SPECIAL ARTICLE

Imaging Features of Pulmonary Immune-related Adverse Events

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ABSTRACT

Pulmonary immune-related adverse events represent rare but potentially severe side effects of immunotherapies. Diagnosis is often challenging, as symptoms and imaging features are not specific and may mimic other lung diseases, thus potentially delaying appropriate patient management. In this setting, an accurate imaging evaluation is essential for a prompt detection and correct management of these drug-induced lung diseases. The purpose of this article is to review the different types of pulmonary immune-related adverse events, describe their imaging characteristics on both high-resolution computed tomography and positron emission tomography/computed tomography and stress their underlying diagnostic challenge by presenting the mimickers.

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Introduction

Immune checkpoint inhibitors (ICIs) are a new class of therapeutic agents, which have profoundly changed the landscape of cancer therapy. The ICIs target specific immune checkpoints located either on T cells or on neoplastic cells down-regulating T-cell stimulation and host immune response against cancer.1,2 To date, several ICIs are approved globally, alone or in combination, in various locally advanced or metastatic cancers, such as follows: nivolumab, pembrolizumab, and cemiplimab, which target programmed cell death protein-1 (PD-1); durvalumab, atezolizumab, and avelumab, which target programmed death ligand-1 (PDL-1); and ipilimumab, which targets cytotoxic T-lymphocyte antigen-4 (CTLA-4).3,4

ICIs administration is associated with specific side effects known as immune-related adverse events (irAEs), which most frequently arise during the first months after treatment initiation, although cases after therapy discontinuation have been reported.4-10 Although the physiopathology of irAEs remains to be fully understood, it is presumed that, in predisposed patients or in the presence of pre-existing
conditions, ICIs may overstimulate the immune system and alter host homeostasis, causing an excessive inflammatory response. These irAEs are most often of low grade and can involve nearly any organ system. They are characterized by uncertain predictive features but are usually reversible with immunosuppression and discontinuation of therapy whenever needed.2,5,11 Colitis, skin toxicities, and endocrine dysfunction are the most frequent events reported in 50%, 45%, and 13% of patients, respectively.5,12

These irAEs have been consistently correlated with a better outcome on ICIs across diseases, whereas their subsequent management has not been firmly found to affect tumor response to date.10,13-16 Conversely, concerning pulmonary and hepatobiliary irAEs, the impact on the patient’s outcome remains controversial.15,17 Nevertheless, especially in patients requiring immunosuppressive treatment for irAEs, the risk of opportunistic infection is increased.16 In addition, treatment “rechallenge” remains an issue, with IrAE recurrence observed in up to one-third of patients.19-21

Pulmonary irAEs are rare, but potentially serious toxicities could happen.5,22,23 Although most patients experience grade 1 to 2 events, such as mild dyspnea (53%), cough (35%), or may even be asymptomatic with irAE incidentally discovered on routine follow-up imaging, life-threatening pneumonitis has been reported in up to 2% of cases.5,10,11 Incidence of ICI-induced pneumonitis (IP) is higher in combined therapy (6.5%–10%) than in monotherapy (3%–4%).6,19,24 Anti–CTLA-4 therapy usually triggers a sarcoid-like reaction (5%–7%) rather than a pneumonitis (<1%).25,26 Conversely, sarcoid-like reactions are uncommon with other ICIs. As for other irAEs, the development of IP is irrespective of the line of therapy and may occur between a few days and up to 1.5 years after the beginning of the therapy, with a mean time to onset of 2.3 to 2.8 months.19,21 Although no risk factors have been clearly identified so far, it is believed that predisposing conditions contribute to the irAE development, according to a “two-hit” model.18 It has been hypothesized that, in addition to possible systemic determinants, local pre-existing conditions, such as smoking exposure, chronic obstructive pulmonary disease, fibrosis, previous pulmonary infection, or radiotherapy (RT) alone or in combination with chemotherapy, may predispose to IP by altering the local homeostasis.24,27-29 Among these, a special attention has been paid to RT. In fact, combined immuno-RT has been introduced as a standard of care after recent trials have reported a prolonged progression-free and overall survival compared with ICIs alone.10-35 The rationale of combining RT with ICI is based on the fact that, besides a direct tumor-cell killing, radiations stimulate the immune system response, resulting in enhancement of the ICI effect.36 Nevertheless, while reassuring on a comparable risk of severe adverse events,30-32,34,35 these trials reported a moderately increased incidence of all-grade pneumonitis in patients with previous thoracic RT.30-32,34,35

The lack of a pathognomonic feature makes pulmonary irAEs a diagnosis of exclusion, which is usually obtained by combining clinical evaluation, imaging findings, and laboratory analyses, including infectious workup and bronchoalveolar lavage (BAL) when feasible, whereas lung biopsy is rarely required.11 BAL analysis is crucial to reach the diagnosis of IP, as it allows to rule out infection or neoplastic cells and to identify alveolar inflammatory cells. At BAL cytology, IP usually reveals a predominantly lymphocytic or a mixed pattern, although a pure neutrophilic pattern has also been observed in case of diffuse alveolar damage.27,37

In clinical practice, ICI pneumonitis remains a diagnostic challenge. The variable time of IP onset during ICI therapy, the wide spectrum of clinical and radiologic presentation mimicking other lung pathologic conditions, especially infection or tumor progression, and the inherent invasive nature of bronchoscopy in patients suffering from respiratory impairment limiting its feasibility may all lead to diagnostic uncertainty and delay in dedicated management.

Hence, familiarity with irAEs is crucial.18 The purpose of this article is to review the imaging characteristics of pulmonary irAEs at high-resolution computed tomography (HRCT) and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT), in order to make all involved physicians familiar with this condition, its potential complications, and diagnostic pitfalls.

The Role of Imaging

Imaging is a key tool in the management of patients receiving ICIs. The main goals of CT and 18F-FDG PET/CT, which are noninvasive and reproducible imaging modalities, are the routine assessment of response to therapy of malignancies. At the same time, they ensure an accurate diagnostic workup of pulmonary irAEs, allowing the detection of any new-onset pulmonary changes whatever their nature. In this case, an acquisition with thin slices at breath-hold full inspiration is required.
Any new respiratory symptoms occurring in patients receiving concurrent or previous ICIs should be promptly investigated to look for complications, such as disease progression, irAEs, or infections. In contrast, radiological manifestations of pulmonary irAEs can be found incidentally before the onset of symptoms in up to 40% of cases.\textsuperscript{19,27} Chest radiograph is not adequate in this setting, as abnormalities are not identified in up to 25% of cases.\textsuperscript{19,38} (Fig. 1). HRCT is the modality of choice, allowing early detection and accurate evaluation of pattern, distribution, and extent of lung abnormalities. Technically, thin contiguous slices during a unique breath-hold full inspiration are required with reconstruction with a sharp kernel, allowing a high-contrast resolution between the interstitium and the airspaces. Comparison with previous examinations, including the most recent and the older ones, is mandatory to identify any new-onset changes with confidence. Contrast agent administration is not required for the diagnosis of irAEs. HRCT is also useful to assess the evolution of irAEs.

At PET/CT, as other inflammatory abnormalities, pulmonary irAEs are \textsuperscript{18}F-FDG avid, which may allow an early detection even before the onset of symptoms. Nevertheless, their characterization may be difficult owing to several technical limitations in CT image acquisition, such as breathing artifacts in free-breathing acquisitions, thick slice thickness, and large field-of-view. Free-breathing acquisition may also generate dependent ground-glass opacities (GGOs) that may preclude a correct recognition of underlying changes that may be related to irAEs. For this reason, in case of new-onset lung changes unlikely to be metastatic, it may be advisable to perform an additional HRCT before BAL for a better assessment (Fig. 2).

**Imaging Features**

Pulmonary irAEs can be schematically divided into IP and sarcoidosis-like reactions.

The radiologic diagnosis of IP is challenging because there are no typical imaging findings. In fact, IP may display a wide range of imaging features, not classifiable in any specific pattern in some cases. Moreover, IP is a dynamic process, which evolves over time. Finally, the presence of underlying abnormalities, such as chronic obstructive pulmonary disease, tumoral spread, fibrotic changes owing to previous RT, or atelectasis, further make the identification of IP-related features difficult.\textsuperscript{7,19-21}

The main radiologic patterns of presentation are found in Table 1. The most frequent imaging pattern of IP is organizing pneumonia (OP).\textsuperscript{19-21,27} OP is characterized by patchy peribronchovascular and subpleural consolidations, often associated with GGOs.\textsuperscript{20,39} The typical migratory feature can be identified on subsequent scans (Fig. 3).\textsuperscript{27} This pattern can be found in all-grade IP, and the extent of pulmonary involvement generally reflects IP severity. Nonspecific interstitial pneumonia (NSIP) and hypersensitivity pneumonitis are two other possible patterns of IP.\textsuperscript{19-21} NSIP most often presents as bilateral peripheral GGOs with irregular reticulations and traction bronchiectasis and bronchiolectasis, with a lower lung zone predominance and typically, but nonsystematically, sparing the subpleural parenchyma.\textsuperscript{39} Nevertheless, in our experience, a pure NSIP pattern has been rarely observed in IP. Centrilobular micronodules and mosaic air-trapping are typical findings of hypersensitivity pneumonitis.\textsuperscript{39} These patterns are generally associated with low-grade events.\textsuperscript{20} Conversely, an acute interstitial pneumonitis/diffuse alveolar damage pattern has been identified in

![Figure 1. ICI pneumonitis detected at CT scan, whereas chest radiography result was negative. A 65-year-old male patient with metastatic renal cell carcinoma (bone, lung) treated with nivolumab since September 2016 underwent radiotherapy of dorsal vertebral metastasis in December 2016. (A) Restaging CT in March 2017. In April 2017, because of a new-onset grade 2 dyspnea, (B) chest radiography was performed revealing no abnormalities, whereas (C) a few ground-glass areas (arrows) in the apical segments of the upper lobes were detected at CT scan performed on the same day. An opportunistic infection was excluded at both serology and BAL; the BAL cytology result revealed a predominantly lymphocytic inflammation. Nivolumab was discontinued, and corticosteroid therapy was introduced. B, bone metastasis; BAL, bronchoalveolar lavage; CT, computed tomography; ICI, immune checkpoint inhibitor; L, lung metastasis.](image-url)
Table 1. Imaging Features and Bronchoalveolar Lavage Findings of the Most Frequent Radiologic Patterns of ICI Pneumonitis

<table>
<thead>
<tr>
<th>Radiologic Pattern</th>
<th>Imaging Features</th>
<th>Bronchoalveolar Lavage</th>
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<tbody>
<tr>
<td>OP</td>
<td>Patchy alveolar consolidations and/or GGOs</td>
<td>Mixed pattern with predominance of lymphocytes (20%-40%) and mild elevation of neutrophils (-10%) and/or eosinophils (-5%)</td>
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<tr>
<td></td>
<td>Distribution:</td>
<td></td>
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<tr>
<td></td>
<td>Peribronchovascular and/or subpleural</td>
<td></td>
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<tr>
<td></td>
<td>Lower lobe predominance</td>
<td></td>
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<tr>
<td></td>
<td>Other suggestive findings:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Band-like consolidations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perilobular GGOs/consolidations</td>
<td></td>
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<tr>
<td></td>
<td>Reverse halo sign</td>
<td></td>
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<tr>
<td></td>
<td>Migratory aspect: location change over time, even without treatment</td>
<td></td>
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<tr>
<td></td>
<td>± Slight bronchial dilatation</td>
<td></td>
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<tr>
<td></td>
<td>May arise in the same area of a tumor (primary or metastatic) and in radiation therapy field</td>
<td></td>
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<tr>
<td>NSIP</td>
<td>Bilateral GGOs with reticulations</td>
<td>Mixed pattern similar to OP, with predominance of lymphocytes and mild elevation of neutrophils and/or eosinophils</td>
</tr>
<tr>
<td></td>
<td>Distribution:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subpleural and/or peribronchovascular</td>
<td></td>
</tr>
<tr>
<td></td>
<td>± Sparing of the subpleural parenchyma</td>
<td></td>
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<tr>
<td></td>
<td>Lower lobe predominance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>± Bronchiectasis and bronchiolactasis</td>
<td></td>
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<tr>
<td>HP</td>
<td>Bilateral GGOs, centrilobular micronodules, and patchy hypoattenuated lobules</td>
<td>Usually purely lymphocytic alveolitis with high lymphocyte count</td>
</tr>
<tr>
<td></td>
<td>Upper lobe predominance</td>
<td></td>
</tr>
<tr>
<td>AIP/DAD</td>
<td>Diffuse GGOs with alveolar consolidation in the dependent parenchyma</td>
<td>Usually neutrophilic alveolitis</td>
</tr>
<tr>
<td></td>
<td>± Small pleural effusion</td>
<td></td>
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<tr>
<td>Bronchiolitis</td>
<td>Centrilobular micronodules with tree-in-bud appearance Bronchial wall thickening</td>
<td>Not precisely defined. Mixed lymphocytic/eosinophilic and neutrophilic patterns have been reported</td>
</tr>
<tr>
<td>Pulmonary nodules or mass-like lesions</td>
<td>Solitary nodule or mass</td>
<td></td>
</tr>
<tr>
<td>Unclassifiable pattern</td>
<td>Abnormalities with no typical aspect/distribution or isolated features, such as ill-defined patchy GGOs</td>
<td>Various patterns</td>
</tr>
<tr>
<td>Sarcoidosis like</td>
<td>Symmetrical bilateral hilar and mediastinal enlargement Bilateral micronodules in a perilymphatic distribution</td>
<td>Moderate lymphocytic alveolitis</td>
</tr>
</tbody>
</table>

AIP/DAD, acute interstitial pneumonitis/diffuse alveolar damage; GGOs, ground-glass opacities; HP, hypersensitivity pneumonitis; ICI, immune checkpoint inhibitor; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia.
the most severe cases.\textsuperscript{20,27} It is characterized by diffuse bilateral GGOs with consolidation in the dependent parts of the lungs.\textsuperscript{39} This pattern is rare but reflects worsening in the clinical course of IP (Fig. 4). Rarely, airway disease without interstitial involvement has been observed.\textsuperscript{40-42} These patients may present with asthma-like symptoms, bronchial wall thickening, and micronodules with a “tree in bud” appearance. Pleural effusion can also be present

Figure 3. Grade III ICI pneumonitis with OP pattern. A 75-year-old male patient with multifocal HCC previously treated with chemoembolization and radiofrequency ablation received 4 cycles of nivolumab between August 2017 and October 2017, which were held owing to progression of disease. After three months, the patient developed dyspnea, cough, asthenia, and thoracic pain. A CT was performed revealing (A) the appearance of patchy ill-defined GGOs (arrows) associated with subpleural GGOs (arrowheads). A lymphocytic-predominant pattern was found after bronchoalveolar lavage, and pulmonary infection was excluded. Steroid therapy was then started with progressive clinical and radiological improvement. Before the introduction of steroids, (B) a CT scan was repeated, revealing the evolution of the previously noted GGOs in peribronchovascular consolidations (arrows) and subpleural and fissural band-like consolidations (arrowheads). The morphologic features and BAL results were consistent with OP pattern. BAL, bronchoalveolar lavage; CT, computed tomography; GGO, ground-glass opacity; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor.

Figure 4. Grade IV ICI pneumonitis with AIP/DAD pattern in an 80-year-old man with parotid carcinoma metastatic to the lung and liver, under treatment with pembrolizumab complicated by Pseudomonas aeruginosa pneumonia in June 2017. CT images (A), (B), and (C) during Pseudomonas pneumonia reveal consolidations (stars) of the right lower lobe and middle lobe and bilateral pleural effusion (E). After initial recovery under antibiotic and steroid treatment, the patient was hospitalized for respiratory failure requiring intubation in July 2017. CT images (D), (E), and (F) reveal partial regression of the previously found consolidations (star), but with the appearance of diffuse ground-glass opacities with geographic distribution (arrows), consolidations in the dependent lung regions (arrowheads), and pleural effusion (E). Bronchoalveolar lavage cytology revealed neutrophilic inflammation and no pathogens. The patient was treated with high-dose steroids, and immunotherapy was interrupted. AIP/DAD, acute interstitial pneumonitis/diffuse alveolar damage; CT, computed tomography; ICI, immune checkpoint inhibitor.
in some cases. Isolated pulmonary nodules or mass-like lesions have also been described and may be misdiagnosed as malignancy (Fig. 5). Finally, the imaging findings do not fit in all cases the criteria of a specific pattern, as with diffuse or patchy GGOs, which would better fit with an “unclassifiable pattern” category (Fig. 2).19-21 Although the recognition of a particular imaging pattern may help physicians to detect/suspect an IP, other possible causes should be kept in mind during ICI treatment and should lead to further investigations to promptly achieve the correct diagnosis.

Thoracic sarcoidosis-like reaction usually reveals symmetrical hilar and mediastinal lymph node enlargement, often associated with bilateral lung micronodules in a perilymphatic distribution, including peribronchovascular and fissural location.7,25,43 Sarcoidosis-like active granulomatosis is hypermetabolic at 18F-FDG PET/CT (Fig. 6).

Figure 5. ICI pneumonitis with nodular pattern in a 63-year-old male patient with metastatic lung cancer (lung, kidney, adrenals, bone). The patient was treated with combination therapy IPI plus nivolumab between July 2015 and September 2015, followed by nivolumab. (A) CT scan in January 2016. (B) In April 2016, a new-onset lung nodule was detected; (C) which increased in size at the following scan in June 2016. (D) 18F-FDG PET/CT fusion image reveals the mild FDG uptake of the nodule. Because the findings were suggestive of malignancy, the patient underwent wedge resection of the nodule. No neoplastic cells were found at pathologic examination, but a chronic lymphocytic inflammation. Immunotherapy was continued. 18F-FDG, 18F-fluorodeoxyglucose; CT, computed tomography; ICI, immune checkpoint inhibitor; IPI, ipilimumab; PET, positron emission tomography.

Figure 6. Sarcoid-like reaction in a 50-year-old woman receiving nivolumab for metastatic cervical cancer (FIGO IV). (A) Whole-body MIP image of 18F-FDG PET/CT before immunotherapy reveals intense FDG uptake of metastatic left supraclavicular, retroperitoneal, iliac, and inguinal nodes (arrows). (B) Whole-body MIP image of PET/CT performed 2 months after the introduction of nivolumab reveals complete regression of the metastatic hypermetabolic areas consistent with complete response to therapy but the appearance of new symmetrical, moderately FDG-avid foci (arrowheads), (C) corresponding to mediastinal and hilar lymph nodes on PET/CT fusion image. (D) Fissural micronodules (arrowheads) are also found on CT image. Resolution of the inflammatory reaction was obtained with cyclophosphamide at immunomodulatory dose. (E) Whole-body MIP image of the next PET/CT reveals regression of the sarcoidosis-like mediastinal nodes, but with progression of the metastatic disease with bone metastasis and upper mediastinal and pelvic lymphadenopathies (arrows). 18F-FDG, 18F-fluorodeoxyglucose; CT, computed tomography; MIP, maximum intensity projection; PET, positron emission tomography.
Relationship Between IP and Radiation Therapy

Recently, it has been observed that in patients treated with radio-immunotherapy, pneumonitis often occurs in a previously irradiated area, irrespective of the time elapsed since RT, and even years after. Although it is well known that RT can cause an acute "radiation pneumonitis" in the radiation field within 4 to 12 weeks after thoracic irradiation, additional mechanisms underlie RT-ICI pneumonitis. Among these, a condition similar to "radiation recall" has been hypothesized. Radiation recall is a rare acute inflammation triggered by systemic drugs that occurs in a previously irradiated area and is mostly limited to a cutaneous reaction. The time elapsed between RT and pneumonitis in some patients receiving ICIs has raised the hypothesis of a "radiation recall pneumonitis." Another hypothesis involves a synergic effect of the modifications of the local pulmonary homeostasis by radiations within the radiation field and the hyper-activation of the immune system by the ICIs.

In any case, relationships between the radiation field and the development of pneumonitis are of high interest, as new-onset pulmonary changes in the irradiated area beyond 12 weeks may represent a form of pulmonary irAEs. Imaging features are similar to those of RP, with consolidations and/or GGOs often presenting as OP pattern, but with possible fibrotic changes. Acute inflammation may arise in a fibrotic scar of a previous RT, thus making difficult the early identification and differentiation from superimposed infection or tumor recurrence. Although some imaging findings, such as an air bronchogram, may help to suggest radiation-related inflammation, BAL is often required. At PET/CT, these pulmonary changes are 18F-FDG avid in the inflammatory phase, whereas they may reveal a barely appreciable metabolism in the fibrotic phase (Fig. 7).

**Figure 7.** ICI pneumonitis arising in a previously irradiated area ("radiation recall") incidentally detected at 18F-FDG PET/CT in a 59-year-old man with metastatic melanoma (brain, lung, small bowel, bone, lymph nodes). In June 2014, the patient underwent wedge resection of a pulmonary metastasis of the right lower lobe followed by radiation therapy. (A) Radiation therapy field (dose delivered for each contoured area: orange area: 45 Gy; yellow areas: 40 to 30 Gy; green areas: 20 to 10 Gy; blue area: 5 Gy). (B) Radiation fibrosis in the irradiated area (arrow). Combined immunotherapy ipilimumab and nivolumab was introduced for progression disease in December 2014. In February 2015, at restaging 18F-FDG PET/CT, (C) the appearance of focal 18F-FDG-avid consolidations (arrows) in the previously irradiated area was reported. The patient was asymptomatic. After 1 month, the patient was admitted for fever and grade II dyspnea and (D) CT scan revealed an increase of the right lower lobe consolidation (arrow) and (E) the appearance of subpleural ground-glass opacities (arrowheads). A lymphocytic-predominant pattern was found at bronchoalveolar lavage, without pathogens or neoplastic cells. Immunotherapy was interrupted, and steroids were introduced. In August 2015, (F) 18F-FDG PET/CT revealed regression of the lung abnormalities, with a limited residual consolidation in the irradiated area compatible with fibrotic changes. Of note, during steroid treatment, the patient developed adrenal failure and opportunistic zoster infection.
Differential Diagnosis

Differential diagnosis of IP mainly includes infection and tumor progression (Figs. 8A, 8B and 9), which share similar clinical symptoms and imaging findings. Although uncommon, infection may occur in patients treated by immunotherapy, particularly in those receiving combined ICIs. Among these, the most common manifestation is pneumonia, and it is often caused by bacteria. Moreover, reactivation of latent infections, such as tuberculosis, has also been described. In addition, in the time of coronavirus disease 2019 pandemic, severe acute respiratory syndrome coronavirus 2 infection should be considered in case of new-onset pulmonary changes detected.

Figure 8. (A) Same patient as in Figure 2. Rhinovirus bronchiolitis during maintenance therapy with nivolumab in a 64-year-old woman with metastatic melanoma. The patient was hospitalized for grade 4 dyspnea and cough. Extensive centrilobular micronodules with “tree in bud” appearance (circle) in the right upper lobe associated with bronchial wall thickening and bronchiectasis (arrows). (B) Legionella pneumonia during combination therapy ipilimumab plus nivolumab in a 44-year-old woman with metastatic melanoma. 18F-FDG PET/CT performed after two cycles of therapy introduction revealed the appearance of a pulmonary 18F-FDG-avid mass (arrows). The patient was asymptomatic, and a bronchoalveolar lavage was performed, revealing an infection by Legionella pneumophila. 18F-FDG, 18F-fluorodeoxyglucose; CT, computed tomography; ICI, immune checkpoint inhibitor; PET, positron emission tomography.

Figure 9. Tumor progression mimicking an ICI pneumonitis in a 72-year-old female patient with lung adenocarcinoma receiving nivolumab. The patient underwent lobectomy of the right upper lobe and right lower lobe in 2010, followed by multiple lines of chemotherapy. In July 2013, palliative immunotherapy was introduced for tumor progression. (A) CT scan before immunotherapy reveals bilateral neoplastic lesions (N). (B) After 3 months, their regression is shown. (C) CT performed in June 2014 revealed the recurrence of the nodule in the left lower lobe (arrow) and the appearance of other lesions in the right lower lobe (arrowhead). Pathologic examination after biopsy was consistent with tumoral recurrence. CT, computed tomography; ICI, immune checkpoint inhibitor; N, neoplastic lesions.
on imaging. In fact, IP and coronavirus disease 2019 may present with similar clinical and radiologic features and both can be incidentally detected before the onset of symptoms.\textsuperscript{52,53} Malignancy progression may be misdiagnosed as irAEs and vice versa, particularly in case of consolidations or lung nodules. This potential misdiagnosis has been reinforced by the predilection of IP around tumors, whether primary or metastatic, independently of a previous RT.\textsuperscript{27} Confounding situations especially concern adenocarcinoma expressing as subsolid nodules. Sarcoidosis-like reaction radiological manifestation can overlap with those found in lymphangitis, dry pleural dissemination, and mediastinal nodal spread. The main differential diagnoses of ICI pneumonitis are presented in Table 2.

<table>
<thead>
<tr>
<th>Table 2. Differential Diagnosis of the Most Frequent Radiologic Patterns of ICI Pneumonitis</th>
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<tbody>
<tr>
<td><strong>Radiologic Pattern</strong></td>
</tr>
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</table>
| **OP** | Multifocal adenocarcinoma  
Lymphoma  
Acute eosinophilic pneumonia:  
Peripheral GGO/alveolar consolidation  
Upper lobe predominance  
Radiation pneumonitis:  
In the radiation field  
Within 6 mo from radiotherapy  
Infectious pneumonia including the following:  
Bacterial  
Aspergillosis  
Other drug-induced pneumonitis |
| **NSIP** | Collagen vascular diseases  
Hypersensitivity pneumonitis  
Acute eosinophilic pneumonia  
Infectious pneumonia, especially nonopportunistic/opportunistic viral infections, including the following:  
- COVID-19, cytomegalovirus  
- Pneumocystis pneumonia  
Other drug-induced pneumonitis |
| **HP** | Acute eosinophilic pneumonia  
Infectious pneumonia  
Other drug-induced pneumonitis |
| **AIP/DAD** | Infectious pneumonia  
Cardiogenic edema:  
Bilateral and symmetrical interlobular septal thickening/peribronchovascular thickening  
GGO/alveolar consolidation in a batwing distribution  
Pleural effusion  
Common cardiomegaly |
| **Bronchiolitis** | Infectious bronchiolitis, including the following:  
Viral  
Bacterial  
Fungal  
Tuberculosis, atypical mycobacteria  
Aspiration bronchiolitis |
| **Pulmonary nodules or mass-like lesions** | Primary or metastatic tumor  
Infectious pneumonia, including the following:  
Bacterial infection  
Septic emboli  
Fungal infection  
Other causes (rheumatoid arthritis, etc.) |
| **Unclassifiable pattern** | Infectious pneumonia  
Hypersensitivity pneumonitis |
| **Sarcoidosis like** | Carcinomatous lymphangitis  
Unilateral or bilateral  
Thickened linear/nodular septal lines  
Peribronchovascular thickening |

\textsuperscript{AIP/DAD, acute interstitial pneumonitis/diffuse alveolar damage; COVID-19, coronavirus disease 2019; GGO, ground-glass opacity; HP, hypersensitivity pneumonitis; ICI, immune checkpoint inhibitor; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia.}

Complications

Opportunistic infection represents the most important complication of irAEs and is often owing to the steroid, immunosuppressive or immunomodulatory, treatment required to control the disease\textsuperscript{18,51} (Fig. 10). Superimposed infection may lead to death in the most severe cases.\textsuperscript{18} Therefore, in patients diagnosed with irAEs, a regular clinical and radiological assessment is required to promptly recognize an opportunistic infection, particularly in those treated with immunosuppressive agents. In addition, the possibility of IP recurrence (“pneumonitis flare”) after initial resolution should be kept in mind, particularly in patients in whom treatment rechallenge with ICIs is attempted.\textsuperscript{19-21}

Conclusion

Pulmonary irAEs are rare side effects of ICIs, which may strongly affect patient management. Because no definitive test is available, they represent a diagnosis of exclusion, which may potentially lead to a clinical emergency. An accurate radiologic assessment plays a critical role, particularly in patients who cannot undergo invasive procedures, such as BAL. The recognition of IP with imaging is not decisive, but awareness of the wide range of imaging features, the differential diagnoses, and the complications enable radiologist and nuclear medicine physician to adequately guide medical oncologist to optimize patient management.
References


