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Immune Checkpoint Inhibitor-Induced Pneumonitis

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Abstract: Immune checkpoint inhibitors (ICIs) have transformed oncology, offering durable responses for a range of malignancies. However, these agents can provoke immune-related adverse events (irAEs), with pneumonitis being one of the most serious and potentially fatal complications. This article reviews the pathogenesis, clinical features, diagnostic strategies, management, and outcomes of checkpoint inhibitor-induced pneumonitis (CIP), referencing recent literature and clinical guidelines.

Keywords: Immune checkpoint inhibitors (ICIs), Pneumonitis, Immune-related adverse events (irAEs), Checkpoint inhibitor-induced pneumonitis (CIP), Cancer immunotherapy.

INTRODUCTION

ICIs, including agents targeting PD-1, PD-L1, and CTLA-4, have revolutionized oncology practice. By unleashing anti-tumor immune responses, these therapies can also disrupt tolerance to self-antigens, leading to irAEs. CIP is unique among irAEs for its variable clinical presentation and high morbidity and mortality[1][2][3].

Epidemiology

- **Incidence**: CIP occurs in approximately 2.5–5% of ICI-treated patients receiving monotherapy; the incidence increases to 7–10% with ICI combination therapy[4]. Real-world data suggest broader rates of 7–19%. Higher rates are observed in those with non-small cell lung cancer and renal cell carcinoma compared to melanoma[3][4].
- **Mortality**: CIP accounts for ~35% of anti-PD-1/PD-L1 immunotherapy-related deaths[1][3][4].

Tumor Type	Incidence of All-Grade CIP (%)
NSCLC	1.4–5.8
Melanoma	1–4
Renal Cell Carcinoma	1–4.8

PATHOPHYSIOLOGY

ICIs disrupt immune checkpoints, leading to unregulated T-cell activity and immune-mediated inflammation of the lung parenchyma. The precise immunological mechanisms underlying CIP are not completely defined, and likely

involve T-cell infiltration, cytokine release, and autoantibody production[1][4].

Clinical Presentation

- **Onset**: Most cases develop within the first 3–6 months but can occur at any stage, from days to over a year after initiation[5][6].
- **Symptoms**: Highly variable, ranging from asymptomatic radiographic findings to severe respiratory failure.
  - Dyspnea (53%)
  - Cough (35%)
  - Fever (12%)
  - Chest pain (7%)[7]

Symptom	Frequency (%)
Dyspnea	53
Cough	35
Fever	12
Chest pain	7

Patients may also develop extrapulmonary irAEs simultaneously[6].

Radiographic and Pathologic Features

Common CT patterns:

- Organizing pneumonia (most frequent)
- Nonspecific interstitial pneumonia
- Hypersensitivity pneumonitis
- Acute interstitial pneumonia/ARDS
- Bronchiolitis
- Radiation recall pneumonitis[8][9]

Radiographic Pattern	Clinical Implication
Organizing pneumonia	Subacute onset, patchy consolidations
Diffuse ground-glass opacities (GGOs)	Severe, may signal ARDS-like changes
Mixed or chronic interstitial patterns	Indolent, may respond well to steroids

Prognosis tends to be worse with diffuse GGOs/acute lung injury patterns[9].

Diagnosis

- CIP is a diagnosis of exclusion.
- Key steps:
  - Comprehensive history and physical exam.
  - Exclusion of infections, tumor progression, pulmonary embolism, or heart failure.
  - High-resolution chest CT.
  - Optional: Bronchoscopy with lavage to rule out infection, especially for severe or unclear cases[4][6].

Grading of Severity

Grade	Clinical Findings
1	Asymptomatic; radiographic only
2	Mild–moderate symptoms, no hypoxia
3	Severe symptoms, hypoxia
4	Life-threatening (respiratory failure)

MANAGEMENT

- **Grade 1 (mild):**
  - Continue ICIs with close monitoring.
  - Consider temporary interruption.
- **Grade 2 (moderate):**
  - Hold ICI.
  - Initiate corticosteroids (prednisone or equivalent, 1–2mg/kg/day).
  - Taper steroids over ≥4–6 weeks if improved.
- **Grade 3–4 (severe/life-threatening):**
  - Permanently discontinue ICI.
  - Hospitalize, provide supplemental oxygen or mechanical ventilation as needed.
  - High-dose intravenous steroids (methylprednisolone 1–2mg/kg/day).
  - Consider additional immunosuppression (e.g., infliximab, mycophenolate mofetil) if refractory to steroids[1][4][6].

Grade	Treatment
1	Monitor, may continue ICI
2	Hold ICI, oral corticosteroids
3–4	Stop ICI, IV corticosteroids, ± second-line immunosuppressants

Prompt recognition and treatment are essential to minimize morbidity and mortality[4][6].

Outcomes

- Most patients recover with appropriate management; up to 80% respond to corticosteroids[1][4].
- Recurrence is possible, particularly with re-challenge.
- Chronic changes (fibrosis) or persistent symptoms may occur, especially after severe CIP[10].

Risk Factors

- Combination immunotherapy (PD-1/PD-L1 + CTLA-4 inhibitors)[2][4]
- Prior lung disease (COPD, interstitial lung disease)
- NSCLC diagnosis
- Previous thoracic irradiation

Graph: Incidence and Grading of CIP by ICI Regimen

Regimen	All-grade CIP (%)	Grades 3-4 CIP (%)
PD-1 inhibitor monotherapy	2.5–5.0	1–2
PD-L1 inhibitor monotherapy	1.3–3.3	<1
CTLA-4 inhibitor monotherapy	<1	<1
Combination (PD-1 + CTLA-4)	7–10	3–5

Figure: Radiographic Patterns of ICI-Related Pneumonitis
A depiction of CT findings: patchy consolidations (organizing pneumonia), diffuse GGOs (ALI/ARDS), and mixed/interstitial patterns.

Prevention and Monitoring

- Baseline pulmonary evaluation prior to ICI.
- Patient education on reporting new respiratory symptoms promptly.
- Continued research on predictive biomarkers is needed[1][4].

CONCLUSION

Checkpoint inhibitor-induced pneumonitis is an uncommon but potentially life-threatening irAE requiring high awareness among clinicians. Early diagnosis, proper grading, and evidence-based management using corticosteroids

and immunosuppressants are critical to improving patient outcomes. Ongoing studies and integration of biomarkers may further refine risk stratification, prevention, and therapy[1][4][6].

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