSIP	Nonspecific interstitial pneumonia
MHC-1	Major histocompatibility complex
PD-1	Programmed cell death receptor-1
PD-L1	Programmed cell death ligand-1
SJS	Stevens–Johnson syndrome
TEN	Toxic epidermal necrolysis

Introduction

There are mainly three molecular targets for immune checkpoint inhibitors, which include programmed *cell death receptor 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)*. Antibodies targeting PD-1 include nivolumab, pembrolizumab, and cemiplimab, among others, whereas antibodies targeting PD-L1 include atezolizumab, avelumab, and durvalumab. Ipilimumab is an antibody targeting *CTLA-4*. All the abovementioned antibodies have been approved for various cancer indications by blocking specific checkpoints, resulting in boosted immune response against cancer cells [1].

Although promising in achieving high efficacy in eradicating cancer, ICI-induced toxicities have gained much attention in the clinical settings due to their wide spectrum of affecting different organ systems, poor tolerance, symptom severity, and frequent interruptions of cancer treatments. Therefore, recognizing and correctly diagnosing ICIs-induced toxicities are paramount in patient care.

ICIs-induced toxicities can literally affect all organ systems in the body, including skin, luminal GI tracts, liver, lung, heart, kidney, pancreas, neuroendocrine, as well as neuromuscular system. Here, we will focus on the major pathological features manifested by ICI-induced toxicities in the abovementioned organ systems in the order of their prevalence. In general, combined ICI therapy regimens cause more extensive adverse events with higher severity grades than monotherapy. It is important to keep in mind that most of the pathological features are not specific and can overlap in a variety of clinical settings. In addition, different courses of ICI treatment, as well as anti-immune medication such as corticosteroid treatment before tissue biopsy, can alter and modify pathological features. Therefore, clinical and pathological correlations are essential.

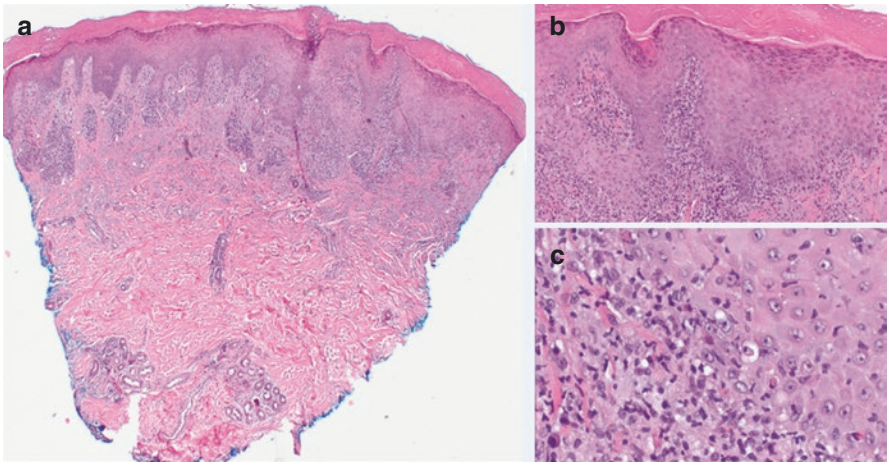

Fig. 13.1 Skin histological features of dermatologic toxicity (lichenoid dermatitis). (**a**) Low magnification of skin with hyperkeratosis, hypergranulosis, irregular acanthosis, and band-like lymphohistiocytic inflammation in the papillary dermis. (**b**) Higher magnification of epidermis with irregular acanthosis and wedge-shaped hypergranulosis. (**c**) High magnification of lymphohistiocytic inflammation obscuring the dermal–epidermal junction and associated dyskeratotic cells. [Hematoxylin and eosin (H&E), original magnification ×40; ×100; ×400] (A = left panel; B = right upper panel; C = right lower panel). (Source: Kindly provided by Dr. Jonathan Curry from the Department of Pathology, The University of Texas MD Anderson Cancer Center)

Pathological Features of ICIs-Induced Toxicities by Organ/System

Dermatologic Toxicity Details are summarized in the dermatologic toxicity chapter. Pathological images are provided below (Fig. 13.1).

Luminal Gastrointestinal Tract Toxicity

Gastrointestinal tract toxicity is one of the most common immune-related adverse events. Clinically, ICI-induced gastrointestinal toxicity mainly manifests as colitis and less frequently as gastroenteritis.

Endoscopy with biopsies of GI tract to assess toxicity can provide very valuable information and has been used as a routine evaluation tool in current practice. Pathological changes of colonic toxicities can be roughly divided into three categories: acute active colitis, microscopic colitis (lymphocytic or collagenous colitis), and chronic colitis. Many of these features are overlapping among each other and also with other inflammatory GI disorders that have been described in the literature

[2]. The following is a summary of the general histological features of commonly encountered luminal gastrointestinal pathology.

1. Active colitis: Increased neutrophilic infiltrates, cryptitis, crypt micro-abscesses, prominent crypt epithelial cell apoptosis (Fig. 13.2a), mucosal injury, and/or glandular dropout (Fig. 13.2b, c). In the setting of active colitis, careful attention is required to rule out superimposed infection, for example, cytomegalovirus (CMV). In case of doubt regarding morphology, CMV immunostaining should be promptly performed due to its high risk of accelerating bowel perforation.
2. Microscopic colitis: Lymphocytic colitis-like pattern with surface injury, whereas the surface epithelium can show a varying degree of flattening, mucin depletion, vacuolization, and nuclear irregularities. Collagenous colitis-like pattern with thickened subepithelial collagen layer of >10 μm [3].
3. Chronic colitis: Atrophic and distorted crypts, fibrosis of lamina propria and lymphocyte infiltrates in the basal lamina propria (Fig. 13.2d), and increased plasma cells in lamina propria (Fig. 13.2e).

In short, these pathological features of colitis induced by ICI are morphologically indistinguishable from those caused by other etiologies. Therefore, close correlation of clinical history of checkpoint inhibitors treatment and clinical symptoms is essential. Though not entirely specific or frequently presented, increased apoptotic bodies could be a helpful hint for diagnosing ICI-induced colitis.

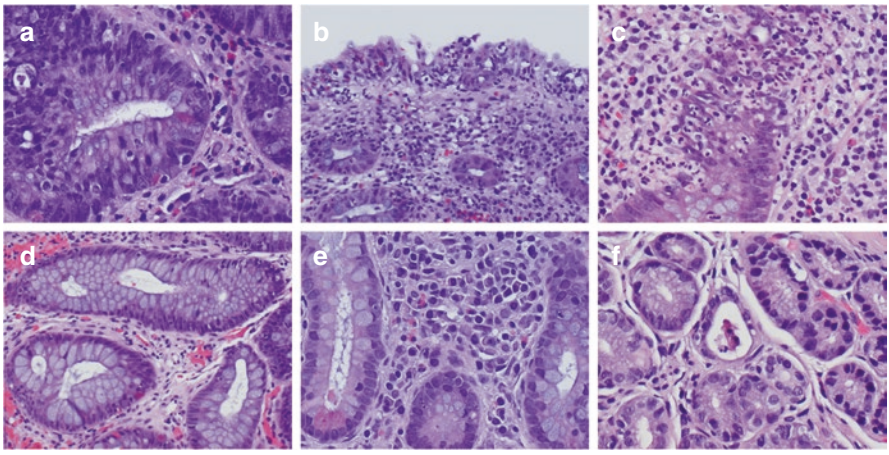

Fig. 13.2 Colon and stomach histological features of luminal gastrointestinal toxicities, (**a**–**e**) are from colon, (**f**) is from stomach: (**a**) mononuclear inflammatory cells and increased crypt apoptotic bodies (H&E stain, original magnification ×400). (**b**) Lymphocytosis and mucosal surface erosion/injuries (H&E stain, original magnification ×200). (**c**) Increased intraepithelial neutrophils, glandular injuries, and expanded lamina propria by markedly chronic inflammation (H&E stain, original magnification ×200). (**d**) Distorted glands, fibrosis in lamina propria, and residual infiltrating chronic inflammatory cells (H&E stain, original magnification ×200). (**e**) Marked increase of plasma cells (H&E stain, original magnification ×400). (**f**) Gastric biopsy reveals mucosal injury and glandular dropout, in a background of relatively mild chronic inflammation (H&E stain, original magnification ×400)

ICI-related upper gastric toxicity can have similar changes, including lymphocytic infiltrating, increased cryptic apoptotic bodies, mucosal injury, and glandular dropout (Fig. 13.2f). These changes can also be seen in ICI-related small bowel toxicity, for example, duodenum, though with lower frequency [4].

Hepatobiliary Toxicity

The incidence of ICI-related hepatobiliary toxicity is relatively low, with a higher risk associated with anti-CLTA-4 than anti-PD-1/L1 therapy [5]. ICI-induced hepatotoxicity most commonly manifests as hepatitis, and rarely as cholangitis.

The main histological feature of an acute hepatitis with a biliary pattern includes pan-lobular inflammation, perivenular infiltrate with endothelialitis, neutrophilic infiltration, with foci of micro-abscesses (Fig. 13.3). Single-cell hepatocytes necrosis (acidophilic bodies) is also frequently seen, while sheets of necrosis are uncommon. Occasionally, there is centrilobular and perivenular zonal cell loss [6]. Biliary pattern of injury includes bile ductular proliferation with mild portal mononuclear infiltrate around proliferated bile ductules [7, 8]. Extramedullary hematopoiesis can also be observed.

There are certain differences observed between ICI hepatitis and other clinical conditions. Compared to primary autoimmune hepatitis (AIH) or non-ICI drug-induced liver injury, confluent necrosis and eosinophilic infiltration are much less common and milder in ICI-induced toxicity. On the other hand, plasmacytosis is a characteristic feature in autoimmune hepatitis, but markedly less common in ICI-induced hepatitis. Bile plugs are slightly more frequent in other drug-induced liver injury than in ICI-induced liver injury. Hepatocellular rosettes and emperipolesis, characteristic findings of AIH, are uncommon in ICI-induced hepatitis [9]. However, in rare conditions, ICI hepatitis could be superimposed with other secondary hepatitis. Therefore, clinical correlation and serum workup are necessary to rule out other etiologies.

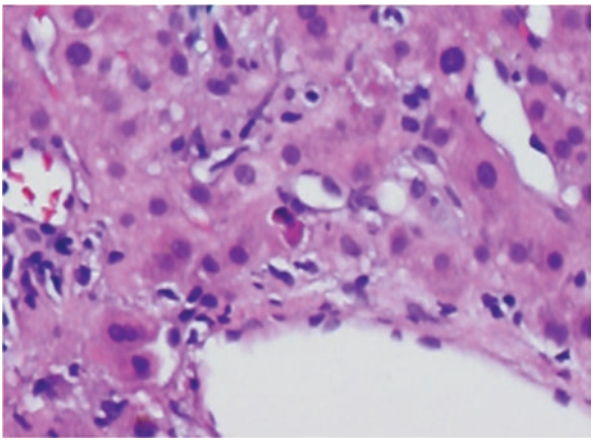

Fig. 13.3 Liver histological features of toxicity: hepatocyte injuries with single-cell necrosis (eosinophilic bodies) and endothelialitis, as well as small bile duct cholangitis and injury (H&E stain, original magnification ×400)

In addition, compared to PD-1/L1 agents, ipilimumab seems to be more commonly associated with better formed granulomatous changes [10], typically associated with a central fibrin ring, resembling those that are found in Q fever (fibrin-ring granuloma) [11].

Pancreatic Toxicity

ICI-induced pancreatic injury can lead to both endocrine and exocrine dysfunction with low incidence [12]. The common presentation of asymptomatic elevation of serum amylase and lipase suggests that the acute inflammatory process occurs in the pancreas. Because of the readily available serum pancreatic enzymes and imaging findings for identifying ICI-induced pancreatic toxicities, biopsy is not commonly utilized and studied for the diagnostic purpose.

Pulmonary Toxicity

ICIs-induced lung injury can be potentially life-threatening [13], even though the overall incidence is low. The clinical presentations can be varied and include interstitial pneumonia, organizing pneumonia, hypersensitivity pneumonitis, acute fibrinous pneumonitis, or diffuse alveolar damage (DAD). Following is a summary of histological features of different pulmonary pathological conditions.

1. Nonspecific interstitial pneumonia (NSIP) pattern: Diffuse and uniform lymphoplasmacytic inflammation in alveolar wall and bronchovascular bundles. There may be loose fibrosis, with frequently preserved lung architecture.
2. Organizing pneumonia pattern: Fibrinous exudates and neutrophils transforming into fibromyxoid masses with histiocytes, and there may be necrotizing changes in bronchi.
3. Hypersensitivity pneumonitis pattern: Airway-centered changes, with interstitial cellular infiltration, and poorly formed non-necrotizing granulomas or interstitial giant cells with cholesterol clefts.
4. Acute fibrinous pneumonitis/DAD pattern: Intra-alveolar fibrin, involving more than 20% of the alveolar spaces in the lesion, with scanty or absent neutrophils.

Cardiac Toxicity

Though it is relatively rare, cardiac toxicity is oftentimes fatal. The incidence is less than 1% of patients treated with ICI and mostly related to anti-PD-1/PD-L1 agents.

Histologically, ICI-induced myocarditis includes a patchy to florid lymphocytic infiltrate (Fig 13.4a) associated with degeneration and necrosis of cardiac muscle

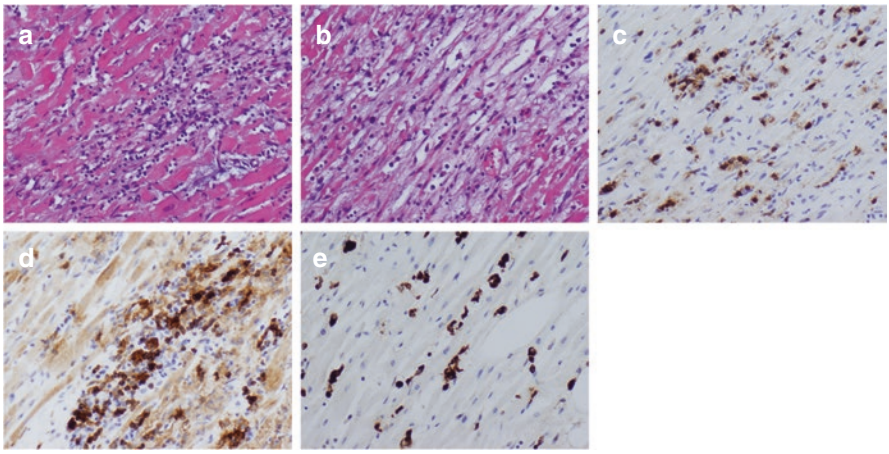

Fig. 13.4 Heart histological features of toxicity: (**a**) diffusely infiltrating small lymphocytes in cardiac muscle (H&E stain, original magnification ×200). (**b**) Confluent necrosis (ghost cells) of cardiac muscle cells in a background of abnormally increased lymphocytes (H&E stain, original magnification ×200). (**c**) Immunohistochemistry demonstrates many lymphocytes are CD8+ T cells (immunohistochemistry, original magnification ×200). (**d**) Immunohistochemistry also reveals virtually equal amount of CD4+ T cells (immunohistochemistry, original magnification ×200). (**e**) Immunohistochemistry further shows some of the infiltrating cells are CD68+ macrophages, while no CD 20+ B cells identified (immunohistochemistry, original magnification ×200)

cells. If myocarditis cannot be recognized and treated promptly with intravenous high-dose cortisol, it can rapidly progress to diffuse endothelialitis and cardiac infarct (Fig. 13.4b), causing fatal outcomes. Johnson et al. showed mononuclear infiltrates in cardiac muscle based on autopsy studies [14]. The inflammatory cells with diffuse infiltration were predominately T cells, for example, CD4+ and CD8+ T cells (Fig. 13.4c, d), as well as CD68+ macrophages (Fig. 13.4e). In contrast, CD20+ B cells were absent in immunofluorescence studies. TCR analysis of infiltrating lymphocytes in cardiac muscle and tumor showed clonal expansion, indicating that antigens present in the muscle were identified by the same T-cell clone [14]. Despite of diffuse mononuclear infiltrates, cardiac toxicity is usually absence of granulomas or giant cells [15].

Neuromuscular Toxicity

Neuromuscular toxicities are rare but potentially severe. The toxicity can involve nerves and muscles, and present as myopathy, neuropathy, and even myasthenia gravis [16].

From a histological perspective, myopathy mainly presenting as myositis which has received the most attention, has focal or multifocal necrotic myofibers which in early phases could be patchy and subtle (Fig. 13.5). Features of sarcolemmal major

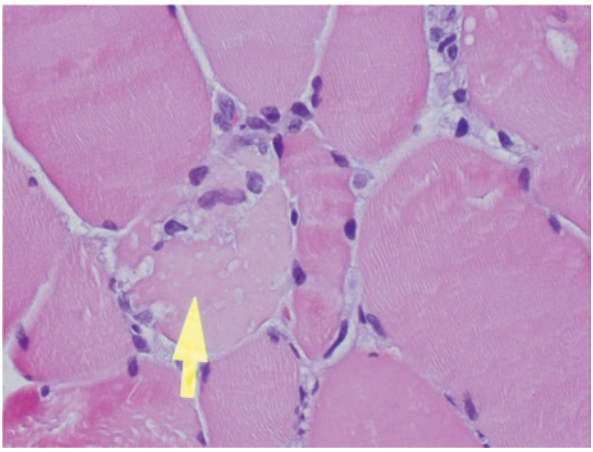

Fig. 13.5 Calf muscle histological features of toxicity: shows swollen skeletal muscle cells and one necrotic cells (arrowed) in a background of mononuclear cell infiltrating (H&E stain, original magnification ×400)

histocompatibility complex I (MHC-I) and endomysial inflammation consisting mainly of CD68+ cells (a marker for monocytes/macrophages) expressing PD-L1 and CD8+ cells expressing PD-1 [17] have been described to aid in the diagnosis of myositis. Similar features of abundance of CD4+, CD8+, and CD68+ cells and absence of CD20+ B cells were also noted in an autopsy study reported in limited cases [16]. For patients who receive corticosteroid treatment before biopsy being taken, sometimes only muscular atrophy is present without myositis being identified, although most such patients still yield positive results.

Renal Toxicity

ICI-related renal toxicity is predominantly acute kidney injury (AKI), which includes acute interstitial nephritis, lupus-like nephritis, granulomatous nephritis, diffuse interstitial nephritis, or minimal change disease. Anti-PD-L1 agents were found to have less risk to cause renal toxicity [18].

The most commonly reported renal pathological histology is acute interstitial nephritis (AIN), either alone or in combination with other glomerular pathologies, which is characterized by diffuse interstitial inflammation and focal severe tubulitis, with a predominantly CD4+ lymphocytic infiltrate, and some eosinophils and plasma cells [19]. However, a recent report has proven that tubular dysfunction could be the first sign of an ICI-induced AIN, even in the absence of AKI [20].

Other pathological changes include granulomatous formation with multinucleated giant cells.

Immunofluorescence typically yielded only background staining for C3 along vessel walls with the absence of tubular basement membrane and glomerular staining. Electron microscopy shows mild-to-moderate foot process effacement and the absence of electron-dense deposits. In some patients, subepithelial and intramembranous deposits can also be seen with no explainable etiology [19].

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Chapter 14
Pulmonology (Lung)

Divya Verma, Saadia A. Faiz, Vickie R. Shannon, Mehmet Altan, and Ajay Sheshadri

Abstract The use of immune checkpoint inhibitors (ICIs), which include drugs that target programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1), and the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), has rapidly expanded over the past decade due to an ever-growing number of indications to treat different cancers. As their use has increased, so has recognition of immune-related side effects. The pulmonary toxicities of ICIs are less common than other immune-mediated toxicities but carry significant morbidity and are the most common cause of treatment-related mortality. This chapter will discuss the various pulmonary toxicities induced by ICIs but will focus most heavily on ICI pneumonitis.

Keywords Pneumonitis · Organizing pneumonia · Lung injury · Sarcoidosis

Abbreviations

ADL	Activity of daily living
ASCO	American Society of Clinical Oncology

Chapter debriefing: Power point video presentation is provided at the end of the chapter.

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BAL	Bronchoalveolar lavage
BRAF	B-raf and v-raf murine sarcoma viral oncogene homolog B1
CMV	Cytomegalovirus
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DAD	Diffuse alveolar damage
DLCO	Diffusing capacity of the lungs for carbon monoxide
EBV	Epstein-Barr virus
ESMO	European Society for Medical Oncology
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GGO	Ground-glass opacity
HP	Hypersensitivity pneumonitis
IBD	Inflammatory bowel disease
ICI	Immune checkpoint inhibitor
ICIP	Immune checkpoint inhibitor pneumonitis
ILD	Interstitial lung disease
IP	Interstitial pneumonitis
irAE	Immune-related adverse event
IVIg	Intravenous immunoglobulin
MEK	Mitogen-activated protein kinase kinase
NSLCL	Non-small cell lung cancer
OP	Organizing pneumonia
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PFT	Pulmonary function test
RCC	Renal cell carcinoma
SITC	Society for Immunotherapy of Cancer
SR-ICIP	Steroid-refractory immune checkpoint inhibitor pneumonitis
TBLB	Transbronchial lung biopsy
TMB	Tumor mutational burden
TNF	Tumor necrosis factor

ICI Pneumonitis

Introduction

Immune checkpoint inhibitors (ICIs) [1] are a quickly growing class of medication that prevent checkpoint receptors on the surface of cells from binding with their ligands, thus targeting some of the immunosuppressive pathways that cancer cells utilize to propagate [2]. ICIs are used to treat an ever-increasing number of malignancies. As the use of ICIs increases, so do the recognized complications.

ICI-related pneumonitis (ICIP) is a complication that is characterized by pulmonary inflammation and manifests with new inflammatory changes on imaging, with or without respiratory symptoms or pulmonary exam findings [3]. Because lung toxicities are the most common cause of ICI-associated fatality, accounting for 35% of treatment-related deaths, it is important for treating oncologists and pulmonary consultants to recognize and treat ICIP promptly [4]. This chapter will discuss the epidemiology and risk factors surrounding ICIP, the diagnostic process, and therapeutic options. While the primary focus of this chapter is pneumonitis, we discuss other rarer pulmonary complications of ICIs toward the end of this chapter.

Clinical Presentation

The clinical presentation of ICIP is highly variable. Symptoms can present as acutely as hours after the first dose of ICI to several months after therapy is stopped [5]. In patients who are at risk for ICIP, a thorough history and physical exam are paramount as the differential diagnosis for respiratory symptoms in a patient with cancer is broad. The main competing diagnoses are respiratory infections (pneumonia, bronchitis), congestive heart failure with pulmonary edema (potentially due to myocarditis), and disease progression (e.g., lymphangitic spread of tumor) [6]. Clinicians should take a thorough history and inquire about infectious symptoms and exposures including fever, chills, and sick contacts; pulmonary symptoms, including cough, shortness of breath, chest pain, and decreased exercise capacity; and cardiac symptoms, including orthopnea, paroxysmal nocturnal dyspnea, and leg swelling. Fever may be more indicative of an infectious etiology, though fever can sometimes be seen with ICIP as well [6]. In particular, clinicians should carefully assess for environmental exposures (e.g., to endemic fungi or occupational exposures that may case pneumoconiosis) and a personal or family history of interstitial lung disease and/or autoimmune disease. Examinations of the lungs can vary greatly in ICIP patients – the exam can be entirely normal, or patients can present with diffuse inspiratory rales on auscultation. The initial workup should include thoracic imaging, sputum cultures, or bronchoscopy with bronchoalveolar lavage (BAL) to evaluate for lower respiratory infection. In some cases, echocardiography, measurement of B-natriuretic peptide, and potentially lung biopsy may be indicated when the diagnosis of ICIP is not clear.

Diagnostic Approach

Imaging Patterns

The sensitivity of chest radiography to detect changes in ICIP is low and can miss early-grade pneumonitis; therefore, patients with suspected ICIP should undergo chest computed tomography (CT) when available [16]. ICIP can manifest with several different radiographic disease patterns, and while imaging findings in other interstitial

lung diseases are often used to contextualize the findings seen in ICIP, it is important to note that the similarity in these patterns does not connote identical mechanisms for the pathogenesis of disease. Patterns noted on imaging do not necessarily influence treatment choice but may be indicative of the severity of illness. Additionally, the imaging patterns seen in ICIP do not always fit neatly into one the classical presentations noted in sporadic interstitial lung disease and can present with an overlap of features from different patterns; for example, one series of ICIP noted that a significant proportion of patients presented with a mixed pattern on CT, and the incidence of specific patterns varied substantially from report to report [7]. Ground-glass opacities are the most common finding on CT, followed by consolidation, bronchiectasis, and intralobular septal thickening [8, 9]. Figure 14.1 shows representative images from patients with ICIP. Below, we will highlight specific patterns which are often seen in ICIP.

- Organizing pneumonia (OP) – OP is the most common pattern seen in ICIP. OP is characterized by bilateral peribronchovascular and subpleural ground-glass

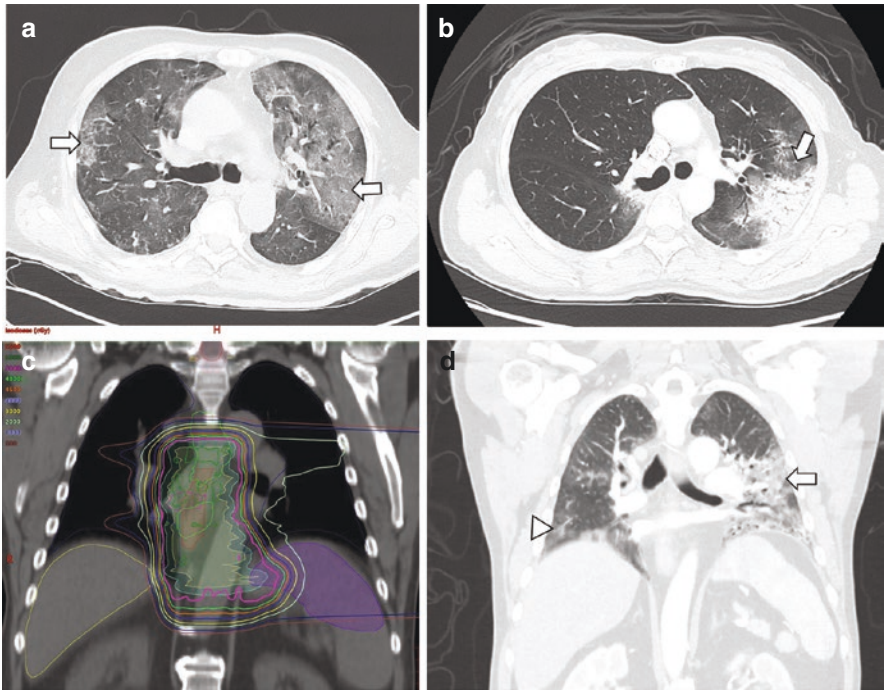

Fig. 14.1 Representative images of patients with ICIP. Panel **a** shows a patient with metastatic renal cell cancer who developed ICI-induced pneumonitis and neurotoxicity. The CT scan of the chest shows diffuse ground-glass opacities. Panel **b** shows an example of consolidation which was proven to be organizing pneumonia. Panels **c** and **d** show an example of ICIP in a patient receiving concurrent radiation, oxaliplatin therapy, and pembrolizumab. Panel **c** shows the limited radiation field, but Panel **d** shows ground-glass infiltrates that developed shortly after radiation and are most dense in the area of radiation, but extend beyond the radiation field. This pattern suggests ICI potentiation of radiation injury to the lung

and airspace opacities. Sub-centimeter pulmonary nodules can sometimes be seen in a peribronchovascular distribution [10]. A "reverse halo" sign can be seen in OP but is also present in other conditions and is not pathognomonic. In one series, 65% of patients who developed ICIP had OP on CT imaging [11]. Importantly, while OP seen with ICIP may often resemble sporadic OP, the response to therapy may vary. In particular, sporadic OP is often highlighted by a recurrence of pneumonitis if the course of anti-inflammatory therapy is not sufficiently long (usually on the order of 3–6 months) [12, 13]. On the other hand, many patients with ICIP are treated successfully with courses of corticosteroids lasting only a few weeks. One cohort of 299 patients treated with ICIs found that 44 developed pneumonitis, and of these, six developed recurrent pneumonitis after a course of 4–6 weeks of corticosteroids [5]. This suggests that the majority of patients with OP-like ICIP do not have a relapsing disease pattern, and therefore the underlying conditions that drive sporadic OP are not necessarily similar to those that drive OP-like ICIP.

- Interstitial pneumonitis (IP) – an IP radiological pattern is typically characterized by patchy ground-glass opacities (GGOs) in a predominantly peripheral and lower lung pattern, but can progress to architectural distortion and traction bronchiectasis. IP often spares the subpleural region. IP is seen as the primary pattern in about 15% of ICIP cases [11]. In some cases, a hypersensitivity pneumonitis (HP)-like pattern may be seen, with centrilobular nodules and mosaic attenuation which may represent air trapping or perfusion differences. HP-like ICIP has been reported to occur in about 10% of ICIP cases [11]. In a series of ICIP patients, some of whom underwent biopsy, the typical histopathology appeared to be cellular interstitial pneumonitis in 4/11 patients, organizing pneumonia in 3/11 patients, and diffuse alveolar damage in 1/11 patients. 3/11 patients did not have any abnormalities noted on their biopsy, even though they had clinically been diagnosed with ICIP [14].
- Diffuse alveolar damage (DAD) – DAD is characterized by extensive GGOs and areas of consolidation, usually worse in dependent regions, that can often progress to scarring and decreased lung volumes. Up to 10% of ICIP patients may develop a DAD-like pattern. In one series, this was the pattern most commonly noted in patients with fatal ICI pneumonitis, suggesting that this pattern may simply be seen in patients with a fulminant disease course [15]. Because of variability in the initial assessment and a lack of corroborating histopathology, it is unclear whether DAD-like ICIP is a separate entity characterized by extensive, widespread alveolar inflammation, or simply severe ICIP which progressed substantially before a diagnosis was made.

Pulmonary Function Testing

Pulmonary function tests (PFTs) should be used prior to starting ICIs to establish a reliable baseline. PFTs can be used to quantify lung damage if ICIP is suspected and can be used to understand the level of impairment compared to baseline

assessments. ICIP most commonly causes a restrictive pattern on pulmonary function testing, which is best detected by comparing the change in total lung capacity at the time of suspected ICIP with baseline values. ICIP does not typically manifest as airflow obstruction, which is commonly detected by a decreased ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC). ICIP may also manifest as a diminished diffusing capacity of the lungs for carbon monoxide (DLCO). A prospective study of patients undergoing treatment with ipilimumab for melanoma examined serial spirometry and DLCO measurements and found clinically significant reductions in spirometry in 24% of patients at a 9-week follow-up, though only about half of the cohort was observable at 9 weeks after enrollment. Mean DLCO decreased by about 4% from baseline values, which is unlikely to be clinically significant. However, only one patient developed clinical and radiographic signs of ICIP, and that patient had resolution of ICIP after corticosteroids [16]. Because PFTs can assist in the diagnosis of ICIP, we recommend obtaining them at baseline and upon suspicion of toxicity, but because of the lack of data concerning the accuracy of PFT impairments in ICIP, their role is more adjunctive than crucial to the diagnosis of ICIP.

Bronchoscopy

The current Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group and others advocate for bronchoscopy in any patient undergoing treatment with an ICI with new or persistent infiltrates on CT scan [17]. The current American Society of Clinical Oncology (ASCO) guidelines suggest offering bronchoscopy with bronchoalveolar lavage (BAL) to patients with suspicion for grade 1 ICI pneumonitis and more firmly state that clinicians should offer bronchoscopy with BAL +/− transbronchial biopsy in patients with grade 3–4 toxicity [18]. The European Society for Medical Oncology (ESMO) guidelines offer more specificity – this group suggests bronchoscopy with BAL in patients with grade 2 or higher toxicity to thoroughly investigate for infection before offering treatment with immunosuppression [19]. We typically perform bronchoscopy with BAL in all patients with suspected pneumonitis due to the possible need for corticosteroids, which may worsen infection, and due to the unpredictable disease course of ICIP.

The primary goal of BAL in patients suspected to have ICIP is to rule out infection. However, a relative lymphocytosis seen upon BAL cytology may indicate the development of pneumonitis [20, 21]. The diagnostic accuracy of BAL lymphocytosis has not been well established. Evaluation of BAL fluid may also lead to insights into the mechanism driving ICIP. In a series of seven patients undergoing treatment with ICIs and who underwent bronchoscopy with BAL for suspected ICIP or infection, a relative increase in the total number of CD8+ cells was observed after ICI treatment. Importantly, this included both patients with ICIP and infection in the setting of ICI treatment. Additionally, though the total CD4+ cell count was comparable in the BAL fluid of ICI patients compared to controls, the percentage of Th17.1

cells, which produce interferon gamma and the inflammatory cytokine interleukin-17, was significantly higher in the ICI pneumonitis group [21]. However, these studies need to be validated in larger cohorts, with clear demarcations which illustrate whether a given patient is likely to have ICIP or a competing diagnosis such as pneumonia.

Lung Biopsy

Some guidelines suggest transbronchial lung biopsy (TBLB) in patients with grade 2 or higher disease [17–19]. The clinical utility of routine TBLB in patients with suspected ICI pneumonitis is debatable, given the documented poor sensitivity of TBLB in the diagnosis of ILD and the risk for complications, including bleeding and pneumothorax [22]. Bronchoscopic lung cryobiopsy has become increasingly common for the diagnosis of ILD and appears to be safer than surgical lung biopsy [23], though at the cost of lower diagnostic accuracy [24]. No clear consensus exists regarding utility of each type of biopsy in the setting of this condition, and practice differs greatly based on availability of various techniques and the center's expertise with ICI pneumonitis [25]. We perform biopsy on a case-by-case basis, particularly when ICIP needs to be distinguished from disease progression, but this is not always part of the standard assessment of every patient.

Assessment of Severity

The gradation of the disease is adapted below from the Common Terminology Criteria for Adverse Events (CTCAE), which has been adapted in a table below (Table 14.1) [26]. Grade 1 toxicities represent asymptomatic patients who have evidence of ICIP as documented by changes on imaging. Grade 2 toxicities represent patients with some symptoms; typically, these patients do not require oxygen, and the degree of symptomatology may vary from barely noticeable to significant impairment in exercise tolerance. Grade 3 toxicities typically warrant close monitoring in an inpatient setting and oxygen supplementation, and symptoms are often present at rest without supplemental oxygen. Grade 4 toxicities require intensive care and ventilatory support with high-flow nasal cannula, non-invasive ventilation, or mechanical ventilation. Grade 5 toxicity represents fatal ICIP.

Table 14.1 Common Terminology Criteria for Adverse Events (CTCAE) 5.0 for ICIP

Grade 1	Asymptomatic, radiographic changes only
Grade 2	Symptomatic, limiting instrumental ADLs
Grade 3	Severely symptomatic, limiting self-care ADLs, oxygen indicated
Grade 4	Life-threatening respiratory compromise requiring mechanical ventilation
Grade 5	Death

Epidemiology and Risk Factors

While ICIP is less common than some of the well-known immune-related adverse effects (irAEs) of ICIs, such as colitis or dermatitis, symptoms can be severe, and pneumonitis is the most common cause of drug-related fatality [27]. The overall incidence of ICIP is estimated to be between 1% and 6% based upon data from clinical trials [4, 28, 29] but varies greatly dependent on type of ICI used – including whether ICIs are used as a single agent or in combination with other ICIs or antineoplastic agents and type of malignancy being treated – and thereby the comorbidities associated with population at risk for that given malignancy, tumor burden, and treatment history [6, 30]. Each of these factors will be described below individually, but incidence rates differ significantly based upon the specific scenario. For example, in a real-world series composed of patients with non-small cell lung cancer undergoing treatment with a PD-1 inhibitor, alone or in combination with a CTLA-4 inhibitor, the overall reported rate of pneumonitis was 19% [31], much higher than observed in clinical trials, in which patients may no longer be observable if they withdraw from the trial or have disease progression and come off study, and in which stopping criteria for ICI therapy may diverge from clinical practice. Furthermore, patients who enroll in clinical trials may be dissimilar to those seen in real-world settings. Another example of setting-specific rates for ICIP is seen in metastatic melanoma. In patients on ipilimumab for metastatic melanoma, rates of ICIP may be less than 1% [32], but this rises to 10% when atezolizumab is given in combination with vemurafenib and cobimetinib [33]. Therefore, the exact rate of ICI-related pneumonitis may be higher or lower depending upon numerous circumstances.

Type of ICI

Rates of any-grade pneumonitis with ICI monotherapy are highest in patients treated with PD-1 inhibitors, with an estimated incidence of between 3% and 5%, compared to 1% and 3% with PD-L1 inhibitors and around 1% with CTLA-4 inhibitor monotherapy [4–14, 28]. In sub-group analyses comparing toxicities associated between different ICIs, there was no significant difference between the rates of pneumonitis in patients treated with nivolumab or pembrolizumab, the most commonly used PD-1 inhibitors [4, 34]. Cemiplimab is the newest of the PD-1 inhibitors, and the incidence of lung toxicity is not as well understood relative to other PD-1 inhibitors. In the initial phase 2 trial examining the efficacy of cemiplimab in locally invasive cutaneous squamous cell carcinoma, 8 of 78 patients (10%) studied experienced any grade pneumonitis, and 4 of 78 patients (5%) experienced grade 3 or higher pneumonitis. These results stand in contrast to the phase 3 open-label, randomized control trial examining cemiplimab in 355 patients with non-small cell lung cancer (NSCLC) with high PD-L1 expression (>50%) wherein the rate of grade 1 and 2 pneumonitis was approximately 3%, and only one case of high-grade pneumonitis (grade 3 or higher) was observed [35].

PD-L1 inhibitors have generally been associated with a lower incidence of ICIP, though once again the exact rate varies greatly based upon setting. In the initial phase 3 trial of atezolizumab and docetaxel in patients with previously treated NSCLC, ICIP was noted in less than 1% of the 609 patients studied, and only four patients had grade 3 or greater ICIP [36]. Durvalumab had a similarly low incidence of ICIP (1%) in the ATLANTIC study, a phase 2 open-label trial in patients with advanced NSCLC [37]. However, in the PACIFIC study, which measured the effect of sequential chemotherapy and radiation and either durvalumab or placebo in locally advanced NSCLC, all-grade pneumonitis was observed in nearly one-third of patients and led to discontinuation of durvalumab in 4.8% of patients receiving the drug [38]. Among patients who developed pneumonitis, 12% were assumed to primarily have ICIP. In practice, distinguishing the relative contribution of radiation and ICI therapy to pneumonitis with sequential chemoradiation/ICI is often not possible.

Ipilimumab (CTLA-4 inhibitor) has been associated with higher rates of other immune-related adverse events (irAEs) such as colitis, rash, and hypophysitis, but ICIP is usually less common with ipilimumab monotherapy, with incidence rates seen at 1% or lower [39, 40]. Tremelimumab, another CTLA-4 inhibitor that has not yet been approved by the FDA, is less well studied as a monotherapy, and little data exists about the incidence of ICIP in this setting. In a 2020 study examining its efficacy and safety profile of tremelimumab with or without durvalumab in patients with hepatocellular carcinoma, no episodes of pneumonitis were reported in 69 patients undergoing tremelimumab monotherapy group (n = 69), and 1 case was reported among 74 patients undergoing durvalumab + tremelimumab combination therapy [41].

While it appears that ICI drug efficacy may sometimes be dose dependent [42], ICIP rates do not vary by ICI dose and are somewhat idiosyncratic, presumably consistent with the unpredictable immune activation inherent to checkpoint blockade [34].

Monotherapy vs. Combination Therapy

Due to the possibility of synergistic effects of targeting more than one immune checkpoint [43], ICIs targeting different checkpoints have been used in combination with each other (e.g., nivolumab and ipilimumab) as well as with chemotherapy, biologics, and targeted therapies. As discussed above, the risk of ICI pneumonitis in melanoma patients being treated with ICI monotherapy is relatively low, but the incidence can increase to as high as 10% in patients who are treated with a combination of PD-1 and CTLA-4 inhibitors [14, 30, 44, 45].

ICIs can be combined with targeted therapies as well and in certain cases can increase the rate of ICIP. For example, in patients with metastatic melanoma with BRAF and MEK mutations, BRAF inhibitors (dabrafenib, vemurafenib), MEK inhibitors (trametinib, cobimetinib), and ICIs have been combined to target several mutations at once [46]. The KEYNOTE-022 trial examining outcomes in patients with BRAF mutated melanoma treated patients with dabrafenib and trametinib in

combination with either pembrolizumab or placebo. The group undergoing therapy with the triple drug regimen had a significantly higher rate of progression-free survival (41% vs 16%) as well as overall survival (63% vs 52%) at 24 months but also had a significantly higher rate of immune-related adverse events (52% vs 15%). 17% of patients in the pembrolizumab group experienced pneumonitis; only 3% of patients in the two-drug regimen experienced pneumonitis. Similarly, as noted above, the combination of atezolizumab, vemurafenib, and cobimetinib is associated with a 10% incidence of ICIP [33]. This data suggests that BRAF and MEK inhibitors contribute to an increased rate of pneumonitis in the presence of PD-1 inhibition – even in melanoma – whereas ICI monotherapy leads to comparatively low rates of ICIP [47].

An increased risk of pneumonitis has also been reported for a subset of targeted therapies in NSCLC. In a clinical trial combining durvalumab with the epidermal growth factor receptor (EGFR) inhibitor osimertinib, 5/23 (22%) developed pneumonitis [48]. The prolonged half-lives of PD-1 and PD-L1 inhibitors also raise concerns for increased pulmonary toxicity when osimertinib is used shortly after ICI therapies. In a retrospective study of 41 patients, 6/41 (15%) of patients treated with PD-1 or PD-L1 inhibitors followed shortly thereafter by osimertinib developed high-grade (grade 3 or higher) pneumonitis [49]. This was most common among those who initiated osimertinib within 3 months of ICI therapy (5/21), as compared with osimertinib initiation at an interval of greater than 3 months. By contrast, no high-grade pneumonitis was identified among patients treated with osimertinib followed by PD-1 PD-L1 inhibitor therapies, or ICI therapies followed by other EGFR inhibitors.

Prior Treatment History

While one might hypothesize that cytotoxic therapies may lead to subclinical lung injuries that increase the rate of ICIP, in fact, the opposite phenomenon is observed. The rate of any-grade ICIP in treatment naïve patients treated with PD-1 and PD-L1 inhibitors is higher than the rate of pneumonitis in previously treated patients (4.3% vs. 2.8%) [4]. There was no statistically significant difference seen when comparing grade 3 or higher pneumonitis in treatment-naïve and previously treated patients. This finding has yet to be linked to a definitive biological mechanism. However, one practical observation is that the patients who are treatment-naïve may be fundamentally different from those who have been previously treated. Those at risk for developing ICIP may have died for other reasons prior to undergoing ICI therapy as a "previously treated" patient. Therefore, the possibility of immortal time bias in previously treated patients needs to be carefully accounted for.

Prior Radiation Therapy

A history of treatment with radiation may also predispose patients to developing ICIP, though this has not been well established in comparative studies. ICIP may be preferentially observed within prior radiation fields [50] and may rarely induce

a distinct form of radiation-recall pneumonitis. The patterns of ICIP seen in radiation-recall injury may be OP-like, similar to ICIP in the general sense [51]. The PACIFIC study, a placebo-controlled study examining durvalumab as consolidative therapy in patients with locally advanced NSCLC after sequential chemotherapy and radiation, found rates of all-cause pneumonitis (both ICIP and radiation-related) of 33% in the durvalumab group, compared to about 25% in the placebo group (presumably all radiation related). This high rate of pneumonitis with sequential chemotherapy and radiation, even without ICI therapy, presents additional difficulty when trying to understand the marginal impact of ICI therapy against the background rate of radiation- and chemotherapy-induced pneumonitis. Higher doses of chest radiation may potentiate ICI pneumonitis; in a prospective observational study of 188 patients with advanced NSCLC and prior treatment with a PD-1 or PD-L1 inhibitor, more patients who developed radiation pneumonitis had radiation therapy with curative intent [52]. These data may suggest that ICIP is more common with more aggressive radiation therapy, but needs to be validated.

Type of Malignancy

ICIP occurs more commonly in the setting of certain malignancies. For example, patients being treated with PD-1 inhibitors for NSCLC or renal cell carcinoma (RCC) have higher rates than in those treated for metastatic melanoma [3]. In a systematic meta-analysis of trials examining the efficacy of PD-1 inhibitors for NSCLC, RCC, and melanoma, the rates of pneumonitis were 4.1% for both NSCLC and RCC, compared to 1.6% in melanoma [53]. High-grade pneumonitis was more common in NSCLC. This difference in incidence has previously been attributed to higher rates of smoking in patients with NSCLC [44]. Squamous cell carcinoma, a lung cancer seen more often in patients who smoke tobacco, also predicted ICIP in one study [31]. However, the higher prevalence of patients who smoke tobacco products among NSCLC and RCC patients may point to another cause for the increased risk of ICIP. Numerous studies have found a higher rate of prior interstitial lung disease, which is associated with the use of tobacco products, among patients treated with ICIs and subsequently develop ICIP, as compared to those who do not [54–57]. This suggests that in smoking-related cancers, the risk for ICIP may be driven by comorbid interstitial lung disease more than the actual type of malignancy.

In two small series of patients being treated for hematologic malignancy, ICI pneumonitis has been observed at rates as high as 10–12% [14, 15]. One study described patients undergoing treatment with azacytidine and nivolumab combination therapy and postulated that the increased rate of ICIP could be due to the observation that azacytidine itself upregulates PD-1 and PD-L1 [58, 59]. This upregulation is thought to contribute to leukemic resistance to azacytidine and may also explain the increased rates of ICIP in this population, which is nearly double the usual rate of ICIP with PD-1 inhibitor monotherapy [58].

Tumor Mutational Burden

Tumor mutational burden (TMB) is defined as the total number of somatic mutations per coding area of a tumor genome [60] and has been associated with an increased likelihood of response to immune checkpoint inhibitor therapy due to increased immunogenicity of these tumors [61]. Many early approvals for PD-1 inhibitors were in patients with solid tumors with a high TMB [62, 63]. While higher TMB has been associated with higher likelihood of irAE, there has been no evidence that ICIP is more common in patients with higher TMB after controlling for type of malignancy and prior lung disease [64].

Prior Lung Disease

The safety of PD-1 inhibitors in patients with underlying lung conditions is an area of active interest, though recent data suggests that patients with prior interstitial lung disease should not be denied ICI therapies [65]. This is an especially important topic given that patients with underlying interstitial lung disease are at higher risk of malignancy, whether related to prior tobacco or occupational exposure or because of chronic lung inflammation [66, 67]. Tobacco exposure predisposes to both pulmonary malignancies and ICIP, and a greater exposure to tobacco smoke (>50 pack-years) predisposed to ICIP in one study of patients with lung cancer treated with PD-1 inhibitors [68]. However, this association was not seen in another study that measured smoking as "no smoking history" vs. "some smoking history" [44]. Whether smoking is the primary upstream factor resulting in interstitial lung disease is unclear, but pre-existing interstitial abnormalities have been repeatedly associated with a higher likelihood for ICIP [56, 69]. In a retrospective analysis of 216 NSCLC patients who had received nivolumab, ICIP following nivolumab therapy occurred in 12% of patients with prior interstitial lung disease as compared to 5% in those without prior interstitial lung disease.

Treatment

The treatment of ICI pneumonitis is based on the severity of illness and requires some combination of holding immunotherapy, clinical reassessment, and steroids.

The 2018 American Society for Clinical Oncology (ASCO) guidelines for the management of ICIP are outlined in Fig. 14.2 [18]. The Society for Immunotherapy in Cancer (SITC) and the European Society for Medical Oncology (ESMO) have also published guidelines which are broadly similar [17, 19, 70].

If a clinical diagnosis of ICIP is being considered, the ICI therapy should be held while the clinical evaluation is being undertaken, but may be resumed in certain low-grade cases. The question of restarting ICI therapy after ICIP is addressed at the end of this section.

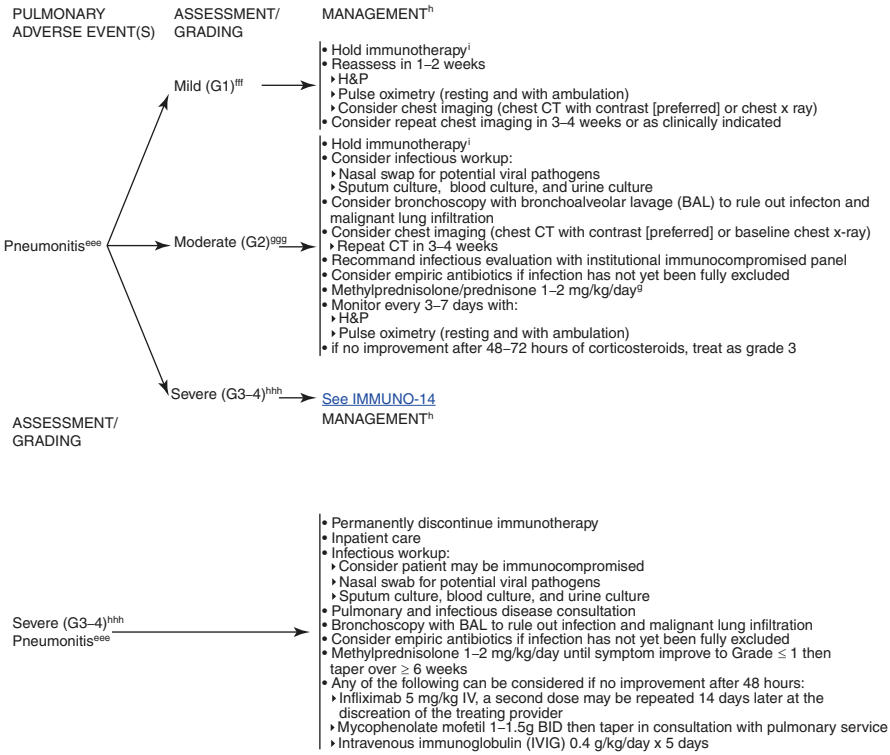

Fig. 14.2 American Society of Clinical Oncology Guidelines for the management of ICIP

Corticosteroids

For grade 1 (asymptomatic) pneumonitis, ASCO recommends holding immunotherapy and considering low-dose steroids [18]. For grade 2 (mildly symptomatic) pneumonitis, steroids can be considered at 1–2 mg/kg/day with close clinical follow-up. For grade 3 and higher pneumonitis, a higher dose of steroids is recommended (2–4 mg/kg/day). These doses are based upon expert clinical opinion, and it may be reasonable to try lower doses or shorter courses in certain cases (e.g., in hematological malignancies where infection is a higher concern), but such approaches are not supported by the guidelines or data.

The ASCO, ESMO, and SITC guidelines all recommend a typical taper of corticosteroids over a 6-week period [17, 18, 70]. One study reported that in 13% of cases, this strategy resulted in a failure to resolve ICIP and considered these cases to be chronic ICIP, which occurred more commonly in patients being treated for NSCLC and in patients with combination ICI strategies [5]. However, all patients with chronic ICIP had OP by TBLB, and this may represent the known predilection for OP to "relapse" without a longer course of steroids. Furthermore, three of six patients required a second-line therapy to control ICIP, consistent with a more

aggressive disease course. The latter group may represent "steroid-refractory" ICIP (SR-ICIP), which we will discuss in detail in the following section.

Steroid-Refractory Pneumonitis

When patients do not respond to corticosteroids, further immunomodulation may be required. Agents such as IVIg, infliximab, mycophenolate mofetil, and cyclophosphamide are suggested by various society guidelines [17–19]. Much of the data supporting these medications' use comes from experience with other autoimmune diseases and had generally not been validated in ICIP other than in case reports or series. Outcomes are often poor, and because SR-ICIP is rare and often associated with severe disease, it will be challenging to conduct an adequately powered prospective randomized controlled trial comparing the various treatment options [71]. Agents are therefore usually chosen based on the patient's own underlying comorbidities as well as the clinician's or center's experience.

IVIg

Intravenous immunoglobulin (IVIg) is one of the drugs described for the treatment SR-ICIP and may be preferred over other immunomodulatory medications due to its milder side-effect profile. The mechanism for IVIg's anti-inflammatory effects in this setting is not firmly established, but may include regulation of inflammatory cells, inhibition of autoantibody-antigen pairing (therefore decreasing autoimmune response), and downregulation of cytokines and chemokines [72]. There have been case reports documenting the improvement in clinical and radiographic features of SR-ICIP after the administration of IVIg, including cases where improvement was observed within 72 hours of IVIg administration [73]. In a retrospective case series, seven patients with SR-ICIP received IVIg; two recovered, and one developed IVIg-related zoster [71]. Therefore, no high-quality studies have examined whether IVIg improves outcomes after SR-ICIP compared to usual care.

Infliximab

Infliximab is a monoclonal antibody directed at tumor necrosis factor (TNF) and commonly used in autoimmune conditions such as inflammatory bowel disease (IBD) and rheumatoid arthritis [74]. It has also emerged as a common second-line therapy for the treatment of ICI-related colitis (which histologically and pathophysiologically resembles IBD). The role of infliximab is less well established in patients with SR-ICIP. In one case series, nine patients were given infliximab for SR-ICIP, and four out of nine improved after infliximab therapy. Of note, each patient had a negative QuantiFERON test prior to initiation of infliximab, but the risk for infliximab-related infections is likely to be lower with the single dose (5 mg/kg) that

is given to treat SR-ICIP, as compared to long-term administration [75]. In another case series, five patients had SR-ICIP; two received infliximab alone, and three received infliximab with IVIg. All five patients died secondary to SR-ICIP or secondary infections [71]. Because of the risk of tuberculosis reactivation, we recommend that a baseline QuantiFERON test is obtained immediately upon the diagnosis of ICIP in case infliximab is needed later on; while rare, tuberculosis reactivation has been reported after a single dose of infliximab [76].

Mycophenolate Mofetil

Another option for the treatment of SR-ICIP is mycophenolate mofetil, an immunosuppressive agent that acts by depleting guanosine nucleotides in T- and B-cells leading to inhibited proliferation and suppression of both cellular and humoral immunity [77]. While all three guidelines (ASCO, NCCM, SITC) list mycophenolate mofetil as an option for the treatment of ICIP, minimal data exists in SR-ICIP. One series described two out of nine patients with SR-ICIP who improved with mycophenolate mofetil administration [31]. Mycophenolate mofetil is associated with opportunistic infections such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV) reactivation when used chronically. While the risk is likely lower when used for short periods of time, antiviral prophylaxis may be necessary in certain high-risk patients [78].

Cyclophosphamide

Cyclophosphamide is an alkylating agent which preferentially damages the DNA of rapidly proliferating lymphocytes, thus acting on both cellular and humoral immunity [78]. In a series of patients described by Nishino et al., two of the five patients that required immunosuppression beyond steroids received infliximab plus cyclophosphamide. Both patients died prior to discharge – one from complications of ICI pneumonitis, the other from invasive infections [11]. Another case report describes a patient with grade 4 ICI pneumonitis successfully treated with cyclophosphamide in combination with tacrolimus [79].

Aviptadil

Aviptadil, a synthetic form of human vasoactive intestinal peptide (VIP), is a novel inhaled anti-inflammatory therapy that was first studied in as a treatment option for patients with pulmonary sarcoidosis. Patients treated with inhaled aviptadil have decreased tumor necrosis factor-α in BAL samples as well as simultaneously increased regulatory T-cell activity and decreased effector T-cell activity. In a cohort of patients with sarcoidosis, cough and shortness of breath improved after therapy, but spirometry and lung volumes remained unchanged [80]. One report described a

patient with a recurrent SR-ICIP who had improved after ICI cessation and 6 months of inhaled aviptadil therapy [81]. Aviptadil, in its inhaled formulation, is a novel therapy that may be able to exert its immunomodulatory effects on inflamed lungs without affecting the systemic immunomodulation triggered by the ICI therapy. Further research is needed to better understand this novel therapy and whether its effect is truly local – an ideal agent would allow treatment of the toxicity while also continuing ICI therapy.

Outcomes After ICIP

Overall, ICIP is a relatively uncommon complication of immunotherapy but accounts for 35% of treatment-related fatalities, in the context of an overall rate of irAE-related fatalities of between 0.3% and 1.3% [27]. The overall fatality rate among those ICIP is estimated to be between 12% and 22.7% [14, 15, 27]. Given the morbidity and mortality associated with ICIP and other irAEs, careful considerations of patient-level risk factors should inform the decision to initiate ICI therapy. However, the risks are often considered tolerable, given that the cancers that are treated with ICIs are often otherwise untreatable and fatal – for example, metastatic melanoma. In patients with several risk factors for ICIP (prior radiation, prior parenchymal lung disease, etc.), ICIs may hasten mortality, but these patients may have few other viable options to treat their malignancies [15].

ICI Re-challenge

For many patients, treatment with an ICI represents second- or third-line therapy and can provide a lifeline for an otherwise fatal cancer. The risks of subsequent irAE when re-challenging with ICI must be weighed against this potential benefit for increased survival, especially since some irAEs may be associated with improved antitumor responses [82], though two recent meta-analyses suggested that this association between irAE and survival is not true for ICIP [83, 84]. ASCO guidelines recommend that in cases of grade 2 ICIP, ICI treatment may be reinstituted after ICIP is grade 1 or totally resolved. In grade 3 cases, ICI re-challenge is generally not recommended, but in rare cases may be considered if the benefit is overwhelming against the possible risk. The rate of recurrence of ICIP is estimated to be between 25% and 30%, though this data is derived from very small studies [8, 11, 14].

ICI Pleural Effusions

Pleural effusions associated with the initiation of ICI therapy have been rarely described but are often difficult to distinguish from disease progression or pseudoprogression. One case series described two patients treated with nivolumab who

were found to have rapidly progressive pleural effusions after the initiation of immunotherapy. Both patients had evidence of malignancy by pleural fluid cytology. One patient experienced resolution of the effusions with continued treatment with immunotherapy, suggesting that the effusions may have been a form of pseudoprogression as opposed to ICI toxicity [85]. Given that no report has adequately described that these effusions are related to immune-mediated injury and not some other process, the role of steroids or other immunosuppressants is not clear, and treatment is mainly focused on pleural drainage; indwelling pleural catheters may be considered in these patients as well, particularly since they may allow for ICI therapy to continue [9].

Sarcoidosis-Like Reactions

Sarcoidosis is known to occur as a rare irAE. Sarcoidosis is a systemic disease that can affect various organ systems and is characterized by the presence of granulomatous inflammation [86]. The most commonly affected organs are the lungs followed by the skin, eyes, liver, nerves, heart, and kidneys (in order of incidence of involvement) [87]. Pulmonary sarcoid was historically staged using the Scadding staging criteria that range from stage 0 (normal chest radiograph) and stage I (hilar or mediastinal lymph node enlargement) to stage IV (overt pulmonary fibrosis). This staging system has fallen out of favor given advancements in imaging modalities, but still adequately represents the wide range of clinical severity that sarcoidosis can present with [88]. Further information about the diagnosis and detection of sporadic sarcoidosis is available elsewhere [89].

The pathogenesis of sarcoidosis is driven by Th17.1 cells in the lung [90]. These cells secrete interferon gamma and therefore historically have been mistaken for Th1 cells, since Th1 cells were often identified on the basis of interferon gamma production instead of modern lineage tracing. Th17.1 cells may not produce interleukin-17 but are crucial to the interferon-mediated formation of granulomas. Interestingly, sarcoidosis is characterized by relative anergy in the peripheral blood, and this was thought to be due to high PD-1 expression in peripheral blood mononuclear CD4+ cells [91]. More recent data suggest that T-cell populations in the sarcoid lung may mimic T follicular helper cells, which secrete IL-21, and are crucial to the formulation of lymphoid organs in non-lymphoid tissue; unlike canonical T-cells, they express PD-1 as a marker of activation (specifically with regards to the ability to stimulate B-cells) and not exhaustion [92]. While B-cells are not found in great number in the BAL fluid from sarcoidosis patients, they are well-known to exist within areas of active inflammation in the sarcoid lung. Further work is necessary to define T-cell populations and function, but the mysteries surrounding the pathogenesis of sarcoidosis are slowly being unraveled.

103 cases of ICI-induced sarcoidosis were identified by the World Health Organization pharmacovigilance database between 1967 and 2019; only two cases were fatal [93]. Ipilimumab is the ICI most commonly associated with sarcoidosis-like reactions, potentially due to the effect of CTLA-4 inhibition on the activation of

T-cell populations implicated in sarcoidosis [21, 94]. Furthermore, these reactions have been most commonly noted in melanoma, where Th17.1 cells may correlate with a better prognosis than in other cancers [95, 96]. Because of the recent data that PD-1 is a marker of disease activity and not anergy in sarcoidosis, this may explain the lower incidence of sarcoid-like reactions after PD-1 or PD-L1 inhibition. ICI-sarcoidosis presents in a variety of ways but most often affects the lung and skin. One case series reported by Nishino et al. described patients with parenchymal lung masses (without accompanying lymphadenopathy) that appeared after initiation of ICI treatment. These masses were biopsied and found to be sarcoid-like in pathology – containing non-necrotizing granulomas with lymphocytic infiltrate [97]. They note the importance of distinguishing these masses from disease progression, since ICI therapy may be continued in the case of sarcoidosis [97, 98]. Other manifestations of ICI-sarcoidosis include hilar lymphadenopathy, splenomegaly, interstitial nephritis, and cutaneous symptoms, all with non-necrotizing granulomatous inflammation found on biopsy [99–101]. Much like in sarcoidosis, if the patient is asymptomatic, treatment may not be required, but at the same time, little is known about how to best treat ICI-sarcoidosis in symptomatic cases.

ICI-Related Eosinophilic Lung Diseases

Eosinophilic lung diseases include a broad spectrum of disorders and phenotypes with a variety of triggers. Two of these diseases have been described as having been triggered by ICIs. Eosinophilic pneumonia is defined as an acute respiratory illness accompanied by upper lobe-predominant infiltrates on imaging, pulmonary eosinophilia on BAL, and/or eosinophilic pneumonia on biopsy, in the absence of another eosinophilic disorder [102]. Eosinophilic bronchitis is a more newly defined condition characterized by hypereosinophilia (in the peripheral blood and/or in BAL), airflow obstruction on pulmonary function testing that does not improve even with 4–6 weeks of inhaled corticosteroid, and characteristic biopsy (inflammatory bronchiolitis with eosinophilic infiltration) or imaging findings (centrilobular nodules, branching, and tree-in-bud opacities) [103, 104]. The exact etiology of the condition remains unknown, and it is often mistaken for severe asthma [105].

A recent retrospective review of a French pharmacovigilance database documented 37 cases of hypereosinophilia secondary to treatment with ICIs; four patients described in this review presented with eosinophilic pulmonary disorders – two with eosinophilic pneumonia and two with eosinophilic bronchiolitis. These eosinophilic disorders often respond to corticosteroids, but the availability of anti-IL-5 inhibitors may allow for ICI continuation without affecting antitumor responses and simultaneously treating the eosinophilic inflammation [105]. Eosinophilic reactions in the lung are very rare, despite the observed peripheral eosinophilia after ICI therapy, and therefore there is scant data to guide appropriate treatment when they do occur.

Conclusion

The pulmonary toxicities of ICIs are diverse in severity and presentation and can lead to significant morbidity and mortality. Many of these toxicities are tolerable given the severity of underlying cancers. Further work is needed to improve diagnostic and therapeutic strategies for ICIP and other ICI-related pulmonary toxicities, particularly in the case of SR-ICIP.

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Chapter 15
Rheumatology (Arthritis and Myositis)

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Abstract Rheumatic immune-related adverse events (irAEs) associated with immune checkpoint inhibitor (ICI) therapy in patients with cancer can be grouped into articular, muscular, granulomatous, vasculitic, and other systemic irAEs. In a large registry study, the two most prevalent types of rheumatic irAEs were articular (36% of cases) and muscular (34%) [1]; these two types are the focus of this chapter. The articular cluster is comprised of arthralgias and arthritis, and the muscular cluster is comprised of myalgias, myositis, and polymyalgia rheumatica (PMR)-like syndrome. Complete resolution of arthritic and myositis symptoms is expected in most patients after the discontinuation of ICI and often a course of treatment with immunosuppression. However, persistent inflammatory arthritis that requires prolonged DMARDs (disease-modifying antirheumatic drugs) has been reported.

Keywords Inflammatory arthritis · Myositis · Rhabdomyolysis · Polymyalgia rheumatica-like syndrome · Giant cell arteritis

Chapter debriefing: PowerPoint video presentation is provided at the end of the chapter.

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Abbreviations

ANA	Anti-nuclear antibody
CK	Creatine kinase
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CTLA- 4	Cytotoxic T-lymphocyte-associated protein 4
DMARD	Disease-modifying antirheumatic drug
GCA	Giant cell arteritis
ICI	Immune checkpoint inhibitor
irAE	Immune-related adverse events
PD-1	Programmed cell death-protein1
PD-L1	Programmed death-ligand 1
PMR	Polymyalgia rheumatica
RA	Rheumatoid arthritis
ReA	Reactive arthritis
RS3PE	Remitting seronegative symmetrical synovitis with pitting edema

Articular irAE

Epidemiology

Arthralgia and arthritis are the most common rheumatic irAEs after ICI therapy [1, 2]. Randomized clinical trials and retrospective chart review studies have revealed that 10.0–13.3% and 1.8–10.0% of patients develop inflammatory arthralgia and arthritis, respectively, after treatment with programmed cell death 1 (PD-1) inhibitors with or without cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors [3–5]. A prospective observational study showed that 20 of 524 cancer patients (3.8%) developed arthritis after PD-1 inhibitor monotherapy [6]. Of note, CTLA-4 monotherapy rarely results in arthritis, and the incidence of arthralgia occurring as an irAE (arthralgia-irAE) is also lower in CTLA-4 monotherapy compared with either PD-1 inhibitor monotherapy or combined PD-1 and CTLA-4 inhibitor therapy [3].

Clinical Characteristics

Patterns of arthritis include monoarthritis, reactive arthritis (ReA)-like oligoarthritis, rheumatoid arthritis (RA)-like-polyarthritis, remitting seronegative symmetrical synovitis with pitting edema (RS3PE), and undifferentiated [7]. The knee is the most common joint affected followed by small joints [8]. While most irAEs develop within 12 weeks after the first ICI infusion [9], arthritis-irAE occurs later [2, 5, 8, 10]. Monoarthritis develops at a median of 9 months (range 1–24 months), and

oligoarthritis and polyarthritis develop at a median of 3 months (range 1–9 months and 1 day–24 months, respectively) after initiation of ICI therapy [7]. Of note, arthritis can develop even after completion of ICI therapy [11]. Most patients with arthritis-irAE have negative autoantibodies, including antinuclear antibody (ANA), rheumatoid factor, and anti-cyclic citrullinated peptide (CCP) antibody [12].

Studies suggest that clinical manifestations and underlying mechanisms of arthritis-irAE might differ by ICI regimen [8, 13]. For example, ReA-like arthritis is preferentially associated with arthritis after combined ICI therapy, while RA-like arthritis is more prevalent after anti-PD-1 monotherapy [8]. The level of serum C-reactive protein (CRP) in patients with arthritis after combined ICI therapy is higher than in patients with arthritis after anti-PD-1 monotherapy [8]. Importantly, patients with arthritis induced by combined ICI therapy tend not to respond to steroid monotherapy and require steroid-sparing disease-modifying antirheumatic drugs (DMARDs) more frequently [8].

Management

Detailed rheumatologic history and physical examination are critical in diagnosing arthritis/arthralgia-irAE. Imaging modalities such as magnetic resonance imaging (MRI), ultrasound (U/S), computed tomography (CT), and positron emission tomography (PET)-CT can also aid with diagnosis [10, 14, 15]. Notably, a study by Leipe et al. [10] demonstrated that synovitis can be detected in patients with arthritis-irAE using CT and PET-CT, routinely used imaging modalities in managing cancer. In seven patients with arthritis-irAE who underwent PET-CT and conventional CT during standard of care for their cancer, synovitis was detected on CT in 6 of 41 evaluable joints and on PET-CT in 10 of 41 joints. These observations suggest that PET-CT and conventional CT, routine tests done as a standard of oncologic care and readily available at the time of rheumatologic evaluation, would be helpful in differentiating arthritis-irAE from arthralgia-irAE, i.e., joint pain without synovial diseases.

Arthritis/arthralgia-irAE can severely affect a patient's quality of life and can cause permanent damage to their joints [14–16]. Therefore, early detection and treatment of arthritis/arthralgia-irAE is critical. Several rheumatology and oncology societies, including the European Alliance of Associations for Rheumatology (EULAR), the Society for Immunotherapy of Cancer (SITC), National Comprehensive Cancer Network (NCCN), and American Society of Clinical Oncology (ASCO), have published guidelines for managing arthritis/arthralgia-irAE [17–20]. In general, mild grade 1 (according to the Common Terminology Criteria for Adverse Events ([CTCAE]) arthritis can be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) while continuing ICIs. For arthritis/arthralgia-irAE of CTCAE grade 2 or higher, steroid therapy is warranted. If one or two joints are inflamed, intra-articular corticosteroid injections can be considered instead of systemic steroid therapy. If the patient cannot taper prednisone (or the equivalent) below 10 mg within 4 weeks after its initiation, DMARDs should be considered. We

have demonstrated the therapeutic efficacy of interleukin (IL)-6 inhibitor for arthritis-irAE [21]. Potential synergism in antitumor effects of IL-6 inhibitor and ICIs was demonstrated in animal models [22]. We recommend inhibition of IL-6 (or IL-6 receptor) as the first-line steroid-sparing treatment for arthritis-irAE. Cases of arthritis-irAE that responded well to tumor necrosis factor alpha inhibitors have been reported [12]. Recent studies also revealed that conventional DMARDs, including sulfasalazine, hydroxychloroquine, and methotrexate, have also shown therapeutic efficacy for arthritis-irAE [23]. ICIs should be held in patients whose arthritis/arthralgia is grade 2 or higher; ICIs can be resumed once symptoms are well controlled and prednisone is tapered below 10 mg. For grade 3 and grade 4 arthritis/arthralgia, ICIs can be resumed if the arthritis/arthralgia recovers to grade 1 or less; however, this decision is best made in consultation with a rheumatologist [24], with detailed plans to monitor recurrence of arthritis/arthralgia or development of other irAEs. Patients with arthritis/arthralgia-irAE should be referred to a rheumatologist if (1) symptoms persist >2 weeks, (2) the CTCAE grade is ≥2, and/or (3) prednisone (or an equivalent) cannot be tapered below 10 mg [19].

Interestingly, there have been case reports/series of patients with newly developed seropositive RA or psoriatic arthritis (PsA) after ICI therapy [21, 25, 26]. In these situations, RA and PsA developed faster than most arthritis-irAE after initiation of ICIs [7]. Similar to arthritis-irAE, patients who develop RA or PsA after ICI therapy are initially treated with glucocorticoids. For steroid-resistant new-onset RA, we have successfully used anti-IL-6 [21]. For steroid-resistant new-onset PsA, traditional DMARDs were used, and a successful treatment case was reported using apremilast [27].

Long-Term Complications and Follow-Up

Two-thirds of patients presenting with ICI-induced arthritis responded to steroid alone, or with additional DMARDs with control of their arthritis, and a third achieved full remission of their arthritis. About 4% of such patients showed continued arthritis and required ongoing treatment.

Near half of patients who experienced ICI-induced arthritis were able to continue with their ICI therapy [28]. Routine clinical follow-up by rheumatologist with disease activity monitoring and therapy adjustment to avoid long-term disability is needed.

Regarding cancer response to ICI therapy, studies showed that patients with arthritis/arthralgia-irAE have superior antitumor responses to ICI therapy compared with patients who did not experience irAEs [6, 10, 29]. Nevertheless, because high-dose steroid significantly abrogate antitumor efficacy induced by ICIs and arthritis/arthralgia-irAE frequently require long-term usage of high-dose steroid [2, 30, 31], mechanism-driven therapeutic strategies need to be formulated to pinpoint arthritis-irAE while preserving antitumor immunity.

Muscular irAEs

Epidemiology

The second most common rheumatic irAE is muscular. The reported prevalence of myalgia ranges from 2% to 21% [32]. Myositis occurs less frequently and has been reported in 0.6% of patients taking ICI therapy [33]. The majority of myositis cases occurred following treatment with anti-PD-1 agents (single or combination therapy), although anti-CTLA-4 agents have also been implicated [32]. In an analysis of VigiBase, the World Health Organization global database of individual case safety reports, Anquetil et al. [34] identified 180 patients with ICI-induced myositis. The median age of these patients was 71 years, and 62% were male. The current hypothesis is that ICI-induced myositis occurs as a de novo inflammatory manifestation rather than the uncovering of a paraneoplastic syndrome [35, 36].

Clinical Characteristics

Myositis presents with varying degrees of muscle weakness and/or pain. The time to development of myositis-irAE is typically shorter than for other rheumatic irAEs, with a mean onset of 25 days [37, 38]. The spectrum of disease presentation is wide, ranging from asymptomatic creatine kinase (CK) elevation to complete inability to walk. Myalgia, proximal muscle weakness, and fatigue are the predominant symptoms. It is paramount to ask the patient about dyspnea. Presence of dyspnea signals more advanced myositis involving respiratory muscles, or possible concomitant myocarditis, which occurs in 16–40% of patients with ICI-associated myositis [38]. It is also key to ask the patient about ptosis, diplopia, dysphagia, and dysarthria, as these symptoms may signal concomitant myasthenia gravis, which is present in up to 25% of patients [37]. Hepatitis has also been reported in 8–10% of patients with ICI-induced myositis [38]. Asking about rash and thorough skin examination are a necessity as there have also been a few reports of patients presenting with classic dermatomyositis rash [39]. The symptoms of ICI-associated myositis may have a more sudden onset and less fluctuation than in classic polymyositis and dermatomyositis [39, 40].

Management

Evaluation begins with a detailed history and physical examination, paying close attention to the musculoskeletal, cardiac, neurologic, and skin examinations. Once ICI-associated inflammatory myopathy is suspected clinically, serum CK, aldolase,

liver panel, erythrocyte sedimentation rate (ESR), CRP, kidney panel, urinalysis, and urine myoglobulin should be assessed. Serum CK and aldolase levels allow evaluation for muscle inflammation. A liver panel with elevated transaminases can also point toward muscle inflammation or liver injury from concomitant hepatitis. ESR and CRP levels allow evaluation for general inflammation and along with CK, can be used for monitoring of disease activity. Kidney panel, urinalysis, and urine myoglobulin will help in evaluation for rhabdomyolysis and renal failure. If rhabdomyolysis is present, urinalysis will show a large amount of blood on the dipstick but will have few red blood cells. This indicates the presence of myoglobulin, which the urine myoglobulin level can confirm.

Serum myositis-associated antibodies should also be checked. These include autoantibodies against Jo-1, Mi-2, SRP, PL-7/12, EJ, OJ, TIF, PM-Scl, MDA5, RNP, Ku, and Ro [38]. Myositis antibodies are positive in approximately 30% of patients with ICI-induced myositis [39]. The paraneoplastic autoantibody panel should also be obtained, of which anti-striated muscle antibody has been reported in many cases [41, 42]. Muscular involvement should be objectively assessed using electrodiagnostic studies and MRI [38]. Electrodiagnostic studies will show evidence of an irritable myopathy [43]. MRI will show muscular enhancement. Evidence of fasciitis on MRI has also been reported [44]. The gold standard for the diagnosis of myositis is a muscle biopsy showing lymphocytic infiltrates [43]. Notably, a study by Touat et al. [45] analyzed ten patients with ICI-associated myopathy and found that their muscle biopsy specimens consisted mainly of CD68+ cells expressing PD-L1 and CD8+ cells expressing PD-1.

All patients with ICI-associated myopathy should undergo cardiac evaluation for myocarditis [37], including troponin level and electrocardiogram. Further tests including echocardiogram and cardiac MRI should also be considered. If oculomotor or bulbar symptoms are present, then concomitant myasthenia gravis should be suspected, and treatment appropriate for both myositis and myasthenia gravis should be initiated. Anti-striated muscle antibody and/or anti-acetylcholine receptor antibodies have been detected in such patients [37, 42]. Of note, a study of patients with thymomas by Mammen et al. found anti-acetylcholine receptor antibodies were detected in the sera of patients prior to ICI therapy and were associated with the development of myositis [46]. The 2018 ASCO guidelines classify myositis-irAE from grade 1 to grade 4. Grade 1 is mild weakness. Grade 2 is moderate weakness that limits age-appropriate instrumental activities of daily living. Grades 3–4 are severe weakness limiting self-care activities of daily living. In all grades, muscle pain may or may not be present [17]. In the presence of elevated muscle enzyme levels, other treatable causes, such as myocarditis, endocrinopathy, and rhabdomyolysis, should be worked up at the same time.

Treatment depends on the severity of the irAE. The following treatment recommendations are adapted from the 2018 ASCO guidelines. For myalgias and grade 1 myositis, acetaminophen or NSAIDs can be used if there are no contraindications. ICIs can be continued. If corticosteroids are offered, patients should be treated as grade 2. For grade 2, if the CK level is elevated by 3 times or more, prednisone or

an equivalent should be initiated at 0.5–1 mg/kg. The patient should be referred to rheumatology. ICIs should be held, but can be re-started with caution if the symptoms have resolved, CK level has normalized, and prednisone dose is <10 mg. Permanent discontinuation of ICIs may be needed when there are objective findings of myositis, such as MRI or muscle biopsy-proven myositis. For grade 3 or grade 4, hospitalization for severe weakness should be considered, and the patient should be evaluated by rheumatology. Prednisone (1 mg/kg) or intravenous (IV) methylprednisolone boluses (1–2 mg/kg) should be given. Plasmapheresis and intravenous immunoglobulin (IVIG) should also be considered if severe compromise is present. Other immunosuppressive agents, such as azathioprine, methotrexate, or mycophenolate, should be considered. If symptoms or CK levels fail to improve after 4–6 weeks of therapy, rituximab may be used. ICIs should be held until symptoms or the CK level decreases to grade 1 or less while the patient is off immunosuppressants, and great caution is advised if the patient will be re-challenged with an ICI. If there is evidence of cardiac involvement in patients with myositis, the ICI should be permanently discontinued [17]. Patients with concomitant myasthenia gravis should be managed by a neurologist with reagents such as pyridostigmine, IVIG, and/or plasma exchange [43].

There have been a few reports of rhabdomyolysis in patients receiving immunotherapy [41, 47]. Rhabdomyolysis can be concurrent with polymyositis. As stated above, if rhabdomyolysis is a concern, urinalysis and urine myoglobulin should be checked. The cornerstone of therapy is aggressive IV hydration. After adequate hydration, furosemide can be considered if urine output is inadequate. By increasing tubular flow, loop diuretics can decrease precipitation of myoglobulin. In our experience, concurrent myositis and rhabdomyolysis secondary to ICI therapy do not respond to corticosteroids or other immunosuppressive agents alone; aggressive hydration is necessary.

Long-Term Complications and Follow-Up

Patients with myositis alone are expected to have symptom and elevated CK level resolved and have longer survival comparing to patient with overlapping syndrome [35]. Patients with myositis and overlapping myocarditis, myasthenia gravis, hepatitis, and rhabdomyolysis can have a more severe clinical course. Myocarditis can be complicated by complete heart block and reduction in the left ventricular ejection fraction [48]. If a patient with myositis is not treated, severe proximal weakness may lead to immobility and the inability to perform self-care activities of daily living. ICI-associated myositis is a dangerous condition, and death occurs in approximately 21% of patients with this condition [34].

Patients with grade 2 or higher myositis-irAE should be concomitantly managed with a rheumatologist. Symptoms, CK level, ESR, and CRP level should be serially assessed [17]. If the myocardium is involved, serial troponin and electrocardiograms should be assessed, and a cardiologist should be consulted.

Polymyalgia Rheumatica-Like Syndrome

Epidemiology

The reported prevalence of PMR-like syndrome in the setting of ICI therapy ranges from 0.2% to 2.1% [49]. In an epidemiologic review, Abdel-Wahab et al. [32] identified 24 case reports of patients with PMR-like syndrome induced by ICI therapy. The median age of these patients was 71.5 years, similar to traditional PMR's presentation, and ICI-induced disease occurs in older adults [50]. Among this population, 64% were male, and 92% received anti-PD-1 agents (single or combination therapy). The median time after initiation of immunotherapy to onset of PMR-like syndrome was 3.3 months [32].

Clinical Characteristics

Symptoms of PMR-like syndrome are similar to those of traditional PMR, including hip girdle and shoulder stiffness and pain without objective weakness. However, in an analysis of 20 patients from 3 centers who were diagnosed with PMR-like syndrome, Calabrese et al. [50] found that some of the patients had more severe symptoms and had atypical features. These include concurrent sicca symptoms, arthritis in knee and/or hand joints, and some lack of elevated acute-phase reactants. Some patients showed response to NSAIDs alone, but many patients required much higher doses of glucocorticoids for symptom control compared to primary PMR.

Similar to traditional PMR, ICI-induced disease has also been associated with giant cell arteritis (GCA) [51]. All patients with PMR-like syndrome should be questioned about concomitant vision loss or diplopia, headache, and jaw claudication.

Management

Evaluation begins with a detailed history and physical examination, paying close attention to the head, eyes, nose, throat, and musculoskeletal systems. Patients with PMR-like syndrome may have limited active range of motion of their shoulders and hips, but they usually do not have objective weakness. Patients with concomitant GCA may exhibit vision loss, temporal artery prominence, and scalp tenderness over the temporal artery.

Once ICI-induced PMR-like syndrome is suspected, ESR, CRP, CK, ANA, rheumatoid factor, and anti-CCP should be obtained [17]. ESR and CRP level will allow evaluation for inflammation. CK assessment will assist with ruling out myositis. ANA, rheumatoid factor, and anti-CCP will assist with evaluating for arthritis.

Ultrasound or MRI to evaluate for tendinosis and bursitis may be helpful in patients who have typical PMR symptoms, but not elevated ESR and CRP level [52]. If GCA is suspected, in addition to the previously listed laboratory studies, prompt temporal artery biopsy after initiating high-dose glucocorticoids is indicated.

The 2018 ASCO guidelines [17] classify PMR-like syndrome irAEs from grade 1 to grade 4. Grade 1 is mild stiffness and pain. Grade 2 is moderate stiffness and pain that limits age-appropriate instrumental activities of daily living. Grades 3–4 are severe stiffness and pain limiting self-care activities of daily living.

Treatment depends on the severity of the irAE. The following treatment recommendations are adapted from the 2018 ASCO guidelines, with modifications. For grade 1 PMR-like syndrome, analgesia with NSAIDs or acetaminophen should be initiated, and ICIs can be continued. For grade 2, prednisone (20 mg) should be started. If symptoms and inflammatory markers are improving, the steroids can be tapered over 4 weeks. The ICI should be held until levels of inflammatory markers have decreased and symptoms are controlled on <10 mg of prednisone. If there is no improvement or higher doses of steroids are needed, the case is escalated to treatment for grade 3. Rheumatology referral is indicated at this point. For grades 3–4, consider steroid-sparing agents such as IL-6 inhibitors or methotrexate [17]. Anti-IL-6 is FDA approved for GCA treatment and should be considered early as the first steroid-sparing reagent in cancer patients receiving ICIs. This strategy minimizes the immunosuppression effects from steroids and other traditional DMARDs. ICIs should be held and re-challenged with caution when symptoms are grade 1 or less and the patient is receiving <10 mg of prednisone. Notably, a case series and systematic review by Calabrese et al. found 37% of identified cases of ICI-induced PMR-like syndrome required more aggressive glucocorticoid therapy than is traditionally required to treat PMR (>20 mg) [50]. We have similar experience with patients requiring prednisone of at least 40 mg daily to control their PMR-like syndrome. Even after the addition of anti-IL-6, a low dose of prednisone has been needed for full symptom control if the ICI is continued. If the patient has concomitant GCA, the patient should be treated with 60 mg prednisone daily for 2–4 weeks and then the dose tapered over 8–12 weeks. ICIs should be held and resumed once inflammatory markers and symptoms have improved and the patient is on <10 mg prednisone daily. If symptoms are not improving, a steroid-sparing agent can be added.

Long-Term Complications and Follow-Up

All patients with PMR-like syndrome with or without concomitant GCA should be monitored with serial ESR and CRP assessment. The major complications of PMR-like syndrome are in patients with concomitant GCA. Complications include vision loss and blindness, scalp necrosis, aortic aneurysm and rupture, and cerebrovascular accident [53].

Table 15.1 Outline of arthritic and muscular irAE management

irAE	Clinical presentations	Evaluation	Management
Arthritis	Joint pain Joint swelling Joint stiffness	Lab: ESR, CRP, RF, anti-CCP, ANA X-rays	NSAIDs Steroid Anti-IL-6 Other DMARDs
Myositis	Weakness Muscle pain	Lab: CK, aldolase, AST, TSH, urine analysis, myositis panel, paraneoplastic panel MRI Muscle biopsy	Steroid PLEX IVIG Other DMARDs
Polymyalgia rheumatica	Proximal muscle pain and stiffness Blurred vision and headache	Lab: ESR, CRP, CK, TSH, cortisol Temporal artery biopsy	Steroid Anti-IL-6 Other DMARDs

Conclusion

With the increasing application of ICIs in the treatment of various types of cancer, rheumatic immune toxicity is emerging as a new field for rheumatologists and oncologists caring for cancer patients. We have summarized three common rheumatic complications of ICI therapy here. These include inflammatory arthritis, myositis, and polymyalgia rheumatica-like syndrome. Patients with rheumatic irAEs demonstrate some features and response similar to primary rheumatology illness. However, they also demonstrate certain notable different features. So far, the mainstay of treatment has been glucocorticoids. As we have summarized above, steroid-sparing DMARDs, either traditional or biological, are used with certain degrees of success in managing such patients (Table 15.1).

Diagnosis and treatment for ICI-induced rheumatic diseases can be complex. More research is needed to define the molecular and cytokine signatures of different types of rheumatic irAEs that can lead to more targeted therapy to effectively manage these complications to ensure the safety of cancer treatment. In addition, more studies are needed to further define other rarer rheumatic complications such as sarcoidosis, Sjogren's syndrome and vasculitis, etc.

Conflict of Interest None of the authors have any conflicts of interest to disclose.

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