Immune Checkpoint Inhibitor Therapy–related Pneumonitis: Patterns and Management

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Abbreviations: AIP = acute interstitial pneumonia, ARDS = acute respiratory distress syndrome, CTCAE = Common Terminology Criteria for Adverse Events, CTLA-4 = cytotoxic T-lymphocyte antigen-4, HP = hypersensitivity pneumonitis, ICI = immune checkpoint inhibitor, irAE = immune-related adverse event, NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia, PD-1 = programmed cell death protein 1, PD-L1 = programmed cell death ligand 1

RadioGraphics 2019; 39:1923–1937

https://doi.org/10.1148/rg.2019190036

Content Codes: CH CT OI

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Describe the indications and mechanisms of action of ICIs and the pathophysiology of ICI therapy–related pneumonitis.
- Illustrate the imaging patterns of ICI therapy–related pneumonitis and related clinical classification schemes.
- Discuss the management of irAEs and the role of the radiologist in treatment course planning in these complex cases.

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In recent years, the use of immune checkpoint inhibitor (ICI) therapy has rapidly grown, with increasing U.S. Food and Drug Administration approvals of a variety of agents used as first- and second-line treatments of various malignancies. ICIs act through a unique mechanism of action when compared with those of conventional chemotherapeutic agents. ICIs target the cell surface receptors cytotoxic T-lymphocyte antigen-4, programmed cell death protein 1, or programmed cell death ligand 1, which result in immune system–mediated destruction of tumor cells. Immune-related adverse events are an increasingly recognized set of complications of ICI therapy that may affect any organ system. ICI therapy–related pneumonitis is an uncommon but important complication of ICI therapy, with potential for significant morbidity and mortality. As the clinical manifestation is often nonspecific, CT plays an important role in diagnosis and triage. Several distinct radiographic patterns of pneumonitis have been observed: *(a)* organizing pneumonia, *(b)* nonspecific interstitial pneumonia, *(c)* hypersensitivity pneumonitis, *(d)* acute interstitial pneumonia–acute respiratory distress syndrome, *(e)* bronchiolitis, and *(f)* radiation recall pneumonitis. Published guidelines outline the treatment of ICI therapy–related pneumonitis based on the severity of symptoms. Treatment is often effective, although recurrence is possible. This article reviews the mechanism of ICIs and ICI therapy complications, with subsequent management techniques and illustrations of the various radiologic patterns of ICI–therapy related pneumonitis.

Introduction

In the last decade, the introduction of immunotherapy has revolutionized the management and treatment approaches for a number of malignancies. As opposed to conventional cytotoxic chemotherapy, which acts by a variety of mechanisms and stages of the cell cycle to directly interfere with cancer cell growth, cancer immunotherapy harnesses the immune system to limit the ability of cancer cells to evade the immune system and combat proliferation. Immunotherapy can be classified as either passive or active. In passive therapy, immunoglobulins are administered and bind to tumor-associated antigens, prompting clearance by the immune system. Active immunotherapy, on the other hand, stimulates the immune system to target tumor antigens and attack tumor cells. This latter category includes immune checkpoint inhibitor (ICI) therapy.

ICIs target the cell surface receptors cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed cell death ligand 1 (PD-L1), resulting in immune system destruction of tumor cells. An ICI therapy first gained U.S. Food and Drug Administration (FDA) approval in 2011 for the treatment of metastatic and unresectable melanoma after phase III

TEACHING POINTS

- ICIs target the cell surface receptors CTLA-4, PD-1, or PD-L1, resulting in immune system destruction of tumor cells.
- Presenting symptoms of ICI therapy–related pneumonitis are variable and nonspecific, necessitating a high index of suspicion and awareness among members of the patient's care team.
- OP pattern is the most commonly observed ICI therapy–related pneumonitis pattern.
- ICI therapy–related pneumonitis is treated by symptom severity as stipulated by the recent American Society of Clinical Oncology Clinical Practice Guideline.
- With ICI therapy cessation and appropriate steroid or immunosuppressive therapy initiation, management of ICI therapy–related pneumonitis has been shown to be highly effective.

trials in which ipilimumab, a CTLA-4 inhibitor, demonstrated increased overall survival in previously treated patients (1). Since then, ICI therapy has expanded to include multiple agents targeting different receptors that have current FDA approval for the treatment of a variety of solid and hematologic malignancies (Table 1).

While many ICI therapies are initiated after failure of first-line or established therapies, several drugs are approved as first-line therapies. For example, pembrolizumab, a PD-1 inhibitor, has FDA approval as frontline treatment of advanced epidermal growth factor receptor and anaplastic lymphoma kinase wild-type non–small cell lung cancer in which tumors have at least 50% PD-L1 expression. ICI therapy can also be used with nivolumab, a PD-1 inhibitor, and ipilimumab, a combination that has FDA approval for the treatment of colorectal cancer and renal cell carcinoma. Furthermore, ICI therapy may also be combined with conventional chemotherapies given the ability of cytotoxic chemotherapy to potentiate the immune response of ICIs (2). With ongoing ICI clinical trials, the number of approvals and combinations and complexity of treatment regimens is expected to grow in the foreseeable future.

While the increased activation of the immune system is responsible for the therapeutic efficacy of ICI therapy, it is also the driver behind the immune-related adverse events (irAEs) of these therapies. Many of these adverse events are unique from those previously observed with conventional chemotherapy regimens. A subset of irAEs is pneumonitis, which is an important and potentially fatal complication of ICI therapy and is the focus of this article. We review the mechanism of ICIs, discuss the pathophysiology and clinical presentation of ICI therapy–related pneumonitis with associated imaging manifestations, and highlight important aspects of treatment and monitoring.

Immune Checkpoint Inhibitors

Mechanism of Action

ICIs ultimately act by inhibiting the signal pathways responsible for the suppression of T-cell–mediated tumor destruction. Normally, an important function of T cells is in the cell-mediated clearance of tumor cells. In the presence of a foreign cell such as a tumor cell, antigen-presenting cells, including dendritic cells or macrophages, incorporate and present a tumor antigen through a major histocompatibility complex, which subsequently binds to a T-cell receptor. In the setting of a requisite costimulatory interaction such as the CD28 receptor, T-cells become activated and further activate a cascade of antitumor activity (3,4). During the process of T-cell activation, various inhibitor receptors also become upregulated, acting as immune checkpoints to limit the overstimulation of the immune response (3). Two critical pathways for ICIs are the CTLA-4 and PD-1 pathways, which normally function to attenuate T-cell response and action (Fig 1) (5,6).

Despite the presence of various cell-mediated immune response pathways, tumor cells have developed means of evading the natural tumor response system of the body. Although this occurs through multiple mechanisms, the CTLA-4 and PD-1 pathways play an important role for tumor proliferation. For example, increased CTLA-4 binding in the presence of certain tumors cells leads to competitive inhibition of costimulatory CD28 binding, leading to decreased T-cell activation. Also, tumors may increasingly express PD-L1 receptors causing decreased T-cell activity and tumor proliferation (7). Thus, blockade of key portions of either or both of these immune checkpoint pathways is thought to be responsible for the antitumoral activity with ICIs (Fig 1).

Imaging Response Criteria

Because of their unique mechanism of action, ICI therapies may produce imaging response patterns that differ from those depicted with conventional chemotherapies. Given the cytotoxic effect of conventional therapies, therapy success (for example in the Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) is determined by the interval disappearance of or decrease in the size of lesions, with treatment failure suggested by increased lesion size or the appearance of new lesions (8). However, conventional imaging response criteria such as RECIST 1.1 have shortcomings in the evaluation of treatment response for ICI therapy, leading to the potential for premature cessation of therapy in patients who might otherwise show benefit with therapy (9).

Table 1: FDA-approved ICI Therapy Agents

Drug	Target	Indications
Ipilimumab	CTLA-4	Melanoma, RCC (with nivolumab), colorectal cancer (with nivolumab)
Nivolumab	PD-1	Melanoma, small cell lung cancer, NSCLC, RCC, Hodgkin lymphoma, head and neck SCC, urothelial carcinoma, colorectal cancer, HCC
Pembrolizumab	PD-1	Melanoma, NSCLC, Hodgkin lymphoma, head and neck SCC, urothelial carcinoma, colorectal cancer, HCC, gastric adenocarcinoma, cervical cancer, Merkel cell carcinoma
Cemiplimab	PD-1	Cutaneous SCC
Durvalumab	PD-L1	Urothelial carcinoma, NSCLC
Atezolizumab	PD-L1	Urothelial carcinoma, NSCLC
Avelumab	PD-L1	Merkel cell carcinoma, urothelial carcinoma

Note.— HCC = hepatocellular carcinoma, NSCLC= non–small cell lung cancer, RCC = renal cell carcinoma, SCC = squamous cell carcinoma.

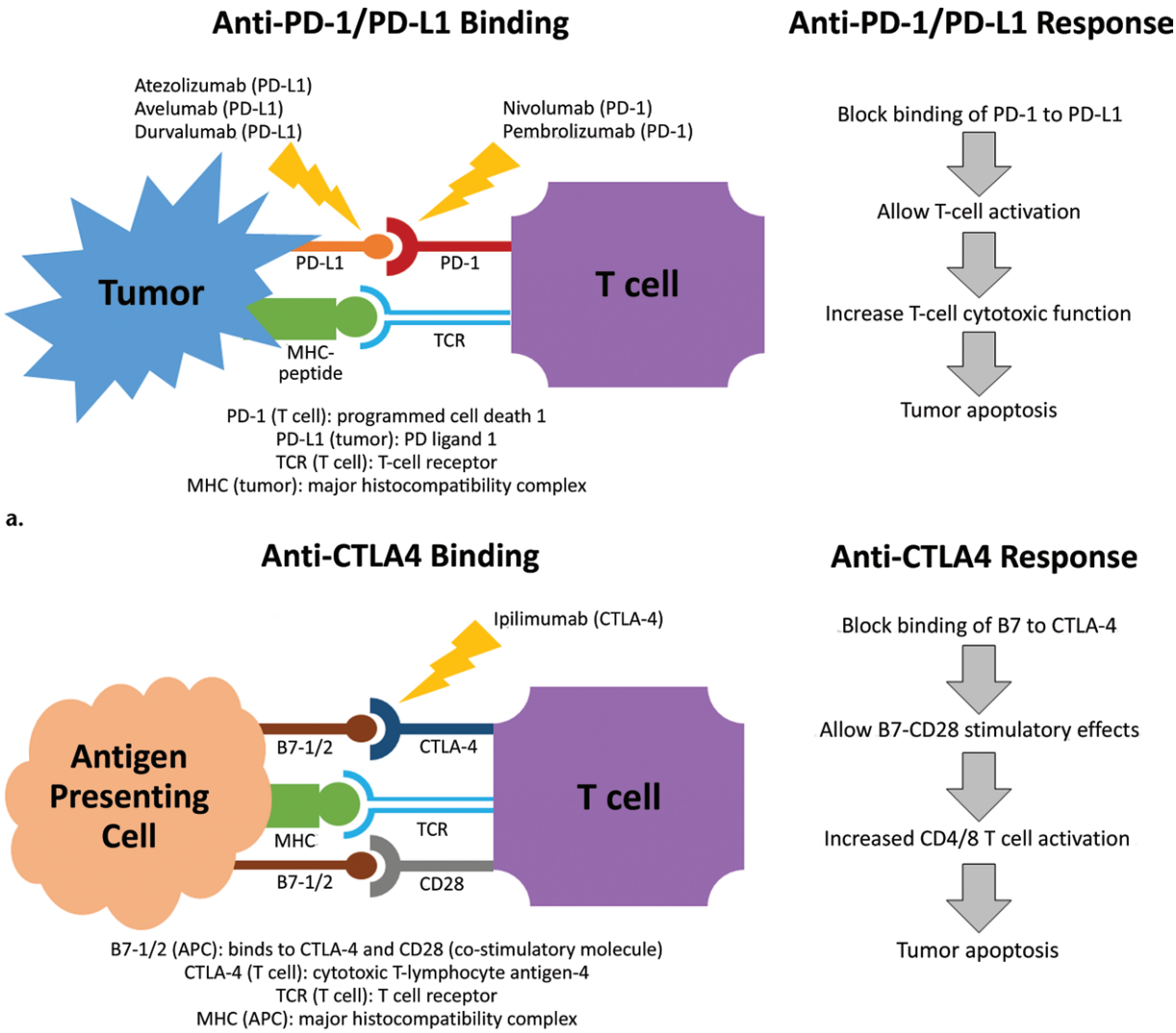


Figure 1. Illustrations show the mechanisms of action (left) of ICIs and the downstream tumor effects (right) for PD-1 and PD-L1 **(a)** and CTLA-4 **(b)** inhibitors. *APC* = antigen-presenting cell, *B7-1/2* = ligands B7-1 and B7-2.

Several key differences in the response patterns of ICI therapeutic agents compared with those of cytotoxic agents include the potential initial transient worsening of disease burden, either through lesion enlargement or the appearance of new lesions (ie, pseudoprogression), and delayed time to treatment response (10). Subsequently, updated treatment response criteria such as the immune-related response criteria (irRC), immune-related RECIST (irRECIST), and immunotherapy RECIST (iRECIST) have been developed to account for these unique imaging features (10–12).

Key differences in these updated criteria include the need for repeat imaging (ie, performed 4 weeks after initial response assessment) to confirm disease progression and the principle that the appearance of new lesions does not necessarily constitute disease progression. Although not yet incorporated in official immunotherapy response criteria, the combination of anatomic and functional imaging such as fluorine 18 fluorodeoxyglucose (^{18}F-FDG) PET/CT or diffusion-weighted imaging with MRI may be beneficial in predicting treatment response in patients receiving ICI therapy (13,14).

Immune-related Adverse Events

Although the disruption of the immune checkpoint pathway is the principle mechanism behind stimulating immune response against tumor cells, this same pathway is also responsible for various irAEs. The development of an irAE is mainly T-cell mediated, and infiltration of CD4 and CD8 cells has been observed in association with irAEs (15). Other immune cells and mediators such as B cells, granulocytes, and cytokines have also been implicated (16). This immune overreaction leads to the autoimmune-type reactions observed with irAEs. These adverse events can be temporary or chronic, mild or life-threatening, and may involve nearly any organ system, sometimes multiple sites simultaneously (Fig 2).

irAEs have been shown to occur in up to 90% of patients undergoing CTLA-4 inhibitor therapy and 70% of those undergoing PD-1 and/or PD-L1 inhibitor therapy (17). A majority of irAEs occur in the induction phase, usually within the first 12 weeks of initiating therapy, although reactions manifesting after 1 year have been observed (18,19). irAE risk has been shown to have a dose-dependent relationship for CTLA-4 inhibitors, but this has not been consistently observed in PD-1 and/or PD-L1 inhibitors (19). Combinations of PD-1 and CTLA-4 inhibitors with nivolumab and ipilimumab have also demonstrated higher irAE rates compared with those of respective monotherapies in patients with advanced melanoma (20).

ICI Therapy–related Pneumonitis

ICI therapy–related pneumonitis is an irAE, potentially resulting in significant morbidity with possible discontinuation of therapy and possible mortality. Overall, the incidence of ICI therapy–related pneumonitis is estimated to be between 3% and 6% (21). Higher rates of pneumonitis have been observed in non–small cell lung cancer and renal cell carcinoma versus those of melanoma (22). In patients with non–small cell lung carcinoma, the incidence and severity of pneumonitis has been shown to be higher in patients undergoing treatment with PD-1 inhibitors compared with those undergoing treatment with PD-L1 inhibitors (3.6% vs 1.3%, respectively), with a lower incidence in those patients undergoing treatment with CTLA-4 inhibitors (23,24).

Pneumonitis is more likely to manifest in patients receiving ICI combination therapy compared with those receiving monotherapy (21). However, large-scale head-to-head studies comparing various ICI therapies are lacking. Treatment-naïve patients have also demonstrated higher rates of pneumonitis relative to those patients who were previously treated (23).

The time to pneumonitis onset is widely variable, reported to range from 9 days to over 19 months after initiation of therapy, with a median time of onset of 2.8 months. Onset has been shown to occur earlier in patients with lung cancer compared with those with melanoma (2.1 versus 5.2 months, respectively) (25). Pneumonitis may manifest with other irAEs, such as dermatitis, colitis, and endocrinopathies (21).

Clinical Presentation

Presenting symptoms of ICI therapy–related pneumonitis are variable and nonspecific, necessitating a high index of suspicion and awareness among members of the patient's care team. The most common presenting symptoms are dyspnea and cough, with less common symptoms including fever and chest pain. Up to one-third of patients may be asymptomatic at onset (21).

To standardize terminology regarding treatment-related adverse events, pneumonitis symptoms are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (26). Currently in its fifth version, the CTCAE categorizes symptoms on a five-point grading scale according to increasing severity (Table 2). Patients with grade 1 or 2 pneumonitis have no or milder symptoms and are typically managed as outpatients, while patients with grade 3 or higher require more intensive management.

Patients with suspected pneumonitis should undergo initial clinical assessment with physical examination and pulse oximetry. For patients with

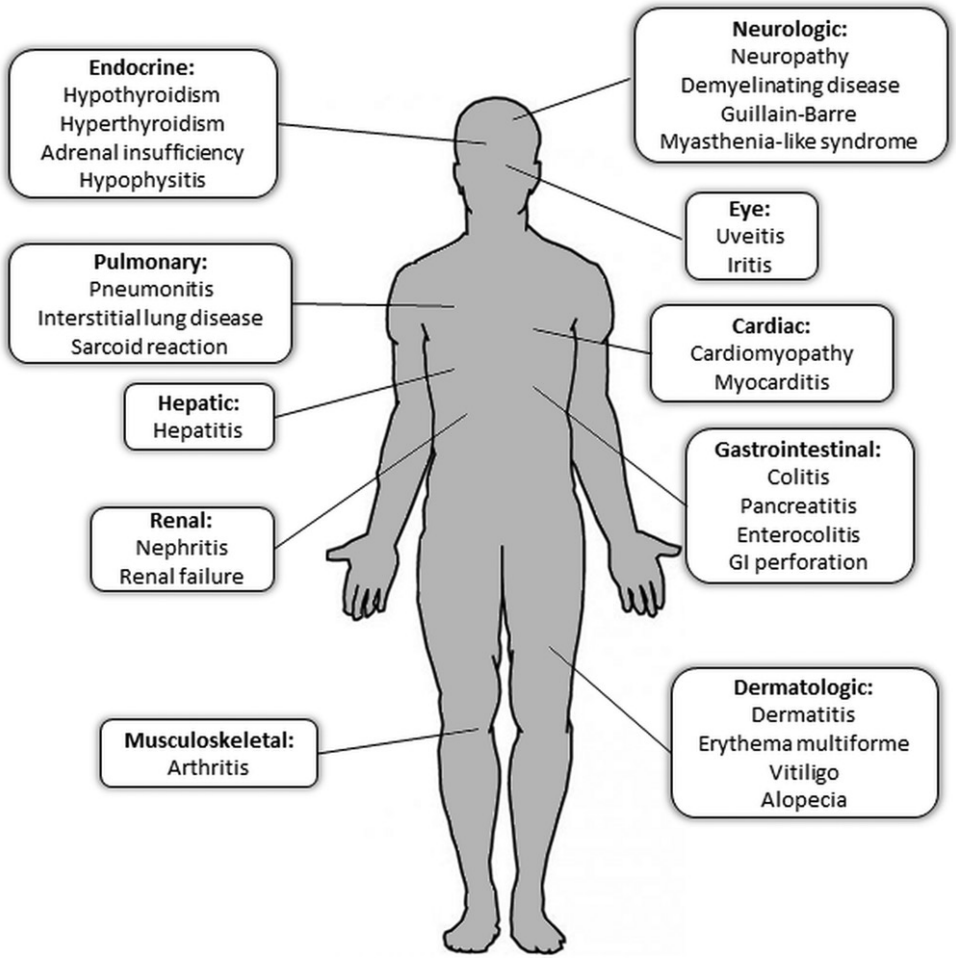


Figure 2. Illustration shows the global effect of irAEs with associated manifestations. *GI* = gastrointestinal.

Table 2: National Cancer Institute CTCAE Pneumonitis Grading System

Grade	Symptom
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; medical intervention indicated; limiting instrumental ADL
3	Severe symptoms; limiting self-care ADL; oxygen indicated
4	Life-threatening respiratory compromise; urgent intervention indicated (ie, tracheostomy or intubation)
5	Death

Source.—Reference 26.
Note.—ADL = activities of daily living.

grade 2 pneumonitis, diagnostic evaluation to rule out infection may be pursued, which can include nasopharyngeal, sputum, and urine culture and sensitivity tests (27). More invasive assessments with bronchoscopy and biopsy are generally unnecessary, particularly in lower grades, if other clinical data are suggestive of pneumonitis.

However, if uncertainty persists, tissue sampling can be pursued to differentiate pneumonitis from the main clinical and radiographic differential considerations of infection and tumor spread. Histopathologic findings include cellular interstitial pneumonitis, organizing pneumonia (OP), and less commonly diffuse alveolar damage (21). In cases of ICI therapy–related pneumonitis, the most common finding at bronchoalveolar lavage is T-lymphocytic alveolitis (25). However, there are currently no specific histologic findings for ICI therapy–related pneumonitis.

Imaging plays a critical role in pneumonitis detection. While chest radiography may be used as an initial screening tool, chest CT can better depict even subtle changes of pneumonitis and help differentiate among subtypes, which are more completely described in the following section. The role of PET in the diagnosis and follow-up of ICI therapy–related pneumonitis is unclear, although there have been several reports of pneumonitis at PET/CT (28–30). However, PET lacks in diagnostic specificity in this scenario, given the potential overlap of hypermetabolic activity with malignancy and infectious processes.

Pneumonitis Patterns

Despite researchers' increasing awareness and experience with ICI therapy–related pneumonitis, large-scale studies categorizing the various radiologic patterns are somewhat limited. The largest study to date by Delaunay et al (25) includes 64 cases of pneumonitis with the following CT patterns described: *(a)* OP (23%), *(b)* hypersensitivity pneumonitis (HP) (16%), *(c)* nonspecific interstitial pneumonia (NSIP) (8%), and *(d)* bronchiolitis (6%). Some patients were diagnosed with concomitant patterns, and a distinctive pattern was not identified in 36% of cases.

The second largest series, by Naidoo et al (21), describes 43 patients with pneumonitis (27 of which had available CT images), with the following CT findings and categories described: *(a)* ground-glass opacities (37%), *(b)* interstitial (22%), *(c)* cryptogenic OP (19%), *(d)* hypersensitivity (7%), and *(e)* unclassified (15%). A smaller series by Nishino et al (31) with 20 pneumonitis cases described similar patterns as well as acute interstitial pneumonia (AIP)–acute respiratory distress syndrome (ARDS) occurring in 10% of patients. The CT appearance of ICI therapy–related pneumonitis generally parallels that visualized in nontreatment-related interstitial lung diseases and is summarized with the main differential considerations in Table 3.

OP Pattern

OP pattern is the most commonly observed ICI therapy–related pneumonitis pattern. In the series by Nishino et al (31), the OP pattern was the most common pattern in all tumor types as well and in both monotherapy and combination therapy and was associated with an intermediate (median CTCAE grade 2) level of toxic effects (31).

OP pattern most commonly manifests as patchy bilateral opacities with a peripheral or peribronchovascular predominance, often with a mid- to lower-lung predominance (Fig 3). Airspace disease may manifest as either consolidative or ground-glass opacities or a combination of both, frequently depicted on air bronchograms with or without a component of bronchial dilatation. A circumferential consolidative opacity surrounding an interior area of ground-glass attenuation (ie, reversed halo or atoll sign), a relatively specific marker for OP in the nontreatment setting, has also been reported in ICI therapy–related pneumonitis (32). Airspace disease can also be migratory, changing location or configuration over time (33). Pulmonary nodules may also be depicted, typically in a peribronchovascular distribution and more commonly as smaller nodules (<10 mm). However, in some cases, nodules may be nodular and masslike with spiculated margins, simulating findings of malignancy (34).

As OP pattern can manifest with new masslike consolidative opacities, an important differential diagnosis is progression of an underlying malignancy. However, true progression will often be associated with progressive disease elsewhere and will lack response to immunosuppressive therapy. Infection, including atypical and fungal causes such as invasive aspergillosis, should also be considered and often can be distinguished by clinical and laboratory findings. The appearance and treatment of OP pattern ICI therapy–related pneumonitis are virtually indistinguishable from those of cryptogenic OP, although the latter is usually a long-standing process without a temporal relationship to the immunotherapy course.

NSIP Pattern

NSIP pattern is the second most commonly described pattern of ICI therapy–related pneumonitis, although it is diagnosed in a minority of reported cases. NSIP pattern is associated with a lower toxicity grade (median CTCAE grade 1) (31). NSIP pattern most commonly manifests with ground-glass and reticular opacities with lower lobe predominance (Fig 4) (35). Airspace disease is temporally homogeneous and relatively symmetric, with consolidative opacities uncommon, features that help in distinguishing NSIP from OP patterns. Subpleural sparing of the posterior and dependent lower lobes has also been reported as a specific finding (34). However, changes of fibrotic NSIP in nontreatment-related cases including lower lobe volume loss and traction bronchiectasis have not been reported in ICI therapy–related pneumonitis, likely because cases are detected and treated in the acute stage.

NSIP pattern should be distinguished from atypical infectious processes, which can often be determined on the basis of clinical parameters. Furthermore, basilar predominance and subpleural sparing in the NSIP pattern are less typical findings of infection. NSIP-associated connective tissue and autoimmune disorders are generally long-standing processes in the setting of other known comorbid conditions.

HP Pattern

HP pattern is an uncommon manifestation of ICI therapy–related pneumonitis. Similar to the NSIP pattern, HP pattern is associated with lower- grade symptoms (median CTCAE grade 1) (31). Described findings of HP pattern mirror those typically found in cases of subacute HP depicted in other settings. Findings include diffuse or upper lobe predominant centrilobular ground-glass nodules, which may be accompa-

Table 3: ICI Therapy–related Pneumonitis Patterns

Pneumonitis Pattern	Radiologic Features	Differential Diagnosis (Distinguishing Features)
OP	Bilateral peribronchovascular and subpleural ground-glass and airspace opacities Mid- to lower-lung predominance Reversed halo or atoll sign	Progression of malignancy (concurrent worsening of disease in other areas) Infection (clinical history, laboratory findings, response to appropriate therapy) Cryptogenic OP (long-standing process, no temporal relationship to immunotherapy course)
NSIP	Relatively symmetric ground-glass and recticular opacities with basilar predominance Immediate subpleural sparing	NSIP associated with autoimmune or connective tissue disease (appropriate medical history and condition-specific markers, no temporal relationship to immunotherapy course) Infection (clinical history, laboratory findings, response to appropriate therapy)
HP	Diffuse or centrilobular ground-glass nodules with mid- to upper-lobe predominance Air trapping	Exposure-related HP (exposure and occupational history, no temporal relationship to immunotherapy course) Respiratory and follicular bronchiolitis (smoking history or underlying connective tissue and/or autoimmune disease history) Atypical infection (clinical history, laboratory findings, response to appropriate therapy)
AIP–ARDS	Patchy or diffuse ground-glass or consolidative opacities Majority or entire lung involvement	Pulmonary edema (other signs of cardiac failure) Pulmonary hemorrhage (hemoptysis, underlying coagulopathy or vasculitis) Infection (clinical history, laboratory findings, response to appropriate therapy)
Bronchiolitis	Centrilobular nodules with tree-in-bud nodularity May visualize adjacent ground-glass opacities and/or consolidation	Aspiration (dependent lungs, airway and esophageal secretion) Infection (clinical history, laboratory findings, response to appropriate therapy)
Radiation recall	Ground-glass or consolidative opacities confined to prior radiation field	Infection (no relation to radiation field; clinical history; laboratory findings; response to appropriate therapy)

nied by air trapping (Fig 5) (21). As with the NSIP pattern, changes of chronic HP including upper lobe fibrosis, volume loss, and traction bronchiectasis have not been reported with ICI therapy–related pneumonitis.

HP pattern can often be differentiated from atypical infection on clinical grounds. HP pattern may also mimic other small airways processes such as respiratory and follicular bronchiolitis, which are classically associated with smoking and underlying connective tissue or autoimmune disease history, respectively. HP pattern is indistinguishable from that of HP associated with allergen exposure (classically birds), and detailed exposure and occupational histories should be sought.

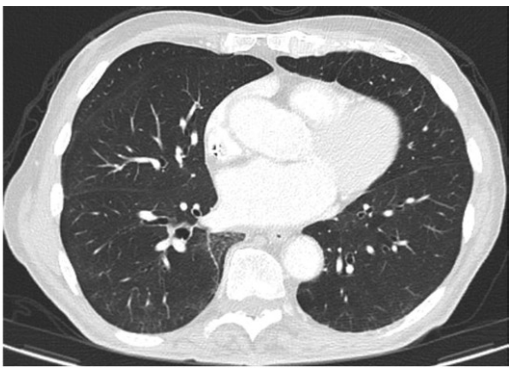
AIP–ARDS Pattern

AIP–ARDS pattern is not a prevalent pattern of ICI therapy–related pneumonitis, although it is associated with the most severe clinical course and extent of lung involvement at imaging, manifesting with median CTCAE grade 3 symptoms (31). AIP–ARDS pattern is characterized by geographic or diffuse ground-glass or consolidative opacities involving a majority, and sometimes the entirety, of the lungs, although areas of lobular sparing can also be visualized (Fig 6). Findings with lower lobe predominance can be depicted. Interlobular septal thickening and a "crazy-paving" pattern may also be present (34).

The differential diagnosis for AIP–ARDS pattern is broad and includes pulmonary edema (often associated with other findings of cardiac failure), hemorrhage (associated with hemoptysis and underlying coagulopathy), and infection. ARDS findings may also be due to extrapulmonary causes such as pancreatitis, sepsis and/or shock, and transfusion reaction.

Bronchiolitis Pattern

A bronchiolitis pattern is not a well-described pattern, only evident in one large case series and several case reports (25,36,37). Classically, bronchiolitis appears as a region of centrilobular nodularity, often in a tree-in-bud pattern. Adjacent bronchial wall thickening is also frequently



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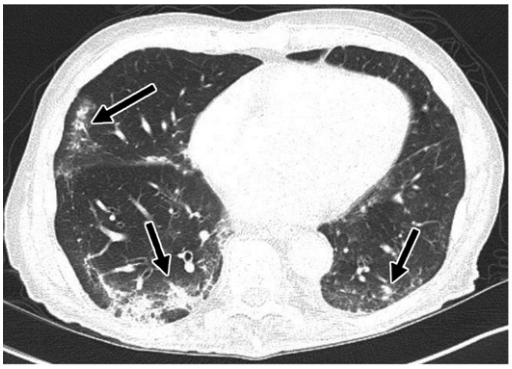

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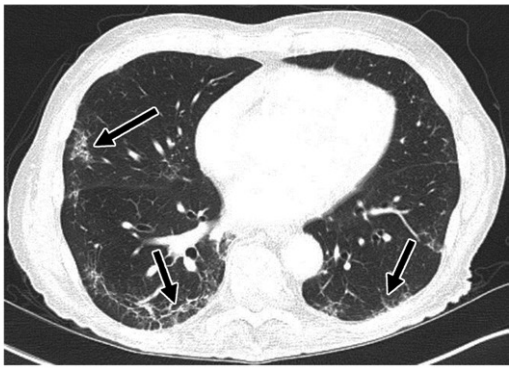
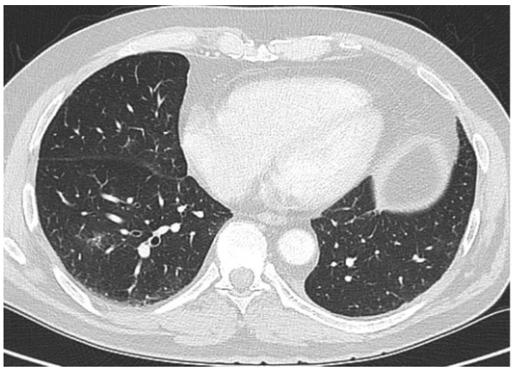


c.

Figure 3. OP pattern in a 51-year-old man undergoing nivolumab therapy for stage IV gastric adenocarcinoma. **(a)** Baseline axial chest CT image shows the lungs before immunotherapy was initiated. **(b)** Axial chest CT image obtained 4 months later after nivolumab therapy shows multifocal peripheral and subpleural mid- and lower-lung airspace consolidations (arrows), a finding consistent with an OP pattern of pneumonitis. **(c)** Axial chest CT image obtained 1 month later after withholding ICI therapy and administering steroid therapy shows residual, although significantly improved, airspace disease (arrows).



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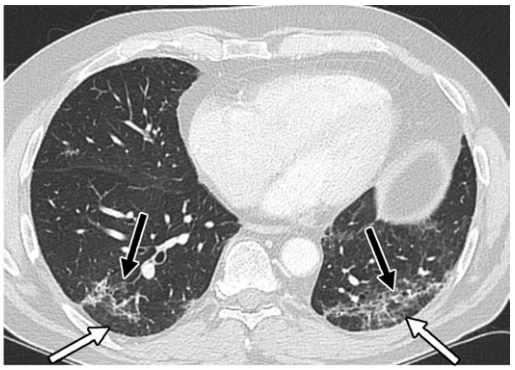

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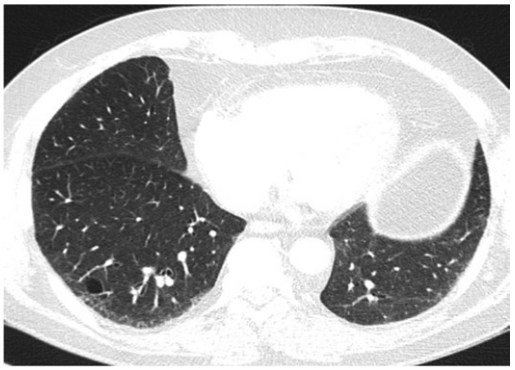


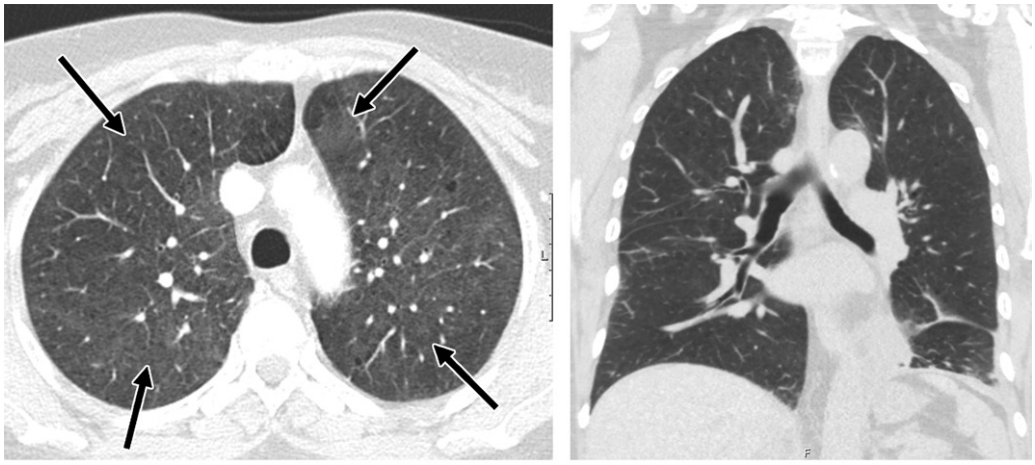
c.

Figure 4. NSIP pattern in a 67-year-old man undergoing pembrolizumab therapy for stage IV lung adenocarcinoma. **(a)** Baseline axial chest CT image shows the lungs before immunotherapy was initiated. **(b)** Axial chest CT image obtained 2 months later after starting pembrolizumab therapy shows bilateral lower lobe ground-glass and reticular opacities (black arrows), with regions of immediate subpleural sparing (white arrows). **(c)** Follow-up axial chest CT image obtained 3 months later after withholding ICI therapy and administering steroid therapy shows resolved pneumonitis. Minimal subpleural ground-glass opacities in the right lower lobe were thought to be dependent atelectasis.

depicted (Fig 7). Associated focal ground-glass and consolidative opacities may be visualized, although this should not the predominant feature.

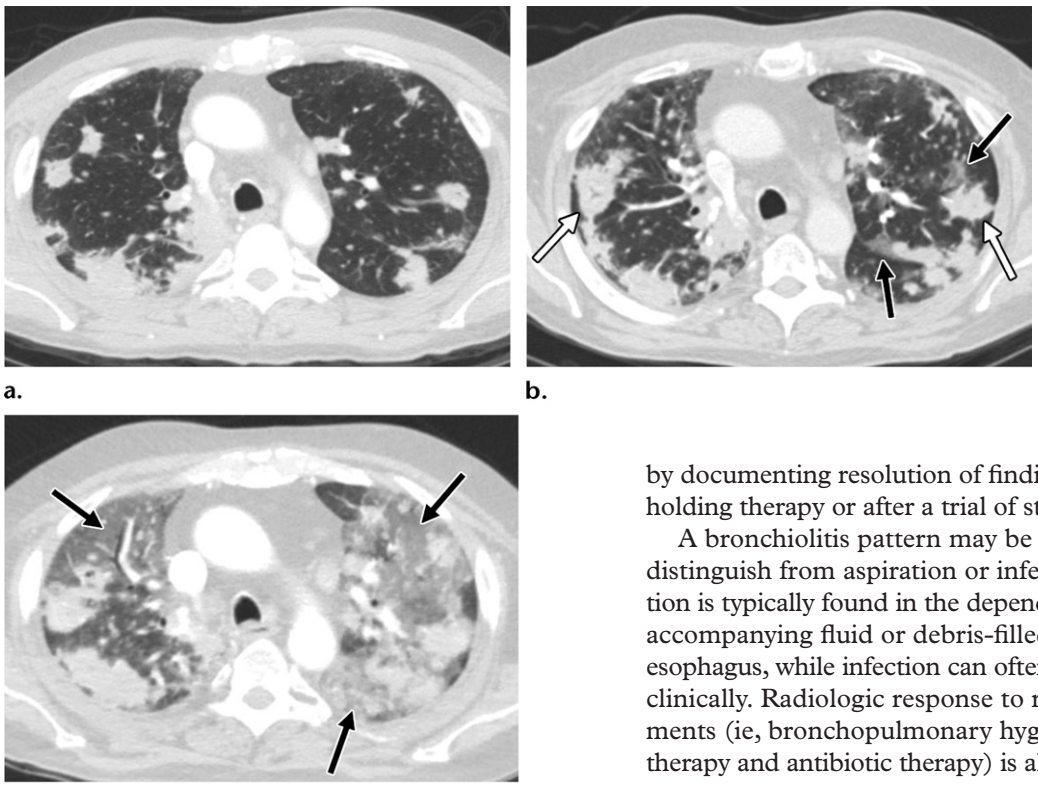
Previously, the bronchiolitis pattern may have been overlooked as a distinct pneumonitis pattern given its identical appearance to infectious and other inflammatory causes of bronchiolitis. However, suspicion for this entity as a distinct pneumonitis pattern should be raised in the absence of infectious symptoms and be confirmed at imaging

Figure 5. HP pattern in a 52-year-old woman who underwent nivolumab therapy for stage IV lung adenocarcinoma. A baseline coronal chest CT image obtained before starting immunotherapy (not shown) showed no airspace abnormalities. **(a)** Axial chest CT image obtained 5 months after starting nivolumab therapy shows diffuse centrilobular ground-glass nodules (arrows). **(b)** Follow-up coronal chest CT image obtained 1 month later after withholding ICI therapy and administering steroid therapy shows resolved pneumonitis, with a return to near-baseline findings.



a. **b.**

Figure 6. AIP–ARDS pattern of pneumonitis in a 57-year-old man undergoing nivolumab therapy for stage IV lung adenocarcinoma. **(a)** Baseline axial chest CT image obtained before starting immunotherapy shows multiple lung nodules and masses. Six weeks after starting nivolumab therapy, the patient presented with severely worsening dyspnea. **(b)** Axial chest CT image shows new multifocal ground-glass opacities (black arrows), with interval enlargement of several pulmonary masses (white arrows). **(c)** Axial chest CT image obtained 5 days later after further respiratory decompensation (despite withholding ICI therapy and initiating intravenous steroid therapy) shows increasing severity and confluence of ground-glass opacities (arrows), with little intervening normal lung parenchyma. The patient died 1 week later.



a. **b.**

c.

by documenting resolution of findings after withholding therapy or after a trial of steroid therapy.

A bronchiolitis pattern may be difficult to distinguish from aspiration or infection. Aspiration is typically found in the dependent lungs, with accompanying fluid or debris-filled airways, and esophagus, while infection can often be delineated clinically. Radiologic response to respective treatments (ie, bronchopulmonary hygiene physical therapy and antibiotic therapy) is also often helpful.

Radiation Recall

Radiation recall is an inflammatory reaction occurring within a previously irradiated area after exposure to an inciting agent that has been observed in

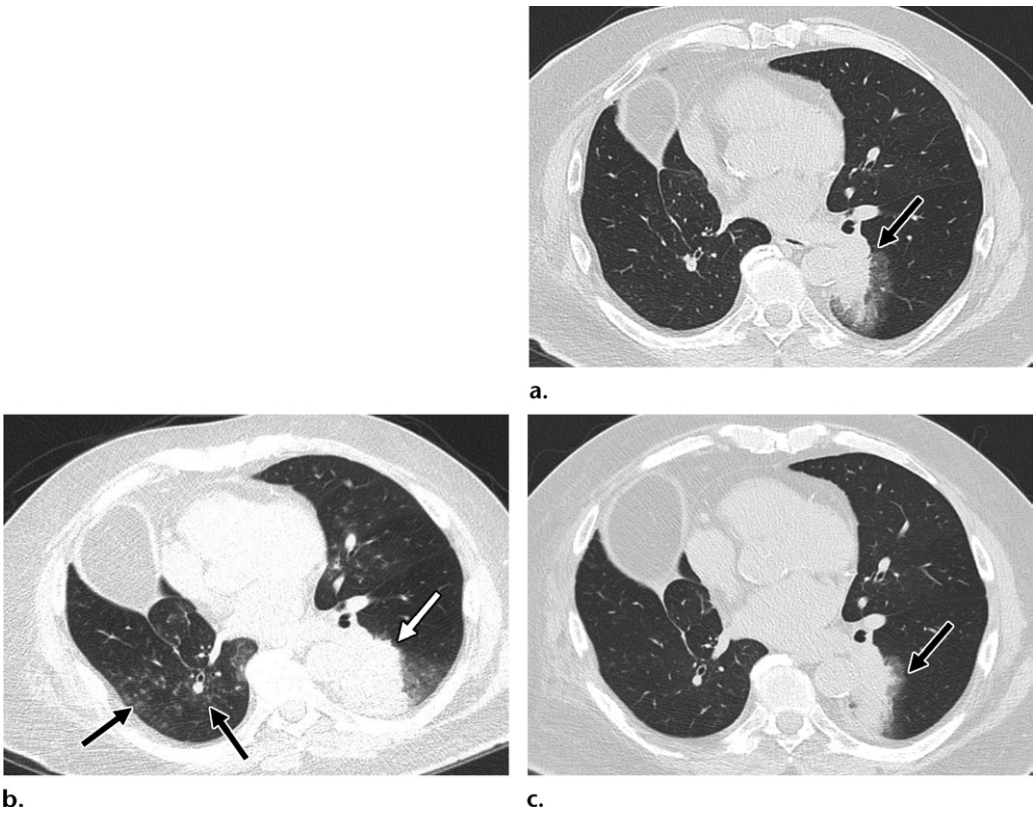


Figure 7. Bronchiolitis pattern of pneumonitis in a 63-year-old woman undergoing nivolumab therapy for lung adenocarcinoma. **(a)** Baseline axial chest CT image shows a medial left lower lobe lung mass with surrounding ground-glass halo sign (arrow), a finding corresponding to adenocarcinoma. **(b)** Axial CT image obtained 2 weeks after starting nivolumab therapy shows a region of centrilobular solid and ground-glass nodularity (black arrows) in the right lower lobe. The left lower lobe mass also increased in size (white arrow). Infection was excluded on the basis of clinical findings. **(c)** Follow-up axial chest CT image obtained 2 months later after steroid therapy shows resolved right lower lobe pneumonitis. The size of the left lower lobe mass (arrow) decreased, suggesting a pseudoprogression on the previous study.

multiple organs and systems, including skin, lung, digestive tract, muscle, and central nervous system. While this reaction is most commonly reported after exposure to chemotherapy agents, other precipitating agents have been implicated (38). The mechanism of radiation recall reactions remains unclear, although possibilities include changes in the function of stem cells in the irradiated field versus idiosyncratic drug hypersensitivity reactions (39).

While better recognized with conventional chemotherapy agents, cases of radiation recall pneumonitis have now been described with ICI therapy (40,41). With conventional agents, the median time of onset of radiation recall pneumonitis after the end of radiation therapy is 95 days, although onset of 2 years after radiation therapy has been reported with nivolumab (38,41).

Findings of radiation recall pneumonitis include consolidative or ground-glass opacities limited to a prior radiation field (Fig 8). It should be suspected in any patient with a history of radiation therapy with new airspace changes sharply demarcated from the adjacent lung in the appearance of a radiation field. The main differential diagnosis is infection, which does not respect the boundaries and occurs outside of the prior radiation field.

Sarcoidlike Reaction

Although generally considered separate from ICI therapy–related pneumonitis, sarcoidlike reaction is another potential pulmonary irAE reported with ICI therapy. Its mechanism is likely multifactorial and is thought to be an autoimmune response with T-cell upregulation and ultimately increased granuloma formation.

Sarcoidlike reactions demonstrate identical histopathologic features to those of sarcoidosis, namely noncaseating granuloma formation. Sarcoidlike reaction has been most commonly reported in patients undergoing ipilimumab therapy and in those with melanoma (42). In the melanoma cohort, the development of a sarcoidlike reaction has been associated with an eventual therapeutic response (43). Outside of the lung, the skin is a common site of involvement.

Imaging features are similar to those of sarcoidosis and include mediastinal and hilar

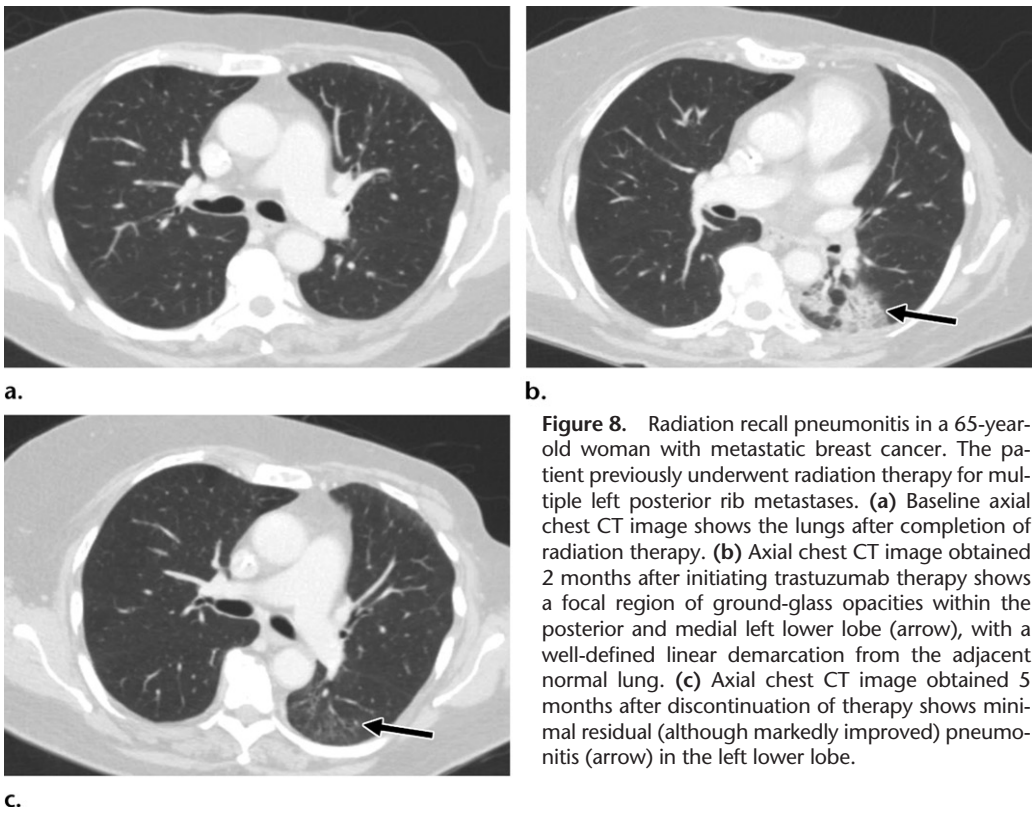


Figure 8. Radiation recall pneumonitis in a 65-year-old woman with metastatic breast cancer. The patient previously underwent radiation therapy for multiple left posterior rib metastases. **(a)** Baseline axial chest CT image shows the lungs after completion of radiation therapy. **(b)** Axial chest CT image obtained 2 months after initiating trastuzumab therapy shows a focal region of ground-glass opacities within the posterior and medial left lower lobe (arrow), with a well-defined linear demarcation from the adjacent normal lung. **(c)** Axial chest CT image obtained 5 months after discontinuation of therapy shows minimal residual (although markedly improved) pneumonitis (arrow) in the left lower lobe.

lymphadenopathy and pulmonary nodules in a perilymphatic distribution, with upper lung predominance (42). Increased FDG uptake within adenopathy has also been observed at PET/CT (44). Sarcoidlike reaction may mimic recurrent or worsening malignancy, and lymphadenopathy may also be mistaken for reactive lymphadenopathy from an infectious process of other irAEs. Treatment typically includes administering corticosteroids and/or discontinuing therapy (42).

ICI Therapy versus Conventional Chemotherapy

Because of the greater experience with larger clinical trials involving ICI therapies and emerging toxicity profiles, different patterns with respect to presentation, imaging findings, and management have become apparent between ICI therapy–related and conventional chemotherapy-related pneumonitis. For example, patients receiving ICI therapy have shown greater susceptibility to the development of treatment-related pneumonitis, with increased risk of high-grade pneumonitis (45). Conventional chemotherapy agents have demonstrated a dose-dependent risk of pneumonitis, while overall this has not been shown with ICI therapy (45,46).

Clinically, ICI therapy–related pneumonitis tends to occur with overall higher severity, potentially requiring higher doses of steroid therapy or more potent immunosuppressive therapy compared with that of conventional chemotherapy pneumonitis. Also, ICI therapy–related pneumonitis is more commonly associated with multiorgan involvement with other irAEs. At imaging, ICI therapy–related pneumonitis tends to be more extensive at patient presentation, with findings likely to be lower lung predominant (Fig 9).

Pneumonitis Management

Treatment and Follow-up

When ICI therapy–related pneumonitis becomes clinically apparent, management should be initiated immediately. ICI therapy–related pneumonitis is treated by symptom severity as stipulated by the recent American Society of Clinical Oncology Clinical Practice Guideline (27) (Table 4). Management of grade 1 pneumonitis, which is asymptomatic and typically found solely on the basis of radiographic or other clinical parameters, is treated by withholding ICI therapy without administering steroid therapy. Short-term repeat imaging can be performed to document resolution of findings, and pulmonary function testing with spirometry and diffusing capacity can be considered if a prior baseline study is available.

Grade 2 pneumonitis can be managed in the outpatient setting by withholding the ICI therapy and initiating steroid therapy, with initial dose burst followed by a 4- to 6-week taper. Bronchoscopy with bronchoalveolar lavage and

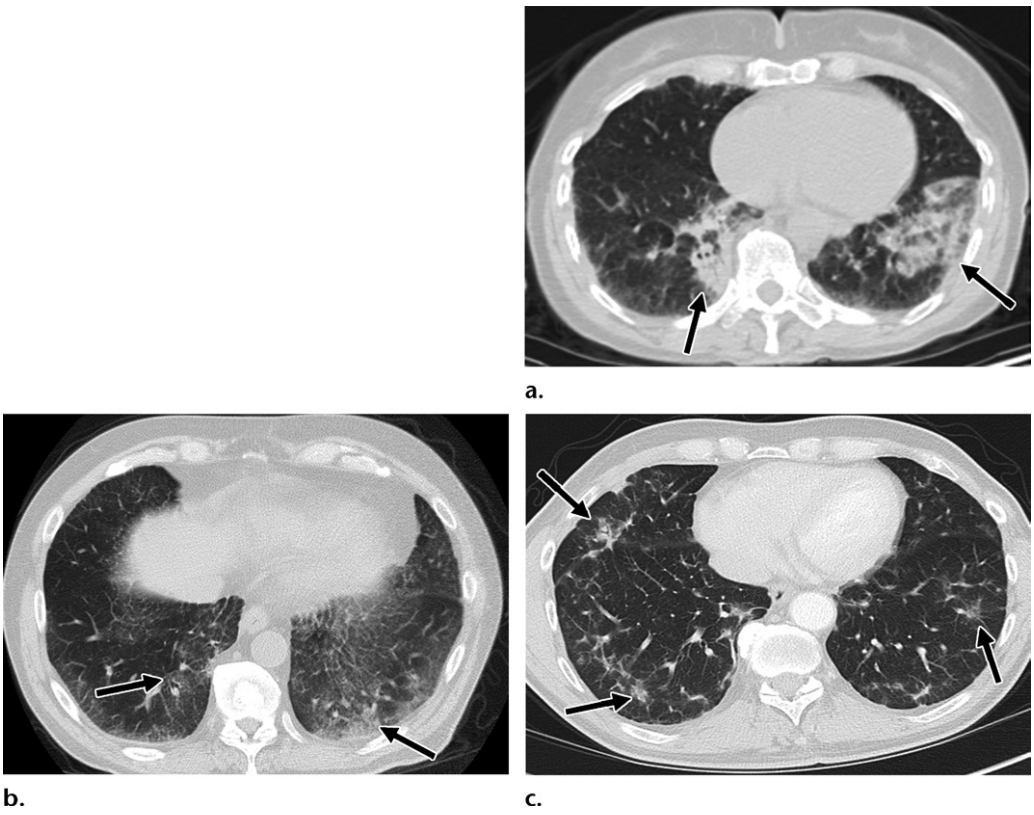


Figure 9. Spectrum of treatment-related pneumonitis among various therapy types. **(a)** Axial CT image in a 65-year-old man undergoing ipilimumab therapy for metastatic melanoma shows large bilateral lower lobe pleural-based consolidative and ground-glass opacities (arrows). **(b)** Axial CT image in a 63-year-old woman undergoing gemcitabine therapy for pancreatic cancer shows bilateral subpleural reticular opacities, with background faint ground-glass and interstitial opacities (arrows) that are more pronounced in the left lower lobe. **(c)** Axial CT image in a 57-year-old man undergoing imatinib therapy for metastatic gastrointestinal stromal tumor shows small patchy peripheral ground-glass opacities (arrows) in the bilateral lower lobes.

Table 4: American Society of Clinical Oncology Clinical Practice Guideline for the Management of ICI-related Pneumonitis

Pneumonitis Grade	Management	Follow-up
Grade 1	Hold ICI therapy with radiographic evidence of pneumonitis progression If there is no improvement after follow-up, treat as Grade 2	May offer one repeat CT examination in 3–4 weeks May offer lung function testing in 3–4 weeks (if baseline testing has been performed)
Grade 2	Hold ICI therapy until resolution to grade 1 or less Administer prednisone dose burst followed by taper over 4–6 weeks Consider performing bronchoscopy and/or BAL and administering empirical antibiotics If there is no improvement after 2–3 days of steroid therapy, treat as a grade 3 diagnosis	Monitor clinical parameters every 3 days Consider performing chest radiography
Grades 3 and 4	Permanently discontinue ICI therapy Empirical antibiotics and intravenous methylprednisolone therapy (may add infliximab, mycophenolate, or IVIG if there is no initial improvement) followed by steroid therapy taper Bronchoscopy and/or BAL; consider performing transbronchial biopsy	Patient should be hospitalized for further management

Source.—Reference 27.
Note.—BAL = bronchoalveolar lavage, IVIG = intravenous immunoglobulin.

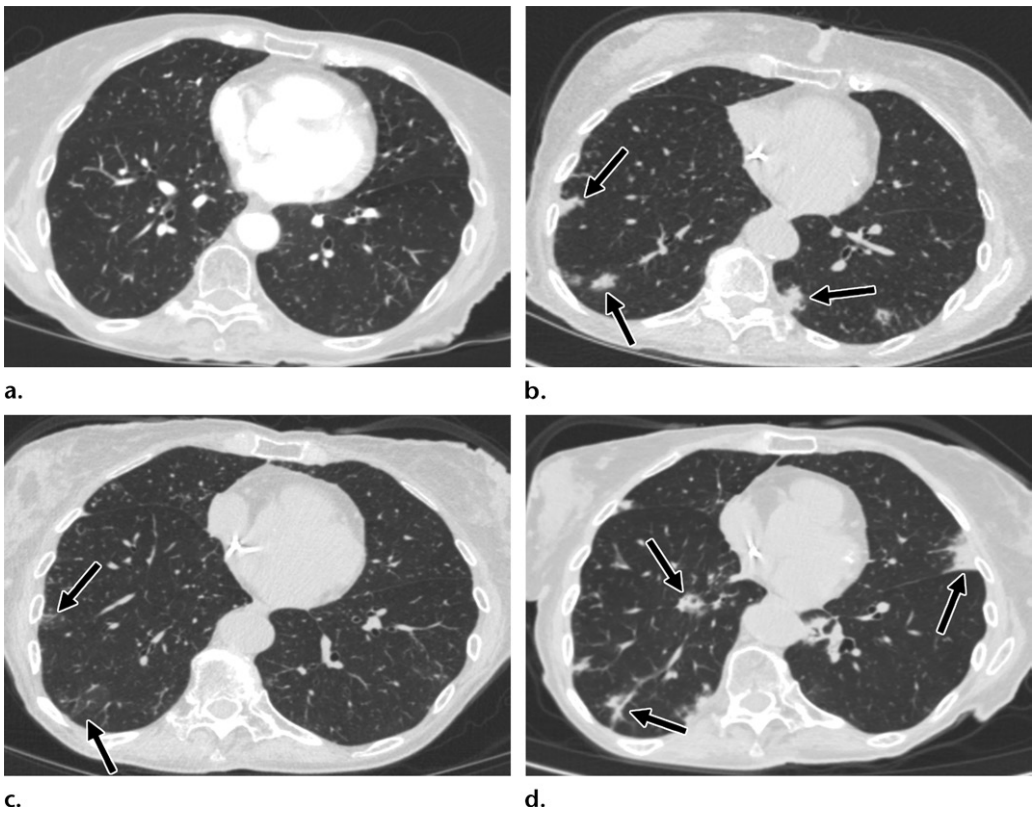


Figure 10. Recurrent pneumonitis in a 78-year-old patient with small cell lung carcinoma. **(a)** Baseline axial chest CT image shows the lungs before starting immunotherapy. **(b)** Follow-up axial CT image obtained 4 months later after administering nivolumab therapy shows multiple predominantly peripheral and subpleural airspace consolidative opacities (arrows), findings consistent with an OP pneumonitis pattern. Immunotherapy was subsequently held, and steroid therapy was administered. **(c)** Follow-up axial chest CT image shows near-complete resolution of pneumonitis, with several remaining faint subpleural right lower lobe opacities (arrows). **(d)** Axial CT image obtained after completing steroid therapy and restarting nivolumab therapy shows recurrence of an OP pneumonitis pattern with new areas of involvement (arrows).

empirical antibiotics can be considered at this stage, although it should not significantly delay initiating treatment (47). Patient symptoms and pulse oximetry results should be closely monitored every 3 days, and if no improvement is seen 48–72 hours after starting steroid therapy, care should be escalated. Chest radiography can be considered to track evolving pneumonitis findings.

Patients with grades 3 and 4 pneumonitis require permanent discontinuation of ICI therapy and more intensive care, requiring inpatient admission with close monitoring. Intravenous steroid therapy with intravenous methylprednisolone along with empirical antibiotic therapy should be administered. Depending on the severity and initial response, other agents such as infliximab, mycophenolate, or intravenous immunoglobulin may also be added. Bronchoscopy and/or bronchoalveolar lavage are typically performed, and transbronchial biopsy can be considered at this stage. Although not specifically addressed in published guidelines given the potential for high steroid doses administered for extended periods, infectious prophylaxis may be warranted. For example, trimethoprim and sulfamethoxazole may be administered for *Pneumocystis jirovecci* prophylaxis (47).

Prognosis and Recurrence

With ICI therapy cessation and appropriate steroid or immunosuppressive therapy initiation, management of ICI therapy–related pneumonitis has been shown to be highly effective. In a case series by Naidoo et al (21), pneumonitis improved or resolved in all 30 patients with grades 1 and 2 at follow-up and in a majority of patients with grade 3 (64%). However, despite therapy incorporating escalating immunosuppression, a minority of patients (12%), all with grade 3 pneumonitis, experienced progressive symptoms (21).

Despite treatment of pneumonitis, approximately one-fourth of patients will develop recurrence (21) (Fig 10). After pneumonitis resolution, clinicians are faced with the decision of whether to restart ICI therapy (ie, rechallenge). A majority of patients do not develop recurrence after restarting immunotherapy, although reports of rechallenge

mainly describe patients with initial grade 1 or 2 pneumonitis. Reported recurrence rate after rechallenge is 17%–29% (21,25,31). Patients initially diagnosed with grade 3 or 4 pneumonitis generally discontinue therapy permanently (47). Recurrent pneumonitis pattern, location of involvement, and severity may vary compared with those at initial presentation. Although not specifically addressed in the American Society of Clinical Oncology Practice Guideline, recurrent pneumonitis is often treated with methods similar to those used in the treatment of the initial occurrence.

Patient and drug-related factors predicting the development of pneumonitis are currently under investigation. Reduced baseline pulmonary function and history of smoking may increase the risk of pneumonitis. In addition, undergoing combination immunotherapy, concurrent radiation therapy, and previous high-dose chemotherapy are also thought to be risk factors (48). Furthermore, the use of serum markers for the prediction and monitoring of ICI therapy–related pneumonitis is also an active area of investigation.

Conclusion

ICI therapies are increasingly being used as first- and second-line agents in the treatment of a growing number of malignancies. Given the novel mechanism of action, the complications of these therapies have unique manifestations compared with those of conventional therapies. ICI therapy–related pneumonitis is an uncommon although potentially serious complication of ICI therapy. ICI therapy–related pneumonitis manifests as several distinct radiologic patterns that overlap with other infectious and inflammatory conditions. A high index of suspicion and prompt recognition of pneumonitis by the radiologist are critical to initiate prompt treatment and prevent further morbidity and mortality for these patients. Going forward, given the potential complexity of diagnosis and management of ICI therapy–related pneumonitis, radiologists must work in conjunction with a broader multidisciplinary team to provide optimal care for these patients.

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