Thoracic Complications of Precision Cancer Therapies: A practical guide for radiologists in the new era of cancer care

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Objectives

• Precision cancer therapies are associated with a variety of thoracic complications and adverse events, which are often unique to the agents or the classes of agents

• The exhibit provides a comprehensive review of and will
  • Address the **molecular mechanisms of responsible agents** that relate to adverse events
  • Emphasize **emerging challenges** during novel therapies
  • Discuss imaging characteristics and demonstrate **the role of radiologists** in detection and monitoring

• The exhibit is designed to serve as a practical reference guide for day-to-day practice in the chest reading room
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These “immune-checkpoint inhibitors” lead to immune-related adverse events (irAEs), a hot topic in oncology!

Bleeding and thrombosis are two major complications of VEGF inhibition!
Drug-related pneumonitis during precision cancer therapies

- Drug-related pneumonitis is a major thoracic complication of cancer therapy
- Can be due to cytotoxic effects, oxidative stress, and immune-mediated injuries
- Lung’s response patterns to injury are limited and show several types of histopathologic manifestations with corresponding radiographic patterns
- Radiographic patterns can be described according to the classification of interstitial pneumonias and related lung diseases

Drug-related pneumonitis during precision cancer therapies

- Recent advances in precision cancer therapy have brought new and emerging challenges of pneumonitis due to novel agents.
- Three major groups of agents increasingly used in precision oncology settings are associated with pneumonitis:
  - **Immune-checkpoint inhibitors**
  - **mTOR inhibitors**
  - **EGFR tyrosine kinase inhibitors**

Cancer immunotherapy and immune-related adverse events (irAE)

- Anti-cancer mechanism of immunotherapy is via blockade of immune inhibition by tumors
- T cell activation specific to cancer cells are regulated by the ligand-receptor pairs (called “immune-checkpoints”) among T cells, tumor cells, and other immune cells in tumor microenvironment
- Inhibitors of these “immune-checkpoint” molecules have emerged as a promising treatment option for advanced malignancy

Mechanisms for immune inhibition by tumors and its blockade by CTLA-4 inhibitor.
Interaction between CTLA-4 on T cell and its ligand (B7) on antigen-presenting cell inhibits the T cell immune response against tumor, allowing tumor cells escape from immune attack. CTLA-4 inhibitors such as ipilimumab block the interaction between CTLA-4 and its ligand, causing blockade of the T cell immune inhibition and activating immune response against cancer.

Cancer immunotherapy and immune-related adverse events (irAE)

- Currently approved agents:
  - CTLA-4 inhibitor
    - Ipilimumab for melanoma
  - PD-1 inhibitor
    - Nivolumab for melanoma, NSCLC, RCC, lymphoma
    - Pembroizumab for melanoma, NSCLC, head/neck squamous cell carcinomas
  - PD-L1 inhibitor
    - Atezolizumab for urothelial carcinomas and NSCLC
- More agents are in the pipeline of development and testing

Mechanism of PD-1 immunosupression as a target for cancer therapy.
The binding of PD-L1 to PD-1 delivers an inhibitory signal and reduces cytokine production and proliferation of T cells, thus enabling tumor cells to evade the host immune response. Antibodies against PD-1 or PD-L1 prevent the binding and block immune inhibition by tumor, inducing anti-tumor immune response.

Cancer immunotherapy and immune-related adverse events (irAE)

- A wide spectrum of immune-related adverse events (irAEs) has been reported during immunotherapy, involving organs from head to toe.
- Imaging helps to detect, characterize, and monitor many of these irAEs.
- Thoracic irAEs include pneumonitis and sarcoid-like lymphadenopathy, and cardiac toxicities.

PD-1 pneumonitis as an irAE

- Pneumonitis is relatively rare, but clinically serious and potentially life-threatening, and is recognized as an “event of special interest”
- Pneumonitis-related deaths are reported in clinical trials of immune-checkpoint inhibitors
- Initial clinical experience showed a spectrum of clinical and radiographic manifestations

Chest CT of a NSCLC patient treated with nivolumab demonstrates multifocal areas of GGO, reticular opacities, and consolidation in predominantly peripheral distribution, demonstrating PD-1 inhibitor-related pneumonitis (COP pattern).

A recent meta-analysis studied 4496 patients treated in 20 trials of PD-1 inhibitors. Overall incidence was 2.7% in monotherapy, and was 6.6% in combination therapy. Incidence was higher in NSCLC for all-grade and high-grade pneumonitis, and in RCC for all-grade pneumonitis, compared to melanoma. Incidence was higher during combination therapy than during monotherapy.

### PD-1 pneumononitis as an irAE

PD-1 pneumonitis as an irAE: Radiographic patterns

- Initial reports of PD-1 pneumonitis indicated a wide spectrum of radiographic manifestations that include different radiographic patterns corresponding to ATS/ERS classifications of interstitial pneumonias and related diseases.

- Clinical courses of pneumonitis were also variable among patients:
  - Some patients required admission to ICU and intubation.
  - Others were treated successfully with oral corticosteroids as outpatient and restarted their PD-1 inhibitors without recurrent pneumonitis.

- In a few patients, pneumonitis recurred after completing corticosteroid taper without resuming PD-1 inhibitor therapy or any other therapy, demonstrating a “pneumonitis flare”, further indicating a complex nature of the entity.

PD-1 pneumonitis as an irAE: AIP/ARDS pattern

A 38-year-old female with advanced melanoma treated with nivolumab. Chest CT scan at 15 weeks of therapy during the ICU admission demonstrated diffuse GGOs, reticular opacities, consolidations, and traction bronchiectasis. The findings involved all lobes and >50% of all lung zones. Lung volumes are markedly decreased, with overall appearance indicative of a radiographic AIP/ARDS pattern. The patient was treated with intravenous corticosteroids and also required infliximab (anti-TNF-alpha immuno-suppressive agent).

A 58-year-old man with advanced melanoma treated with nivolumab. Chest CT scan at 7 weeks of therapy demonstrated bilateral GGOs, reticular opacities and small areas of consolidation in predominantly lower, peripheral distribution, indicative of a radiographic NSIP pattern. He was successfully treated with oral corticosteroid as an outpatient, and resumed nivolumab after 8 weeks. He was able to complete all the doses of nivolumab, did not experience recurrent pneumonitis and also remained progression-free for his melanoma.

A 72-year-old man with stage IV squamous NSCLC treated with second-line nivolumab monotherapy

A, B. Chest CT at 8 weeks of nivolumab therapy demonstrated new GGO, reticular opacities, and consolidation in lower lobes predominantly on the left, with a peripheral and lower distribution, radiographically representing a COP pattern (arrows).

C-D. On chest CT at 15 weeks of therapy, the findings significantly increased, with multifocal areas of GGO, reticular opacities, and consolidation (arrows), as well as centrilobular nodularity and traction bronchiectasis in predominantly peripheral distribution, again demonstrating a COP pattern.

E-F. Further follow-up CT after 4 weeks of prednisone treatment showed a significant decrease of the CT findings.

PD-1 pneumonitis as an irAE: “Pneumonitis flare” phenomenon

A 72-year-old man with stage IV squamous NSCLC treated with second-line nivolumab monotherapy (continued)

G-H. Chest CT scan 4 weeks after the completion of prednisone treatment showed a development of dense consolidations with GGOs and reticular opacities in peripheral and multifocal distributions, again demonstrating a COP pattern. The patient restarted prednisone for treatment of a “pneumonitis flare”.

I-J. Follow-up chest CT taken 2 weeks after starting the 2nd course of prednisone therapy demonstrated decrease of consolidation and GGOs, indicating improving pneumonitis in response to corticosteroid therapy.

“Pneumonitis flare”, a phenomenon where similar clinical and radiographic patterns of pneumonitis come back upon completing steroid taper, without restarting immunotherapy or any other therapy

A recent study evaluated radiographic patterns and clinical course of PD-1 pneumonitis in 170 patients treated in 10 trials of nivolumab.

- 20 patients (10 melanoma, 6 lymphoma, 4 lung cancer) developed pneumonitis (Grade 1, n=5; 2, n=10; 3, n=5).

- Radiographic pattern was COP pattern in 13, NSIP pattern in 3, HP pattern in 2, and AIP/ARDS pattern in 2 patients.

- COP pattern was most common in all tumors and regimens.

- AIP/ARDS pattern had the highest grade, followed by COP pattern, while NSIP pattern and HP pattern had lower grade (median Grade: 3, 2, 1, 1, respectively; p=0.006).

Most patients (17/20; 85%) received corticosteroids, and 3 (15%) also required infliximab (anti-TNF-alpha immunosuppressant)

7 patients restarted nivolumab therapy, and two of them developed recurrent pneumonitis and were successfully retreated with corticosteroids

One of the patients experienced a pneumonitis flare after completion of corticosteroid taper without nivolumab retreatment

Further studies are needed to identify risk factors and early markers for pneumonitis and to optimize treatment approaches

Pneumonitis in a 33-year-old female with Hodgkin lymphoma treated with nivolumab and ipilimumab combination therapy.

A, B. Chest CT scan at 1.4 months of therapy demonstrated GGOs and consolidations with multifocal distribution, indicative of a COP pattern of pneumonitis. Left perihilar opacities are due to prior radiation therapy.

C, D. She was treated with oral prednisone taper, and the findings have resolved after 1.5 month.

E, F. She restarted therapy and received 2 doses of nivolumab and ipilimumab and 2 doses of nivolmab monotherapy, then developed recurrent pneumonitis after 2 months since restarting therapy. The scan demonstrated similar findings with multifocal GGOs and consolidations, again representing a COP pattern. The findings were more extensive than the first episode.

G, H. Nivolumab was held and the patient was treated again with prednisone taper, with subsequent improvement.

Pneumonitis in a 33-year-old female with Hodgkin lymphoma treated with nivolumab and ipilimumab combination therapy (continued).

I, J. She completed 2 months of corticosteroid taper, and experienced another episode of pneumonitis after 1 month, without nivolumab retreatment or other systemic therapy, indicating a pneumonitis flare.

K, L. Another course of corticosteroid taper was given and with subsequent improvement.

M, N. Steroid taper was completed and after 2 weeks, the patient again developed a pneumonitis flare with a similar radiographic pattern as the prior episodes. The patient underwent transbronchial biopsies.

O, P. Histology showed interstitial pneumonitis evolving to organizing pneumonia, including lymphocyte-predominant interstitial pneumonitis (arrowhead, O) with rare eosinophils (arrow, O), and areas of organizing pneumonia (asterisks, P). The patient started another course of prednisone with subsequent improvement.

Sarcoid-like lymphadenopathy as an irAE

- Sarcoid-like lymphadenopathy is noted in 5-7% among ipilimumab treated patients
- Can be clinically silent, and can spontaneously resolve
- Lung parenchymal changes on CT can co-exist
- Histology shows granulomatous changes resembling sarcoidosis
- Challenging to differentiate from metastasis and tumor progression

Sarcoid-like lymphadenopathy in an 81-year-old asymptomatic man with metastatic melanoma treated with ipilimumab. Chest CT at 4.9 months of therapy showed new bilateral symmetric mediastinal and hilar lymphadenopathy, resembling sarcoidosis.

mTOR inhibitors in cancer therapy

- Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase and is involved in the critical junctures of PI3K/Akt/mTOR pathway, which is an established oncogenic driver in humans.
- Everolimus and temsirolimus are rapamycin analogues and exert anti-cancer activity by inhibiting mTOR.
- Everolimus is approved for renal cell carcinoma (RCC), subependymal giant cell astrocytoma, and certain types of breast, GI, pancreatic and lung cancers.
- Temsirolimus is approved for RCC.

A simplified overview of PI3K–AKT–mTOR pathway

Modified from: Holms, D. Nature Reviews Drug Discovery 10, 563-564
mTOR pneumonitis

- Drug-related pneumonitis is a recognized class effect toxicity of mTOR inhibitors
- In 178 RCC patients treated with temsirolimus, 52 (29%) had pneumonitis; Of these, 36 (69%) were asymptomatic and may not be recognized clinically
- In 64 patients with advanced NSCLC treated with everolimus, 24 patients (25%) had newly occurring or worsening radiographic changes suggestive of drug-related pneumonitis

mTOR pneumonitis

- Recent studies described radiographic patterns of mTOR pneumonitis in advanced neuroendocrine tumors and Waldenstrom macroglobulinemia.
- In both cohorts, the most frequent CT findings of pneumonitis were bilateral GGOs and reticular opacities, with or without consolidation, in peripheral and lower lung distributions, indicative of COP pattern or NSIP pattern.
- Similar radiographic patterns of mTOR inhibitor-related pneumonitis across different tumor types further support the concept of class-effect toxicity.


A 66 y.o. female with Waldenstrom macroglobulinemia treated with mTOR inhibitor therapy. Chest CT at 6 months of therapy demonstrated consolidation, GGO and reticular opacities, demonstrating a COP pattern.
EGFR-TKIs for precision therapy in lung cancer

- Epidermal growth factor receptor (EGFR) regulates important tumorigenic processes, such as proliferation, apoptosis, angiogenesis, and invasion
- Somatic activating mutations of EGFR in NSCLC is associated with a dramatic response to EGFR TKIs, gefitinib, erlotinib, and afatinib
- Third-generation EGFR-TKI, osimertinib, was recently approved for EGFR-mutant NSCLC with acquired resistance

Overview of EGFR signaling pathway

Pneumononitis during EGFR-TKIs

- Pneumonitis during EGFR-TKI therapy is recognized as a class-effect, and has been studied mostly in the context of erlotinib and gefitinib.
- Incidence appears to be higher in Japanese population, noted in approximately 5%, with high mortality rate (30-35%).
- Risk factors derived from Japanese cohorts include old age, smoking history, pre-existing interstitial lung disease, poor performance status, short duration since NSCLC diagnosis, ≤50% normal lung areas.
- Among different radiographic patterns, “diffuse alveolar damage (DAD)-like” pattern, characterized by non-segmental GGO or consolidation with traction bronchiectasis and volume loss, was associated with higher mortality (65%).

A 42-year-old male with EGFR exon 19 deletion mutation treated with erlotinib in the United States. At 8 weeks of therapy, chest CT demonstrated multifocal areas of ground glass opacities in both lungs, representing pneumonitis. Note the absence of traction bronchietasis and volume loss.
VEGF (vascular endothelial growth factor) is a key factor in angiogenesis, regulates vascular proliferation and permeability, and functions as a major endothelial mitogen.

- VEGF inhibition may decrease the renewal capacity of the endothelial cells, cause endothelial defects in the vascular lining and expose subendothelial collagen, and decrease matrix deposition in the supporting layers of vessels.

- **Bleeding** due to a decreased renewal capacity of endothelial cells
- **Thrombosis** due to tissue factor activation secondary to exposure to subendothelial collagen

Pulmonary hemorrhage is increasingly noted with new precision therapies especially with anti-angiogenic agents. Reported in 2.3% of patients with nonsquamous NSCLC on bevacizumab therapy. More common in squamous cell carcinoma, reported in up to 31% of patients. In a phase 2 trial of bevacizumab in NSCLC, bleeding was the most prominent adverse event and included minor mucocutaneous hemorrhage and major hemoptysis. Major hemoptysis was associated with squamous cell histology, tumor necrosis and cavitation, and disease location close to major blood vessels.

Pulmonary embolism during VEGF inhibitor therapy

In a phase II trial of bevacizumab in colorectal cancer patients, thrombosis was the most significant adverse event. Occurred in 19% (13/67). 2 patients had PE, which was fatal in one patient.

Other VEGF inhibitors, sunitinib (for GIST and RCC) and sorafenib (for RCC), are also associated with thrombosis and PE.

A 40-year-old male with glioblastoma, presenting with shortness of breath during bevacizumab therapy. CTA demonstrated extensive filling defects involving bilateral lobar arteries and their branches, demonstrating PE.

Anti-cancer agents can cause injury to pneumocytes and alveolar capillary endothelium, leading to leaky capillaries and increased permeability.

Common responsible agents include imatinib (TKI for leukemia, GIST), dasatinib (TKI for leukemia) and rituximab (CD20 antibody for leukemia and lymphoma).

Edema is more common with imatinib, while pleural effusion is more common with dasatinib.

A 71-year-old male with chronic myelogenous leukemia, presenting with shortness of breath during dasatinib therapy. Chest radiograph demonstrated new bilateral pleural effusions, which is a known complication of dasatinib therapy.

Souza et al. Cancer Imaging 2014, 14:26
Take Home Message

- Knowledge of the radiologic manifestations of thoracic complications in specific cancer therapies is essential for radiologists.
- Awareness of the emerging immune-related adverse events is becoming increasingly important.
- Radiologists play a major role in diagnosing and monitoring these events in the front line of precision cancer therapy as a key member of multidisciplinary team.

Diagram:

- Thoracic complications of precision cancer therapy
  - Diagnosis
  - Treatment
  - Monitoring

- Oncologists
- Pulmonologists
- Cardiovascular physicians
- Radiologists
- Communication
- Feedback
- Collaboration
- Multidisciplinary team
References

References


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