Immune checkpoint inhibitor therapy-related pneumonitis: How, when and why to diagnose and manage (Review)

SALVATORE LAVALLE[1], EDOARDO MASIELLO[2], MARIA ROSARIA VALERIO[3], ALBERTO ALIPRANDI[4], GIUSEPPA SCANDURRA[1,5], VITTORIO GEBBIA[1,6] and DANIELA SAMBATARO[1,7]

[1]Department of Medicine and Surgery, Kore University of Enna, I-94100 Enna, Italy; [2]Radiology Unit, University Vita e Salute, Institute San Raffaele, I-20132 Milan, Italy; [3]Medical Oncology Unit, Policlinic P Giaccone, University of Palermo, I-90127 Palermo, Italy; [4]Radiology Unit, Zucchi Clinical Institutes, University of Milan-Bicocca, I-20900 Monza, Italy; [5]Medical Oncology Unit, Cannizzaro Hospital, I-95126 Catania, Italy; [6]Medical Oncology Unit, Torina Clinic, I-90145 Palermo, Italy; [7]Medical Oncology Unit, Umberto I Hospital, I-94100 Enna, Italy

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Abstract. Immune checkpoint inhibitor (ICI) therapy has revolutionized cancer treatment by enhancing the immune response against tumor cells. However, their influence on immune pathways can lead to immune-related adverse events such as pneumonitis, necessitating rapid diagnosis and management to prevent severe complications. These adverse events arise from the activation of the immune system by immunotherapeutic drugs, leading to immune-mediated inflammation and tissue damage in various organs and tissues throughout the body. The present review article discusses the pathophysiology, clinical presentation, diagnostic modalities and management strategies for ICI-related pneumonitis, emphasizing early recognition and tailored interventions. Future research endeavors should focus on elucidating the underlying mechanisms of pneumonitis and identifying predictive biomarkers to guide personalized treatment strategies in this evolving field of oncology.

Contents

Correspondence to: Professor Vittorio Gebbia, Department of Medicine and Surgery, Kore University of Enna, Contrada Santa Panasia, 192 Strada Comunale, I-94100 Enna, Italy
E-mail: vittorio.gebbia@unikore.it

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1. Introduction

To date, immune checkpoint inhibitors (ICIs) represent a cornerstone in treating various cancers as they harness the potential of the immune system to treat malignancies. However, their influence on immune pathways can lead to immune-related adverse events (irAEs). IrAEs are a spectrum of side effects that can occur because of treatment with ICIs (1). These adverse events arise from the dysregulation of the immune system by immunotherapeutic drugs, leading to immune-mediated inflammation and tissue damage in various organs and tissues throughout the body (2). The spectrum of irAEs is broad and can involve any organ system, including the skin, gastrointestinal tract, liver, endocrine glands and lungs (3). Common irAEs include dermatitis, colitis, hepatitis and thyroid dysfunction, with pneumonitis standing as a particularly significant concern (4). Pneumonitis, characterized by inflammation of lung tissue, emerges as one of the notable irAEs due to its potential for severe morbidity and mortality if not promptly recognized and managed (5). However, the severity and specific manifestations of irAEs can significantly vary among patients depending on the type of immunotherapy, the underlying cancer, and the immune status of patients (6). The clinical presentation of irAEs can range from mild, self-limited symptoms to severe, life-threatening complications (7). Rapid identification and management of irAEs are crucial to prevent severe morbidity and mortality (8). Treatment typically involves the temporary or permanent discontinuation of immunotherapy and the initiation of immunosuppressive medications, such as corticosteroids or other immunomodulators such as infliximab or vedolizumab related to the severity and nature of the adverse event (9). The mechanisms underlying irAEs are complex and need to be fully elucidated. However, the dysregulation of immune checkpoints and the resultant

immune activation against normal tissues is considered to play a central role (10). The diversity of irAEs underscores the need for a multidisciplinary approach to diagnose and manage these adverse events best, involving collaboration between oncologists, immunologists, rheumatologists and other specialists as needed.

2. Incidence

ICI-related pneumonitis is relatively rare compared with other irAEs, such skin reactions, flu-like- and gastrointestinal symptoms, yet it is the most fatal complication associated with programmed cell death protein 1 inhibitors (PD-1/PD-L1) (1). Studies indicate that ICI-related pneumonitis is responsible for a substantial proportion of deaths attributed to PD-1/PD-L1 inhibitor monotherapy, accounting for ~35% of such fatalities (11-13). The overall incidence rate of ICI-related pneumonitis in clinical trials involving ICI monotherapy is 2.5-5.0%, while that in trials involving ICI combination therapy is higher, at 7-10% (12). Clinical trials typically enroll patients without underlying lung disease or autoimmune conditions, and thus, real-world data reveal a broader incidence of 7-19% (13). Additionally, studies have demonstrated that PD-1/PD-L1 inhibitors exhibit a greater incidence and severity of pulmonary toxicity compared with anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) agents (14,15). Specifically, PD-1 inhibitors have been found to have a higher occurrence and severity of pulmonary toxicity than PD-L1 inhibitors (14). Moreover, the incidence of ICI-related pneumonitis tends to be higher in non-small cell lung cancer compared with other tumor types, such as melanoma and renal cell carcinoma (15). The overall incidence of ICI-related pneumonitis for all grades is 1.4-5.8% in patients with non-small cell lung cancer (NSCLC), 1-4% in patients with melanoma and 1-4.8% in those with renal cell carcinoma (15). These statistics underscore the importance of cautious monitoring and prompt management of pneumonitis in patients undergoing ICI therapy.

3. Pathophysiology

The pathogenesis of ICI-related pneumonitis is complex and multifactorial, involving dysregulated immune responses against pulmonary tissues triggered by the blockade of immune checkpoints such as CTLA-4 and PD-1 or its ligand PD-L1 (16). While the exact mechanisms remain not fully understood, several vital processes contribute to the development of pneumonitis in ICI therapy. As depicted in Fig. 1, the disruption of immune tolerance lies at the core of ICI-related pneumonitis pathogenesis (17). Due to the action of these immunotherapeutic drugs, including checkpoint inhibition and blockade, aimed to disrupt immune regulation in tumor tissue, such alteration, may also occur in normal tissues, such as lungs, even though a full elucidation of the mechanisms underlying irAEs is still lacking. Consequently, the irAE mechanism appears similar to insufficient immune regulation of tissue homeostasis rather than activation of the immune system. This is supported by the lack of laboratory confirmation of autoimmunity, since in most cases, auto-antibodies are absent.

Immune checkpoints are crucial in maintaining self-tolerance and preventing excessive immune activation against normal tissues (18). Blockade of CTLA-4, PD-1, or PD-L1 releases the 'brakes' on the immune system, leading to increased activation of T cells (19). In some cases, this heightened immune response may result in recognizing self-antigens in lung tissue, triggering an autoimmune reaction (20). Consequently, the release of pro-inflammatory cytokines and the infiltration of immune cells into the lung parenchyma perpetuate tissue damage and contribute to the development of pneumonitis (21). The activation of effector T cells plays an essential role in the pathogenesis of lung inflammation. ICIs promote the activation and proliferation of effector T cells, crucial for mounting an effective antitumor immune response (20-22). However, in the context of pneumonitis, the activation of effector T cells may lead to their infiltration into the lung parenchyma. Once within the lung tissue, these activated T cells release a cascade of pro-inflammatory cytokines and chemokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interferon-γ (IFN-γ) (20-22). This inflammatory milieu contributes to tissue damage and exacerbates the immune-mediated lung injury characteristic of pneumonitis (20-22). The dysregulated cytokine production (TNF-α, IL-6 and IFN-γ) orchestrates a cascade of inflammatory responses, recruiting immune cells to the injury site and amplifying the immune-mediated lung injury process (22). Moreover, they can disrupt the delicate balance between pro-inflammatory and anti-inflammatory signals, further exacerbating tissue damage and contributing to the severity of pneumonitis (23). Lastly, genetic and environmental factors play crucial roles in influencing the development of ICI-related pneumonitis (24). Specific genetic polymorphisms, such as the gamma-aminobutyric acid type A receptor subunit pi, the desmocollin and the bromodomain adjacent to zinc finger domain 2B genes, related to immune regulation and inflammation have been implicated in the susceptibility to irAEs, although further research is needed to elucidate their particular roles in pneumonitis (23,24). Additionally, factors such as microbiota composition, prior lung injury, smoking history and concomitant use of other medications may modulate the risk of developing pneumonitis in patients receiving ICIs (25,26).

4. Clinical presentation

ICI-related pneumonitis typically presents nonspecific respiratory symptoms that can mimic other pulmonary conditions such as infection or malignancy (27). Patients may initially complain of nonspecific symptoms such as dyspnea, cough, pain and chest discomfort, which can gradually worsen (28). In more severe cases, respiratory distress and hypoxia may develop rapidly, warranting urgent medical attention (29). Constitutional symptoms such as fatigue, malaise and low-grade fever may accompany respiratory complaints, further complicating the clinical picture (Table I) (30). It is important to note that the onset of symptoms can vary widely, occurring weeks to months after initiating ICI therapy (31). Clinical suspicion should be high in patients receiving ICIs who develop new or worsening respiratory symptoms, especially in the absence of alternative etiologies and particularly in patients receiving PD-1/PD-L1 inhibitors (32). Close monitoring for respiratory symptoms and early intervention is paramount to mitigate

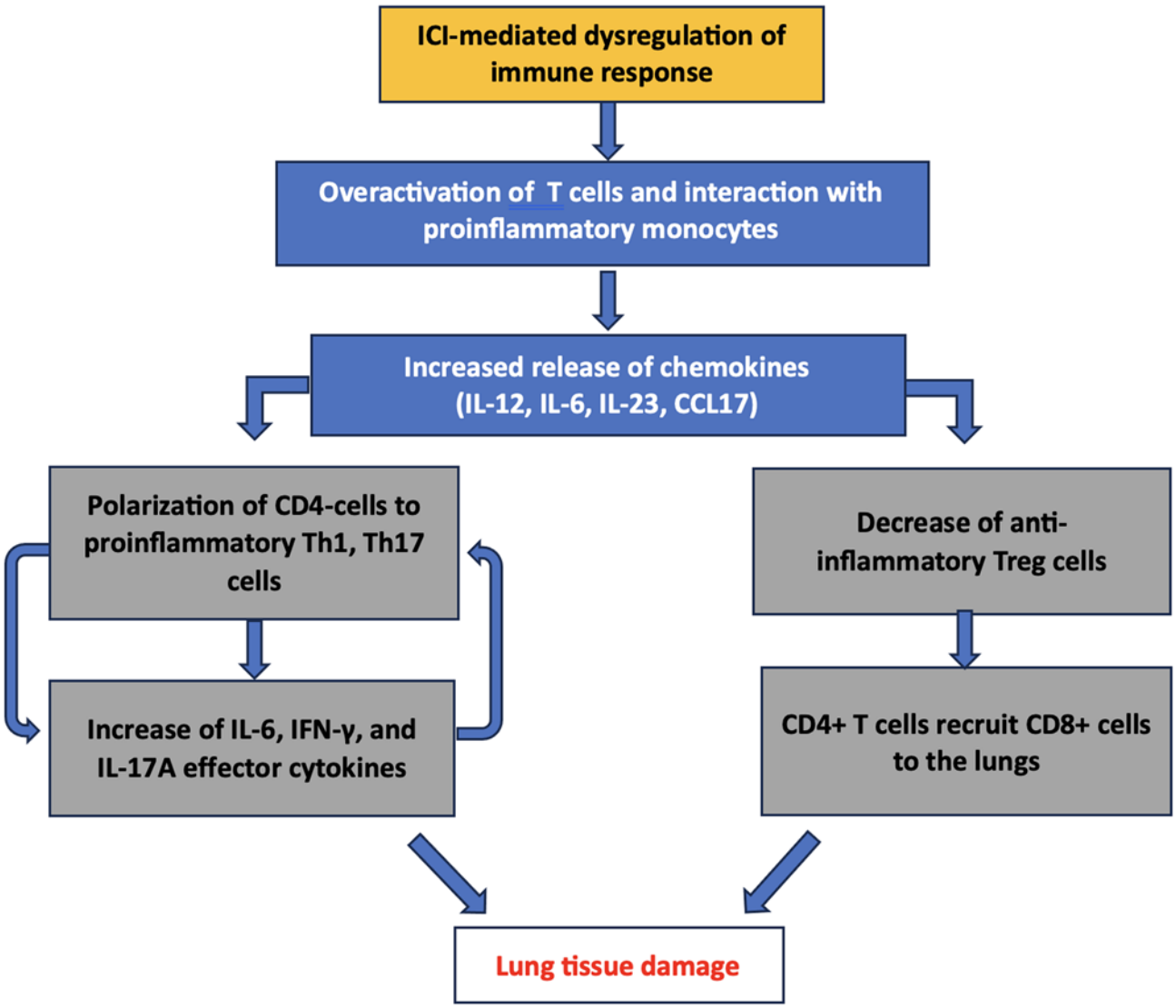

Figure 1. Outline of the pathophysiological mechanisms of ICI-related pneumonitis. The pathogenesis of immune-related adverse events seems linked to the disruption of immune regulation of tissue homeostasis rather than the activation of the immune system, as suggested by the lack of laboratory confirmation of autoimmunity. ICI, immune checkpoint inhibitor; Treg cell, T-regulatory cell; Th1 cell, type 1 T-helper cell; CCL17, C-C motif chemokine ligand 17.

the risk of disease progression and minimize morbidity and mortality associated with this adverse event.

5. Diagnostic evaluation

Diagnosing ICI-related pneumonitis requires a comprehensive assessment encompassing clinical, radiological and laboratory findings (1-3). The detailed description of these examinations extends beyond the scope of the present review. Pulmonary function tests (PFTs), including spirometry and diffusion capacity testing, provide valuable information about lung function and may reveal restrictive or obstructive patterns indicative of lung involvement (1-3). However, PFT findings can be nonspecific and should be interpreted with clinical and radiological findings (3). The European Society for Medical Oncology and the American Society for Clinical Oncology recommend bronchoscopy with bronchoalveolar lavage, and, in some cases, transbronchial lung biopsy may be performed to obtain samples for analysis (33,34). Bronchoalveolar lavage fluid analysis, including cell counts, protein level analysis and microbiological cultures, can evidence a high lymphoid infiltrate consistent with immune-mediated pneumonitis, helping to exclude alternative diagnoses and guide therapeutic decisions (35). Transbronchial biopsy may be utilized in cases of diagnostic uncertainty or severe disease to obtain histological samples for pathological evaluation (33-35). Surgical lung biopsy using video-assisted thoracoscopic surgery to ascertain differential diagnosis from tumor progression may be used in cases where the suspicion of progressive cancer persists (33,34). However, these investigations must be integrated with clinical and radiological findings. Specifically, CT scanning of the chest serves as the cornerstone in radiological evaluation, revealing characteristic patterns of pneumonitis such as ground-glass opacities (GGOs), consolidations or interstitial infiltrates (1-3,36-38).

6. Radiological findings

Pneumonitis is a rare irAE following ICI therapy, and it manifests as interstitial lung disease (36). Table II summarizes the main CT patterns observed in ICI-related

Table I. Concise overview of the main clinical features of ICI-related pneumonitis.

Clinical features	Description
Respiratory symptoms	Dyspnea, cough and chest discomfort
Constitutional symptoms	Fatigue, generalized weakness or tiredness, malaise and low-grade fever
Onset	Variable: Symptoms may develop weeks to months after initiating ICI therapy
Severity	Range: Symptoms can range from mild to severe, with potential for rapid progression
Progression	• Gradual worsening: Symptoms may worsen over time, impacting daily activities and quality of life • Respiratory distress: Severe cases may present with acute respiratory distress, requiring urgent medical attention
Associated risk factors	• Treatment type: Higher incidence with PD-1/PD-L1 inhibitors compared to anti-CTLA-4 agents • Tumor type: Increased risk in non-small cell lung cancer compared with other malignancies • Pre-existing lung disease: History of lung disease may predispose to pneumonitis
Management challenges	• Diagnosis: Nonspecific symptoms may mimic other pulmonary conditions, necessitating careful evaluation • Severity assessment: Accurate assessment of disease severity is crucial for appropriate management.
Monitoring and treatment	• Close monitoring: Regular assessment of respiratory symptoms and clinical status is essential • Prompt intervention: Early recognition and initiation of treatment can minimize morbidity and mortality

ICI, immune checkpoint inhibitor; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell death 1; PD-L1, programmed cell death protein 1.

Table II. Main CT patterns of ICI-related pneumonitis.

CT Pattern	Pattern	Features	Histopathology
Organizing pneumonia	Consolidation with a peri-bronchial and subpleural distribution, often migrating over time	GGOs with areas of consolidation and air bronchograms	Granulation tissue plugs within airspaces
Nonspecific interstitial pneumonia	Bilateral, symmetric, peripheral and basal predominant	GGOs with reticular or linear opacities, traction bronchiectasis, and honeycombing	Uniform interstitial inflammation and fibrosis
Hypersensitivity pneumonitis	Centrilobular nodules with a ground-glass or reticular pattern, often with upper lobe predominance	Centrilobular nodules, GGOs, mosaic attenuation, and air trapping	Peribronchiolar inflammation and granuloma formation
Diffuse alveolar damage	Diffuse GGOs and consolidations with a bilateral and symmetric distribution	Diffuse involvement of both lungs, often associated with severe respiratory compromise	Alveolar damage with hyaline membrane formation

GGOs, ground-glass opacities; ICI, immune checkpoint inhibitor.

pneumonitis. Pneumonitis secondary to ICI treatment presents in four distinct patterns: i) Organizing pneumonia (OP); ii) nonspecific interstitial pneumonia (NSIP); iii) hypersensitivity pneumonitis (HP); and iv) diffuse alveolar damage (DAD) (36). While chest X-ray findings in ICI-related pneumonitis may be nonspecific, characteristic abnormalities can aid the diagnostic process (37). Common radiographic manifestations include patchy or diffuse opacities, consolidations and interstitial infiltrates, which may be bilateral and involve multiple lung lobes (37,38). Additionally, air bronchograms or a 'ground-glass' appearance may suggest alveolar involvement and inflammatory changes within the lung parenchyma as shown in Figs. 2-4, which report on a case of gastric, lung and rectal cancer, respectively. However, it is essential to recognize that chest X-ray findings alone may not be sufficient to diagnose or

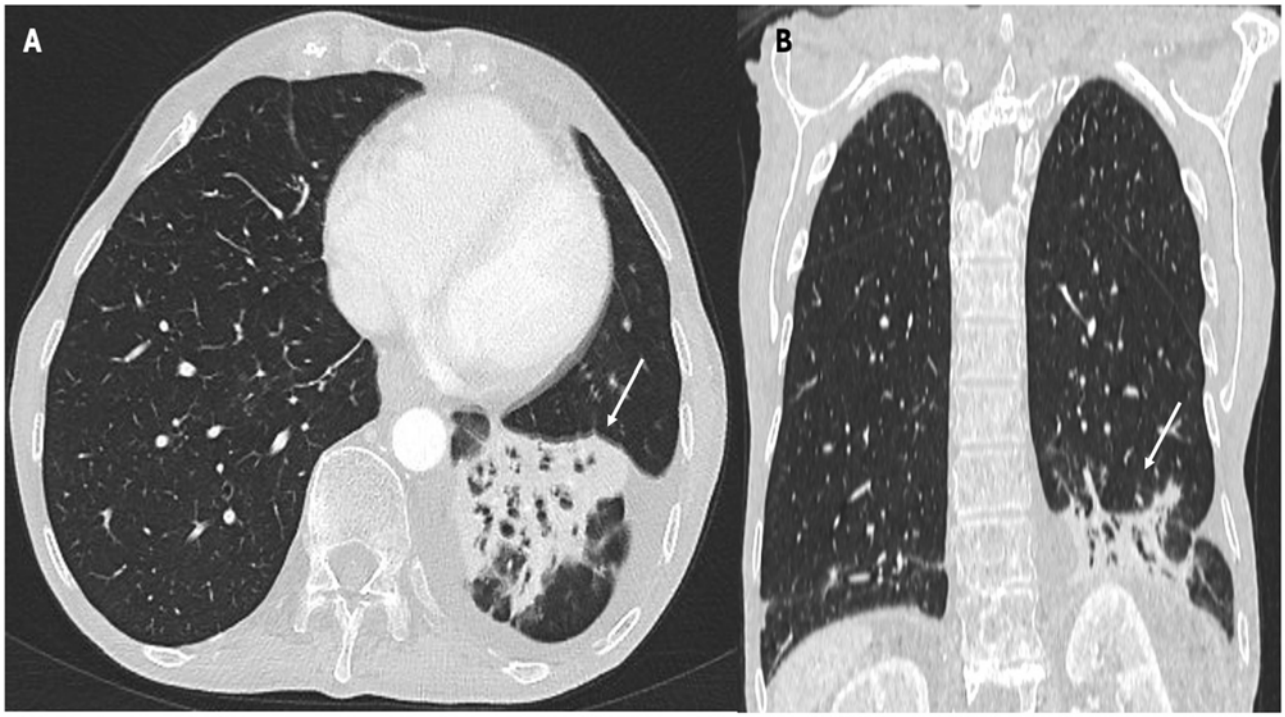

Figure 2. (A) Axial and (B) coronal CT scan with lung parenchyma reconstruction demonstrating consolidation in the left lower lobe characterized by air bronchograms (see arrows). The image is from a 52-year-old patient undergoing therapy with nivolumab for locally advanced gastric cancer.

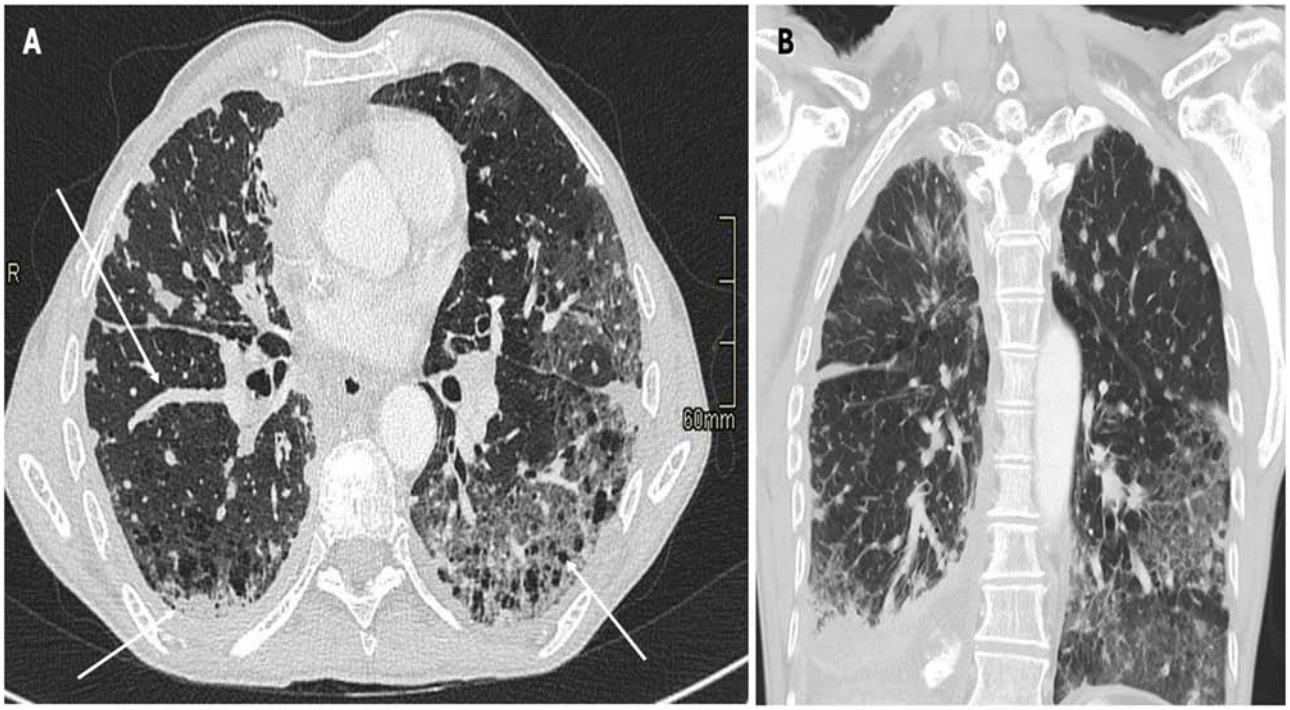

Figure 3. (A) Axial and (B) coronal CT scans with lung parenchyma reconstruction revealed extensive ground-glass opacity predominantly distributed peripherally in the lower lung lobes, accompanied by interstitial septal thickening and more consolidated regions (see arrows). The consolidations are notably pronounced and extensive in the right lower lobe, confirming immunotherapy-induced pneumonia in a 58-year-old patient recently diagnosed with lung adenocarcinoma and undergoing osimertinib therapy.

exclude pneumonitis (37) definitively. Further imaging with CT of the chest is often necessary to delineate the extent and nature of pulmonary abnormalities and guide subsequent management decisions (38).

OP. The characteristic radiographic pattern of OP in ICI-related pneumonitis often manifests as patchy areas of consolidation with or without GGOs on high-resolution computed tomography (HRCT) of the chest (39). OP is characterized

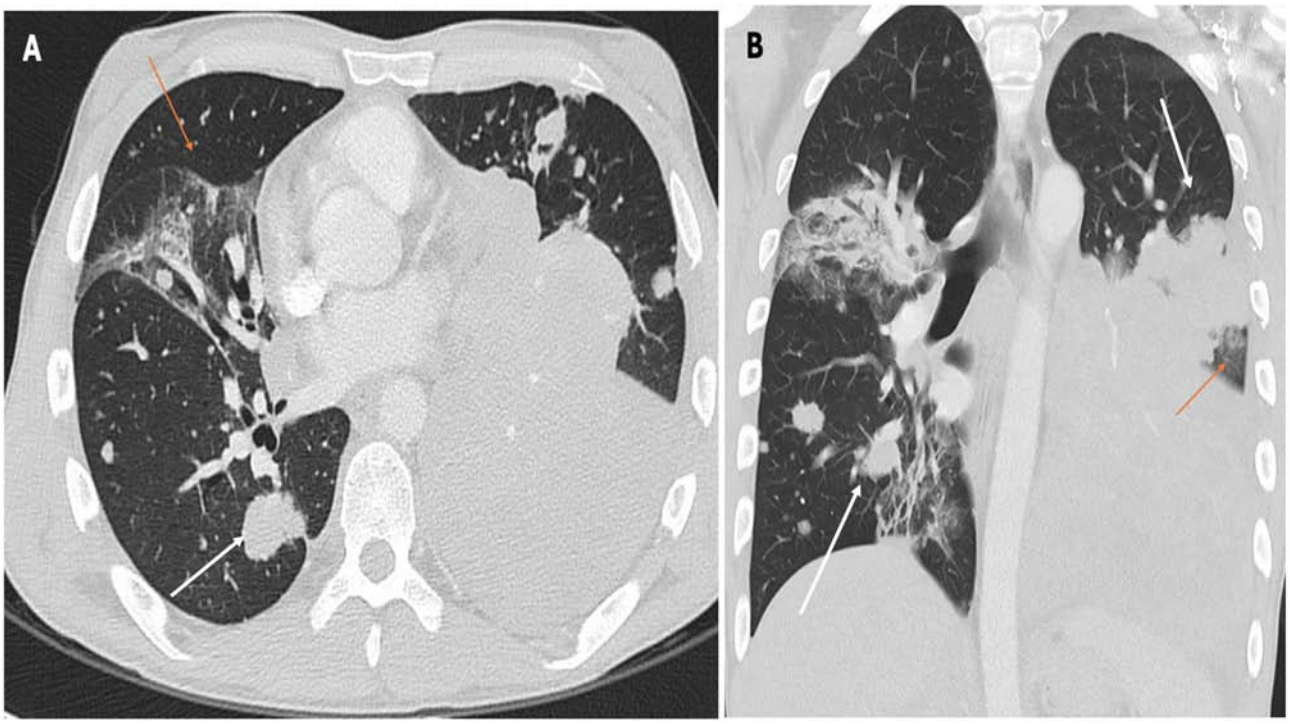

Figure 4. (A) Axial and (B) coronal CT scan with lung parenchyma reconstruction depicting a 58-year-old female patient with metastatic rectal adenocarcinoma with progressing pulmonary metastases undergoing experimental immunotherapy with Nivolumab (see white arrows). Note several areas of increased parenchymal density, predominantly perilesional, characterized by ground-glass opacity (see orange arrows).

by intraluminal plugs of granulation tissue within the distal airspaces, leading to consolidative opacities on imaging (37). These consolidations typically have a subpleural and peri broncho vascular distribution (37). They may show a migratory or 'reverse halo' pattern, where a rim of consolidation surrounds a central area of ground-glass opacity but is not pathognomonic (40).

NSIP. The HRCT pattern of NSIP in ICI-related pneumonitis typically manifests as bilateral, patchy ground-glass and reticular opacities with a basal and peripheral distribution (37,38). These findings may be accompanied by traction bronchiectasis and architectural distortion (37,38). Additionally, unlike usual interstitial pneumonia, NSIP in ICI-related pneumonitis tends to spare the subpleural regions and show less honeycombing (41).

HP. The CT pattern of HP can resemble certain features observed in ICI-related pneumonitis, particularly with NSIP. The characteristic pattern typically includes diffuse GGOs, centrilobular nodules and mosaic attenuation patterns, reflecting the characteristic involvement of the airspaces and small airways (12,41,42). Findings such as bronchial wall thickening, air trapping, and mosaic perfusion on perfusion imaging may also indicate HP (12). Conversely, NSIP typically presents with bilateral and symmetric reticular opacities, GGOs, or a combination of both, with a predominantly basal and subpleural distribution (12). Honeycombing, traction bronchiectasis and architectural distortion are more commonly observed in advanced stages of NSIP and may aid in distinguishing it from HP (42).

DAD. On CT scans, DAD manifests as diffuse bilateral GGOs with or without associated consolidations and interstitial thickening, often accompanied by traction bronchiectasis (43). These findings reflect the underlying pathophysiology of pneumonitis, characterized by widespread injury to the alveolar epithelium and capillary endothelium, leading to alveolar flooding, interstitial edema and inflammatory cell infiltration (44). This pattern has been observed in patients treated with EGFR-TKIs, anaplastic lymphoma kinase inhibitors and ICIs in various stages of their disease (45-47). Its severity increases over time and is associated with severe clinical outcomes.

7. Management strategies

At present, there are no validated recommendations for ICI-related pneumonitis treatment; patient management relies on clinical experience and a multidisciplinary approach (3,35). The ASCO expert consensus developed clinical practice guidelines according to The Common Terminology Criteria for Adverse Events (35). The grading was as follows: i) Grade 1, asymptomatic disease; ii) grade 2, symptomatic disease with limited instrumental activities of daily living (ADL) needing medical intervention; iii) grade 3, severe symptoms limiting self-care ADL requiring oxygen; and iv) grade 4, life-threatening respiratory compromise requiring urgent intervention (35). Managing ICI-related pneumonitis necessitates a tailored approach balancing immunosuppression with oncologic efficacy (48,49). Treatment algorithms involve prompt cessation of ICIs and initiation of corticosteroids, typically prednisone or

Table III. Features of ICI-related pneumonitis vs. cancer progression.

Feature	ICI-related pneumonitis	Disease progression
Onset	Variable, can occur weeks to months after initiating ICI therapy	Typically gradual, may occur at any stage of cancer progression
Symptoms	Respiratory symptoms including dyspnea and cough; constitutional symptoms including fatigue and malaise	May be asymptomatic and respiratory symptoms may worsen gradually
Radiographic findings	Ground-glass opacities, consolidations, interstitial infiltrates and air bronchograms	Progression of known or new pulmonary nodules, infiltrative or cavitary lesions and pleural effusions (in advanced stages)
Progression of symptoms	May fluctuate with treatment and symptoms and may improve with corticosteroid therapy	Progressive worsening of symptoms over time and symptoms may not respond to corticosteroids
Response to treatment	Improvement in symptoms and radiographic findings with corticosteroid therapy	Lack of improvement or worsening despite treatment
Clinical context	Recent initiation or ongoing treatment with immune checkpoint inhibitors	Known history of lung cancer or evidence of disease progression on imaging
Multidisciplinary approach	Collaboration among oncologists, pulmonologists and radiologists is essential for diagnosis and management	Collaboration among oncologists, radiologists and pathologists is crucial for accurate staging and treatment decisions

ICI, immune checkpoint inhibitor.

methylprednisolone, at a dose of 1-2 mg/kg/day (48). Close monitoring of clinical and radiological response is paramount, with gradual tapering of corticosteroids guided by symptom resolution and radiographic improvement (49). In refractory cases or those with severe pneumonitis, additional immunosuppressive agents such as infliximab or mycophenolate mofetil may be considered, although their efficacy remains uncertain (50). Infliximab or cyclophosphamide have been proposed in clinical trials and initially approved by the US FDA for patients receiving ipilimumab, especially for severe, immune-mediated gastrointestinal side effects (33,50). Anecdotal reports have suggested the use of interleukin-17 blockade may provide relief from immune-mediated skin and gastrointestinal toxic effects (33,50). Collaborative efforts between oncologists, pulmonologists and rheumatologists are essential in optimizing patient outcomes and minimizing treatment-related complications (33).

8. Differential diagnosis from disease progression in lung cancer

Distinguishing between ICI-related pneumonitis and disease progression in lung cancer demands a comprehensive evaluation incorporating multiple criteria, including variations in tumor growth rate and tumor growth kinetics (51-53). It typically represents a diagnosis of exclusion, necessitating the comprehensive exclusion of alternative etiologies such as infection and radiation-related pneumonitis (54). Given the overlapping clinical and radiological features of these conditions, a thorough evaluation is essential to differentiate ICI-related pneumonitis from other potential causes of pulmonary symptoms (Table III). Firstly, the clinical context is crucial, as recent initiation or ongoing treatment with ICIs raises suspicion for pneumonitis (51-53). At the same time, a history of lung cancer or evidence of disease progression suggests tumor advancement (51-53). Secondly, the temporal relationship plays a pivotal role, with ICI-related pneumonitis typically manifesting weeks to months after therapy initiation, contrasting with the more gradual progression of lung cancer (33). Symptomatology, including respiratory and constitutional symptoms, offers additional insight, as does the response to treatment; improvement with corticosteroids favors pneumonitis, while lack thereof may indicate disease progression (16). Radiographic findings, mainly CT, provide further differentiation, with characteristic patterns such as GGOs favoring pneumonitis and progressive nodules suggesting tumor growth (44).

9. Concluding statement

ICI-related pneumonitis represents a clinically significant irAE associated with immunotherapy, necessitating timely recognition and management to mitigate morbidity and mortality. A systematic diagnostic approach integrating clinical, radiological and laboratory findings is imperative for accurate diagnosis and appropriate therapeutic interventions (55). Future research endeavors should focus on elucidating the underlying mechanisms of pneumonitis and identifying predictive biomarkers to guide personalized treatment strategies in this evolving field of oncology.

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SL, MRV and EM equally participated in the conceptualization of the paper. EM and VG wrote and edited the manuscript. AA, GS and DS critically revised the literature and manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent to publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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