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Pulmonary adverse events due to immune checkpoint inhibitors: A literature review

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Abstract

Cancer immunotherapy aims to stimulate the immune system to fight against tumors, utilizing the presentation of molecules on the surface of the malignant cells that can be recognized by the antibodies of the immune system. Immune checkpoint inhibitors, a type of cancer immunotherapy, are broadly used in different types of cancer, improving patients' survival and quality of life. However, treatment with these agents causes immune-related toxicities affecting many organs. The most frequent pulmonary adverse event is pneumonitis representing a non-infective inflammation localized to the interstitium and alveoli. Other lung toxicities include airway disease, pulmonary vasculitis, sarcoid-like reactions, infections, pleural effusions, pulmonary nodules, diaphragm myositis and allergic bronchopulmonary aspergillosis. This review aims to summarize these pulmonary adverse events, underlining the significance of an optimal expeditious diagnosis and management.

Key words: Immunotherapy; cancer; drug toxicity; immune checkpoint inhibitors.

Introduction

Cancer immunotherapy refers to the stimulation of the immune system to fight against tumors by improving on the immune system's ability to fight malignancies. Cancer immunotherapy utilizes the fact that cancer cells often present on their surface cancer cells' antigens, which are frequently proteins or various macromolecules and are detectable by the antibodies of the immune system. The altered immunotherapy antibodies are attached to the cancer cells' antigens and therefore they mark and identify cancer cells to be inhibited or killed by the immune system [1,2].

Immunotherapies for cancer are divided into active and passive. Active forms of immunotherapy stimulate the immune system in order to destroy malignant cells. This attack is performed by targeting tumor antigens. Active cellular therapies remove cells of the immune system from the circulation or from the malignant lesion. Immune cells that can be utilized as active cellular therapies include

dendritic cells, natural killer cells, cytotoxic T-lymphocytes and lymphokine-activated killer cells [1,3].

Passive forms of immunotherapy promote current anti-cancer responses using monoclonal antibodies, cytokines and lymphocytes. Passive antibody therapies usually target the receptors on malignant cell's surface. They include CD274, CD279 and CD20 antibodies. The modified antibodies are able to induce antibody-dependent cytotoxicity, to cause activation of the complement cascade, or can block a receptor from interrelating with its ligand, leading to cell apoptosis. Antibodies that have been approved are alemtuzumab, nivolumab, ofatumumab, ipilimumab, durvalumab, rituximab and pembrolizumab. Alemtuzumab is an anti-CD52 humanized IgG1 monoclonal antibody. Nivolumab is a human IgG4 antibody that acts through preventing T-cell inactivation by blocking the binding programmed death (ligand) 1 or 2 (PD-L1 or PD-L2). Ofatumumab is a human IgG1 antibody that binds to CD20. Ipilimumab is a human IgG1 antibody that targets the surface T lymphocyte-associated protein 4 (CTLA4) which binds to CD80 or CD86, preventing the binding of CD28 to these proteins, leading to negative regulation of T-cells activation. Durvalumab is an IgG1k monoclonal antibody that acts by blocking the interaction of PD-L1 with the programmed death 1 (PD-1) and CD80 (B7.1) molecules. Rituximab is a chimeric monoclonal IgG1 antibody which targets CD20, being effective in treating specific B-cell malignancies. Pembrolizumab acts through blocking PD-1. The types and targets of these monoclonal antibodies are summarized in Table 1.

Immune checkpoints inhibitors (ICI), which are a form of passive immunotherapy including nivolumab, ipilimumab, durvalumab and pembrolizumab, is a revolutionizing treatment in a wide range of cancer types, as monotherapy or in combination with other agents, including chemotherapy [5]. In addition, these therapies are associated with improvement of health-related quality of life [6]. However, treatment with PD-1, PD-(L)1 and CTLA-4 inhibitors, is associated with a wide range of immune-related adverse events, caused by hyperactivation of the immune system, leading to, sometimes fatal, autoimmune reactions. These reactions may have an impact in every organ system [7].

The frequency of these adverse events depend on the agents used and on the specific features of patients. The incidence of fatal ICI related adverse events is estimated to be 0.3-1.3 %. Although adverse events from lungs are less common than toxicities to other organs, lung toxicity may be fatal and one of the most frequent causes of therapy withdrawal. Interstitial lung disease is the most frequent adverse event from lungs. Besides, pleural, vascular and airway involvement, sarcoid-like reactions and lung infections associated with ICI have been described mostly in case reports [8]. This review provides an overview of pulmonary adverse effects due to ICI. To our knowledge, is the first review to summarize all the types of lung toxicity, including the impact on small airways.

Search Strategy and Article Selection

The following search strategy was used. A systematic search of Pubmed/MEDLINE and Google Scholar was conducted in order to identify articles, reporting pulmonary adverse events due to ICIs. There were no language restrictions. The following terms were searched in combination: “Pulmonary Toxicity” OR “Lung Toxicity” OR “Pulmonary Adverse Events” OR “Lung Adverse Events” AND “Immune Checkpoint Inhibitors”.

The search was conducted by three reviewers (E.D, A.G and A.G). Articles were first screened for relevance by title. Then, they were evaluated by abstract. The relevant articles were enrolled for full-text review. Moreover, a manual search of the lists of the references of these texts was performed for identifying additional relevant articles.

Systematic search identified 1181 possibly relevant records, after exclusion of duplicates. Eight hundred and twenty-seven records were excluded after title, abstract or full text screening, since they were irrelevant. From the remaining 354 records, 278 records were excluded after careful screening of the titles and abstracts, since they did not mention pulmonary adverse events due to ICIs.

In the end, 76 articles, including case reports, case series and original articles, describing pulmonary adverse events due to ICIs, were enrolled.

Potential mechanisms for lung toxicity due to ICIs

The mechanism of pulmonary adverse events remains unclear, but it is thought to be associated with the immune dysregulation caused by ICIs. Three potential underlying mechanisms have been reported for the development of pulmonary adverse events due to ICIs [9]. First, the development of adverse events may be associated with increased T cell activity against cross-antigens expressed in malignant and normal cells. This hypothesis is supported by the finding in a study of increased lymphocytosis in bronchoalveolar lavage (BAL) obtained from patients with pneumonitis due to ICIs, mainly composed of CD4⁺ T cells. More specifically, the researchers found elevated central memory T cell (T_{cm}) counts and decreased CTLA-4 and PD-1 expressions in the Treg cells. PD-1⁺ and CTLA-4⁺ Tregs have negative regulatory impact on CD8⁺ T cells, conventional T cells, and pro-inflammatory responses of macrophages. Increasing activated alveolar T cell counts and attenuating the anti-inflammatory Treg phenotype may result in dysregulation of T cell activity. Second, increased levels of preexisting autoantibodies may also be an underlying mechanism.

Recent researches have demonstrated that preexisting anti-thyroglobulin antibodies, anti-rheumatoid factor antibodies, anti-thyroid peroxidase antibodies and antinuclear antibodies are probably associated with the development of adverse events in patients with lung cancer. However, the specific antibodies associated with pulmonary toxicity are still under exploration. Third, increased levels of inflammatory cytokines are also related to the occurrence of pulmonary adverse events. It has been

reported that in a patient with non-small cell lung cancer (NSCLC) who developed lung toxicity after atezolizumab administration, increased levels of C-reactive protein and interleukin-6 (IL-6) were observed. Cytokines can also be used as biomarkers for adverse events, and their increased expression correlates with severity of toxicity [10-14]. Figure 1 shows the potential mechanisms for lung toxicity due to ICIs.

Interstitial Lung Disease

Immune-related pneumonitis is a noninfectious inflammation confined to the interstitium and alveoli leading to a variety of computed tomography (CT) features and patterns of histopathology. These findings are stated as interstitial lung disease (ILD) [8]. Pneumonitis is graded from 1 to 4 based on the severity of the clinical symptoms [8]. Chest CT is the preferred imaging modality for the diagnosis of ILD. Opacifications with ground glass appearance, consolidations, and reticular opacities which predominate in sub-pleural and bibasilar regions are frequent radiology characteristics of numerous patterns of lung tissue injury [8]. However, imaging observations are insufficiently sensitive to differentiate drug-induced pneumonitis from other responsible factors for pneumonitis [8].

The risk factors for ICI-related ILD are unclear. It is suspected that factors such as sex, older age, tobacco use, history of lung disease, lung surgery or pulmonary radiotherapy may be related to development of ICI-related ILD. The incidence of ICI-related ILD may be influenced by type of tumor (especially NSCLC) and renal cell cancer) and type of ICI (higher incidence for PD-1 inhibitors compared to PD-L1 inhibitors) [14].

According to a meta-analysis, the overall ICI-related ILD incidence was estimated 2.7% for all grades and 0.8% for the most severe grades (grade ≥ 3). The incidence of ICI-related ILD is higher in combination therapy (including nivolumab and ipilimumab, given concurrently or sequentially, or nivolumab plus peptide vaccines) than in monotherapy. On the contrary, a combination of pembrolizumab with chemotherapeutic agents was not related to an increased risk of ICI-related ILD in patients with lung cancer. Moreover, the administration of durvalumab after chemoradiation in patients with locally advanced NSCLC was associated to an acceptable rate of pulmonary toxicity [15,16].

Clinical manifestations highly vary ranging from subclinical findings on chest CT to mild symptoms such as cough, mild dyspnea, low-grade fever and chest pain or to severe dyspnea, expeditiously progressive to respiratory insufficiency [8]. Moreover, there are no characteristic CT lesions or serological markers for ICI-related ILD [8]. The duration from ICI administration to development of ICI-related ILD varies from beginning of administration to withdrawal of the agent. According to a study, early-onset ICI-related ILD may have more severe course. ICI-related ILD is defined as the

occurrence of breathlessness and/or other respiratory symptoms, with new inflammatory manifestations on chest CT following treatment with ICI. The diagnosis is made after exclusion of pulmonary infection, progression of malignancy and other reasons [8]. Bronchoscopy with BAL is a significant diagnostic modality. Lymphocytosis with predominance of CD8-positive lymphocytosis and increased number of eosinophils are frequently noticed on BAL fluid [8]. Bronchial biopsies may provide supplementary data [8]. Evaluating the pulmonary function tests, abnormal findings in diffusing capacity might be early indication of lung injury preceding clinical symptoms and radiographic findings [8].

The injury patterns that are most commonly noted due to ICI toxicity in lungs are: nonspecific interstitial pneumonitis (NSIP), organizing pneumonia (OP) and diffuse alveolar damage (DAD) [7]. Organizing pneumonia is a type of ILD in which affecting sites are distal bronchioles, respiratory bronchioles, alveolar ducts and alveolar walls [17]. It is often associated with respiratory infections but clear mechanisms are unknown. Chest CT of patients with OP usually appears as ground-glass opacities or consolidations mainly observed in the lung periphery. Characteristic pathological finding is the abnormal proliferation of granulation tissue in distal airspaces [18]. In the literature there are several studies that describe organizing pneumonia as a type of lung toxicity due to cancer immunotherapy [19-37].

Nonspecific interstitial pneumonitis (NSIP) and diffuse alveolar damage (DAD) are additional patterns of lung toxicity associated with cancer immunotherapy [34-39, 41]. Nonspecific interstitial pneumonitis is a rare ILD. This type of ILD is frequently associated with human immunodeficiency virus (HIV) infection and autoimmune disorders such as dermatomyositis and scleroderma. Chest CT characteristic features of NSIP are ground-glass opacities, reticular infiltrates, and traction bronchiectasis while histologically, NSIP is characterized by uniform diffuse inflammatory cell infiltration, thickening of alveolar walls and dense fibrosis [40]. DAD is a severe type of pneumonitis originating from diffuse alveolar injury resulting in severe capillary leak and noncardiogenic pulmonary edema. Thoracic CT images of DAD reveal widespread airspace opacities while histological features of DAD are the formation of thickened alveolar membranes, deposition of hyaline membranes, and inflammatory cell infiltration [41].

Other reported histological and radiological patterns are “diffuse alveolar hemorrhage (DAH)” [8, 42-43], “hypersensitivity pneumonitis (HP)” [8, 34,36], “acute interstitial pneumonitis (AIP)” [8, 36-38], “acute respiratory distress syndrome (ARDS)” [8,39], “pulmonary fibrosis (PF)” [8, 48-49] and radiation recall pneumonitis [50-51].

Treatment

Corticosteroids are the basic treatment for ICI-related ILD, with 70%–80% of cases being controlled by regular corticosteroids administration. The overall duration of treatment with corticosteroids is approximately 6–8 weeks, usually less than 12 weeks. Empirical antibiotics, based on the principles of antimicrobial treatment, are also recommended during the initial treatment of ICI-related ILD. For patients with grade 2 pneumonitis or above, ICIs should be discontinued during treatment with corticosteroids [52].

Refractory ILD should raise thoughts about alternative diagnoses that should be excluded, such as infection and pulmonary embolism. There is no definite treatment for refractory ICI-related ILD. Agents that have been used according to existing literature include immunoglobulin, IL-6 receptor inhibitor and anti-tumor necrosis factor antibody. Additional immunosuppressive agents with slow effects, such as mycophenolate mofetil and cyclophosphamide, have also been recommended in some guidelines [52].

After recovery, rechallenge can be considered for selected individuals. The decision for rechallenge depends on response of the malignancy to ICI, grade of ICI-related ILD and response to corticosteroids and pulmonary function and the use of monotherapy or combination therapy. For patients who are rechallenged, close monitoring is required for ICI-related ILD. If patients present with relapse, permanent discontinuation of ICI administration is recommended [53].

Other pulmonary disorders

Additional pulmonary adverse events due to ICI have been described, including pleural, vascular and airway manifestations, sarcoid-like reactions, lung infections, diaphragm myositis and allergic bronchopulmonary aspergillosis. Tables 2,3,4 and 5 summarize all the cases describing additional pulmonary adverse events.

Airway Disease

Airway disease due to cancer immunotherapy is a rarely described pattern of lung toxicity. Bronchiolitis refers a nonspecific inflammation involving the small airways. Pembrolizumab-related obstructive bronchiolitis has been described in a 69-year-old woman with metastatic lung cancer. The diagnosis was made by lung function tests with severe obstructive pattern, without bronchodilator reversibility and mosaic attenuation on angiography [54]. Pembrolizumab-related obstructive bronchiolitis has also been described in a patient who presented with dry cough while receiving pembrolizumab for lung adenocarcinoma. The diagnosis of bronchiolitis was made by radiography and lung biopsy findings and his symptoms improved after the discontinuation of pembrolizumab and

with administration of erythromycin, an inhaled corticosteroid, a long-acting muscarinic antagonist, and a long-acting β_2 agonist [55].

Asthma is a chronic inflammatory disease of the airways of the lungs characterized by variable and recurring symptoms and reversible airflow obstruction with cough, wheezing, tightness, and dyspnea as the main symptoms [56]. Nivolumab-induced asthma without radiological or histological evidence of severe airway disease has been reported in a patient with non-small cell lung cancer [57]. In addition, in two cases, one with metastatic melanoma and one lung adenocarcinoma, both treated with nivolumab, patients developed isolated severe airway disease due to ICI. This report is the first to describe severe isolated airway disease associated with ICI with variable outcomes [58].

Pulmonary Vasculitis

The association of pulmonary vasculitis with immune checkpoint inhibitors has been described. Development of granulomatosis with polyangiitis (GPA) has been mentioned in a patient with metastatic melanoma who received ipilimumab and pembrolizumab [59]. In addition, development of Goodpasture's vasculitis has been mentioned in a patient suffering from advanced lung cancer treated with nivolumab [60].

Sarcoid-like reactions

Sarcoidosis is a systemic inflammatory disorder, resulting from an aberrant immune response to unknown factors and affecting multiple organ systems. Sarcoidosis inflammation is characterised by the development of non-cheating granulomas in affected tissues. Lungs and intrathoracic lymph are involved most frequently. However every organ can be affected [61]. Sarcoid-like reaction describes granulomatous inflammation in the setting of active cancer or after the administration of effective therapy [62].

Several cases of sarcoidosis-like reactions due to cancer immunotherapy have been reported. Treatment with nivolumab has been associated with sarcoid-like granulomatosis in bronchi and mediastinal and hilar lymph nodes [61], [63-64]. Pembrolizumab administration has been described as the cause of sarcoid-like reactions such as bilateral hilar and mediastinal adenopathy and interstitial bilateral pulmonary lesions [63], [65-69]. The most frequent ICI associated with sarcoid-like reactions in respiratory system is ipilimumab. This inhibitor of cytotoxic T lymphocyte antigen (CTLA)-4 has been correlated with granulomatous lesion in lungs, pleura and intrathoracic lymph nodes [67], [69-77]. In addition, sarcoid-like reactions in lungs and intrathoracic lymph nodes can occur in the setting of combination of cancer immunotherapies [78, 79]. Besides, durvalumab has been described to cause granulomatous lung lesions in a case report [79].

It has been reported that a possible underlying mechanism for these responses may involve interleukin 17-producing cells, including CD4+ Th17 cells, that are thought to be expanded in sarcoidosis. A correlation between the presence of increased numbers of circulating Th17.1 cells in patients with melanoma before treatment with anti-PD-1 antibody therapy and the development of sarcoidosis has been mentioned, indicating that anti-PD-1 antibody therapy may enhance the actions of Th17.1 cells to lead to sarcoidosis. Th17.1 cells represent pathological inflammatory cells that produce several pro-inflammatory cytokines, such as interferon- γ , IL-17A, TNF- α and granulocyte-macrophage colony-stimulating factor (GM-CSF), which are related to rheumatoid inflammatory disorders [80].

Lung Infections

The treatment of refractory or severe adverse events due to cancer immunotherapy sometimes needs significant immunosuppression, including corticosteroids or tumor necrosis factor-alpha antagonists (anti-TNF α), increasing the risk for infections. In 2014, the first case of an opportunistic infection in a patient who received passive cancer immunotherapy, was described. The patient received ipilimumab for metastatic melanoma and developed adverse events for which he was treated with infliximab and corticosteroids. As a result of this immunosuppressive therapy he presented with *Aspergillus fumigatus* pneumonia [81]. A case of invasive pulmonary aspergillosis complicating treatment with pembrolizumab for metastatic lung carcinoma that got worse by multidrug-resistant *Pseudomonas aeruginosa* superinfection has also been described. The patient was treated concurrently with systemic steroids as anti-edema treatment for brain metastases [82].

Two lethal cases of patients who developed immune-related pneumonitis requiring immunosuppressive therapy during treatment with immune checkpoint inhibitors, consequently leading to *Pneumocystis jirovecii* pneumonia have also been presented [83]. In a retrospective study, by reviewing medical records of 740 patients with melanoma who received immune checkpoint inhibitors, 13 patients were found to have developed pneumonia, 2 patients have developed invasive aspergillosis and 3 patients have developed *Pneumocystis* pneumonia during their treatment [84].

The development of severe infections in cancer patients treated with immunotherapy, independently of immunosuppressive therapy, has rarely been mentioned in the literature. Inthasot et al. reported two cases of severe lung infections in patients receiving nivolumab for NSCLC who had not received any other immunosuppressive agents [85]. Moreover, the development of pleural aspergillosis in a patient who received durvalumab for non-small cell lung cancer has been reported [86]. Besides, the progression of chronic progressive pulmonary aspergillosis in a patient treated with nivolumab for lung adenocarcinoma, in the absence of obvious immunosuppression, has been described [87].

Additional toxicities of PD-1 and PD-(L)1 inhibitors include acute or reactivation of tuberculosis and infection from atypical mycobacteria. A recent retrospective review, that used the US Food and Drug Administration Adverse Events Reporting System (FAERS), revealed 14 cases of pulmonary active tuberculosis or reactivated tuberculosis and 5 cases of pulmonary infections from atypical mycobacteria in cancer patients treated with PD-1 and PD-(L)1 inhibitors [88]. It has been described that these responses may result from a hyperresponse of tuberculosis immunity, similar to immune reconstitution inflammatory syndrome (IRIS) [89]. Moreover, Jurado et al. in their study demonstrated the inhibitory function of the PD-1:PD-(L)1 pathway during *M. tuberculosis* active infection, demonstrating that this pathway has a key role in the modulation of the immune response against mycobacteria [90].

Pleural effusion

Rapidly recurrent pleural effusion has been reported following cancer immunotherapy. Two cases of patients suffering from lung cancer receiving nivolumab, developed rapidly accumulating recurrent pleural effusions which required multiple thoracenteses [91]. According to one study, identical T cell clones in peritumoral pleural effusion and in bronchoalveolar lavage from areas with pneumonitis in a patient with cancer during therapy with immune-checkpoint inhibitors were found, suggesting that pleural effusion and pneumonitis might be induced by drug activated lymphocytes originating from tumor tissue [92].

Pulmonary nodules

Immune checkpoint inhibitors have been associated with the development of pulmonary nodules appearing misleadingly as metastases. Two patients who received pembrolizumab for metastatic melanoma presented pulmonary nodules. The histological examination of these nodules biopsy revealed inflammatory process without any malignant cell [93]. Pulmonary nodules occurring during the treatment with ICI may mimic malignant lesions and pose challenge in the differential diagnosis with cancer progression [94].

Diaphragm myositis

Two cases of diaphragm myositis have been mentioned with anti-PD-1 monotherapy and with a combination of anti-CTLA-4 and anti-PD-1 therapy. In the first case, anti-PD-1 treatment led to fatal

respiratory failure due to necrotising diaphragm myositis. [95]. In the second case, the combination of agents led to fatal progressive hypoventilation [96].

Allergic Bronchopulmonary Aspergillosis

One case of recurrent allergic bronchopulmonary aspergillosis has been described [97]. The diagnosis was based on elevated serum immunoglobulin E and positive *Aspergillus fumigatus* IgE antibodies.

Conclusions

In conclusion, cancer immunotherapy, by disrupting the homeostasis of the immune system, can cause a wide range of pulmonary adverse events. An increasing number of patients treated with ICI have been reported to develop several lung toxicities and clinicians are gradually gaining more knowledge for these complications and for their appropriate management. Thus, clinicians should suspect this type of toxicity among patients receiving ICI, who present with pulmonary symptoms or abnormal findings on lung imaging.

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Table 1. Targets of monoclonal antibodies alemtuzumab, nivolumab, ofatumumab, ipilimumab, durvalumab, rituximab and pembrolizumab.

Antibody	Type	Target
Alemtuzumab	Humanized	CD52
Nivolumab	Human	PD-1
Ofatumumab	Human	CD20
Ipilimumab	Human	CTLA-4
Durvalumab	Human	PD-L1
Rituximab	Chimeric	CD20
Pembrolizumab	Humanized	PD-1

*CTLA-4: T Lymphocyte-Associated Protein 4; PD-1: Programmed Death-1; PD-L1: Programmed Death Ligand-1

Table 2. Cases describing airway and vascular disease due to ICIs.

#	Case	Age/gender	ICI	Type of toxicity	Type of cancer	Management
1	Blanchard et al. [54]	69/F	Pembrolizumab	Obstructive bronchiolitis	NSCLC	Discontinuation of the drug Corticosteroids Inhaled bronchodilators Azithromycin
2	Yamaya et al. [55]	76/M	Pembrolizumab	Obstructive bronchiolitis	Lung adenocarcinoma	Discontinuation of the drug Erythromycin Inhaled bronchodilators and corticosteroids
3	Maeno et al. [57]	50/M	Nivolumab	Asthma	Lung adenocarcinoma	Corticosteroids Inhaled bronchodilators and corticosteroids
4	Mitropoulou et al. [58]	65/F	Nivolumab	Isolated severe airway disease	Melanoma	Discontinuation of the drug Corticosteroids Inhaled bronchodilators and corticosteroids Azithromycin
5	Mitropoulou et al. [58]	58/M	Nivolumab	Isolated severe airway disease	Lung adenocarcinoma	Discontinuation of the drug Corticosteroids
6	van den Brom et al. [59]	56/F	Ipilimumab/Pembrolizumab	Granulomatosis with polyangiitis	Melanoma	Corticosteroids
7	Takahashi et al. [60]	74/M	Nivolumab	Goodpasture's disease	Lung adenocarcinoma	Discontinuation of the drug Corticosteroids Plasma exchange

*F: Female; ICI: Immune Checkpoint Inhibitors; M: Male; NSCLC: Non Small Cell Lung Carcinoma

Table 3. Sarcoid-like reactions due to ICIs

#	Case	Age/ gender	ICI	Location	Type of cancer	Management
1	Montaudie et al. [61]	56/M	Nivolumab	Lung Eyes Parotid glands	Melanoma	Corticosteroids
2	Frohlich et al. [63]	57/M	Nivolumab	Mediastinal lymph nodes	Melanoma	Discontinuation of the drug
3	Frohlich et al. [63]	53/M	Pembrolizumab	Mediastinal lymph nodes	Melanoma	Discontinuation of the drug
4	Danlos et al. [64]	57/M	Nivolumab	Mediastinal lymph nodes Skin	Melanoma	Discontinuation of the drug
4	Cousin et al [65]	55/F	Pembrolizumab	Mediastinal lymph nodes Lung	Uterine leiomyosarcoma	Discontinuation of the drug
5	Al-Dliw et al. [66]	65/F	Pembrolizumab	Mediastinal lymph nodes Lung	Melanoma	Discontinuation of the drug Corticosteroids
6	Tetzlaff et al. [67]	76/M	Pembrolizumab	Gastric, Retroperitoneal, Paratracheal lymph nodes, Erythema and swelling of the forearms	Melanoma	Discontinuation of the drug
7	Tetzlaff et al. [67]	44/F	Ipilimumab	Mediastinal and hilar lymph nodes Skin	Melanoma	Discontinuation of the drug
8	Tetzlaff et al. [67]	68/M	Pembrolizumab	Mediastinal and hilar lymph nodes	Melanoma	No specific intervention
9	Cotliar et al. [68]	72/F	Pembrolizumab	Skin Lung Mediastinal and hilar lymph nodes Bones Eyes	Hodgkin lymphoma	Discontinuation of the drug Corticosteroids
10	Firwana et al. [69]	41/M	Ipilimumab	Retroauricular, occipital, cervical, axillary, hilar, mediastinal, iliac, inguinal lymph nodes Spleen	Melanoma	Discontinuation of the drug
11	Firwana et al. [69]	57/F	Ipilimumab	Skin	Melanoma	N/A

				Mediastinal and hilar lymph nodes		
12	Firwana et al. [69]	37/F	Pembrolizumab	Cervical, axillary, mediastinal, and retroperitoneal lymph nodes Lung Skin Joints	Melanoma	Discontinuation of the drug
13	Eckert et al. [70]	67/F	Ipilimumab	Mediastinal lymph nodes Lungs	Melanoma	Discontinuation of the drug
14	Vogel et al. [71]	49/M	Ipilimumab	Mediastinal and hilar lymph nodes	Melanoma	No specific intervention
15	Wilgenhof et al. [72]	48/F	Ipilimumab	Neck, axillae, mediastinal and retroperitoneal lymph nodes Lungs Spleen	Melanoma	Corticosteroids
16	Berthod et al. [73]	63/M	Ipilimumab	Lung	Melanoma	Corticosteroids
17	Tissot et al. [74]	57/M	Ipilimumab	Bilateral hilar lymph nodes Lung Skin	Melanoma	Discontinuation of the drug
18	Reule et al. [75]	55/M	Ipilimumab	Hilar and mediastinal lymph nodes Lungs Skin	Melanoma	Corticosteroids
19	Toumeh et al. [76]	26/F	Ipilimumab	Mediastinal lymph nodes Lungs Skin	Melanoma	Corticosteroids
20	Reuss et al. [78]	32/F	Ipilimumab/ Nivolumab	Supraclavicular, mediastinal, right hilar and left iliac lymph nodes Skin	Melanoma	Discontinuation of ipilimumab
21	Faviez et al. [79]	61/N/A	Ipilimumab/ Nivolumab	Subdiaphragmatic lymph nodes Lungs Spleen	SCLC	Discontinuation of treatment
22	Faviez et al. [79]	47/N/A	Ipilimumab/ Nivolumab	Mediastinal lymph nodes Lungs	Melanoma	Discontinuation of therapy Corticosteroids

23	Faviez et al. [79]	53/N/A	Durvalumab	Mediastinal lymph nodes Lungs	Lung Adenocarcinoma	Discontinuation of the drug Corticosteroids
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*F: Female; ICI: Immune Checkpoint Inhibitors; M: Male; N/A: Not Available; SCLC: Small Cell

Lung Cancer

Table 4. Cases describing lung infections due to ICIs.

#	Case	Age/ gender	ICI	Pathogen	Type of cancer	Management
1	Kyi et al. [81]	48/M	Ipilimumab	<i>Aspergillus fumigatus</i>	Melanoma	Voriconazole and liposomal amphotericin B
2	Oltolini et al. [82]	62/F	Pembrolizumab	<i>Aspergillus spp</i> <i>P. aeruginosa</i>	Lung Adenocarcinoma	Voriconazole Ceftolozane/ tazobactam Ciprofloxacin
3	Schwarz et al. [83]	79/M	Nivolumab	<i>Pneumocystis Jirovecii</i>	NSCLC	Trimethoprim-Sulfamethoxazole
4	Schwarz et al. [83]	52/M	Nivolumab	<i>Pneumocystis Jirovecii</i>	NSCLC	Trimethoprim-Sulfamethoxazole
5	Inthasot et al. [85]	69/M	Nivolumab	<i>Mycobacterium tuberculosis</i>	Lung Adenocarcinoma	Antituberculosis treatment
6	Inthasot et al. [85]	57/F	Nivolumab	<i>Aspergillus fumigatus</i>	Squamous cell lung carcinoma	Voriconazole
7	Gupta et al. [86]	63/M	Durvalumab	<i>Aspergillus fumigatus</i>	NSCLC	Voriconazole
8	Uchida et al. [87]	65/M	Nivolumab	<i>Aspergillus fumigatus</i>	Lung Adenocarcinoma	Voriconazole
9	Fujita et al. [89]	72/M	Nivolumab	<i>Mycobacterium tuberculosis</i>	Squamous cell lung carcinoma	Antituberculosis treatment

*F: Female; ICI: Immune Checkpoint Inhibitors; M: Male; NSCLC: Non Small Cell Lung

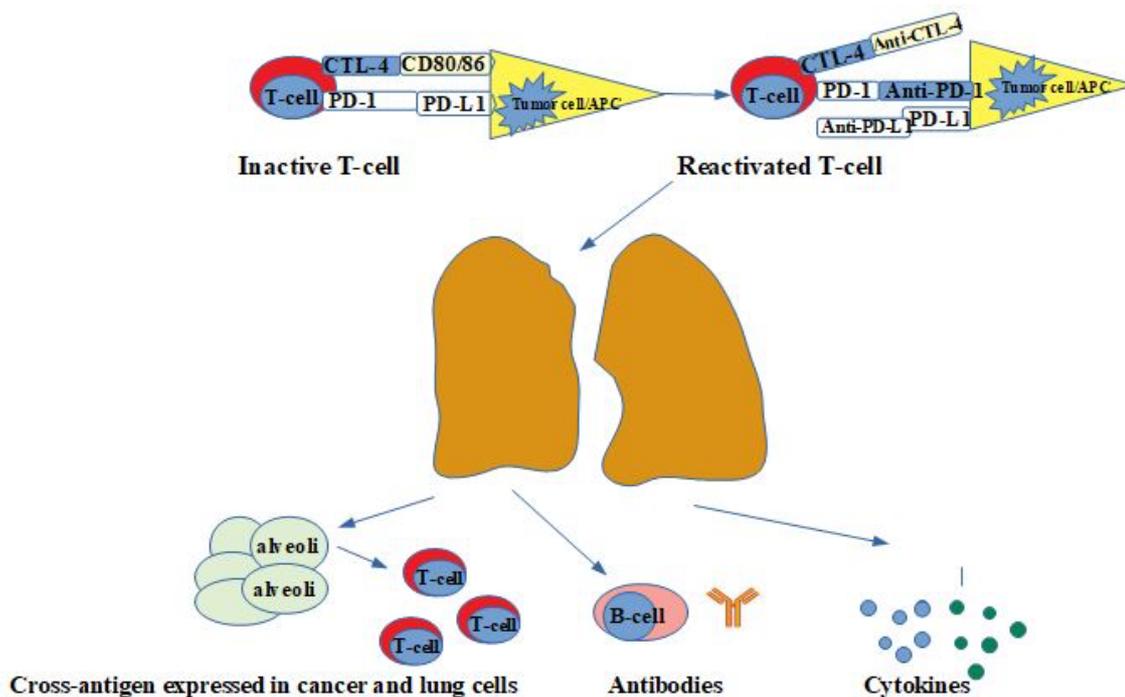
Carcinoma

Table 5. Cases describing pleural disease, pulmonary nodules, diaphragm myositis and ABPA due to ICIs.

#	Case	Age/ gender	ICI	Type of toxicity	Type of cancer	Management
1	Kolla et al. [91]	46/M	Nivolumab	Pleural Effusion	SCLC	Multiple thoracocenteses
2	Kolla et al. [91]	54/F	Nivolumab	Pleural Effusion	Lung Adenocarcinoma	Multiple thoracocenteses Corticosteroids
3	Pradère et al. [93]	40/M	Pembrolizumab	Pulmonary Nodules	Melanoma	Discontinuation of the drug Corticosteroids
4	Pradère et al. [93]	44/M	Pembrolizumab	Pulmonary Nodules	Melanoma	Discontinuation of the drug
5	Safa et al. [94]	46/M	Nivolumab	Pulmonary Nodules	Melanoma	Discontinuation of the drug
6	Haddox et al. [95]	78/M	Pembrolizumab	Necrotizing myositis of the diaphragm	Melanoma	Discontinuation of the drug Corticosteroids
7	John et al. [96]	64/F	Tremelimumab/Durvalumab.	Myositis of the diaphragm	Lung Adenocarcinoma	Discontinuation of the drug Corticosteroids Continuous bilevel positive airway pressure Intravenous polyvalent Plasma exchange Pyridostigmine
8	Pradere et al. [97]	58/M	Anti-program death 1 (PD-1) monoclonal antibody	ABPA	Renal cell carcinoma	Itraconazole Corticosteroids

*ABPA: Allergic Bronchopulmonary Aspergillosis; F: Female; M: Male; SCLC:Small Cell Lung Carcinoma

Figure 1. Potential mechanisms for lung toxicity due to Immune Checkpoint Inhibitors.



*Three potential underlying mechanisms have been reported for the development of pulmonary adverse events due to ICIs. First, the development of adverse events may be associated with increased T cell activity against cross-antigens expressed in malignant and normal lung cells as it is indicated by observation of increased lymphocytosis in bronchoalveolar lavage (BAL) obtained from patients with pneumonitis due to ICIs, mainly composed of CD4⁺ T cells. Second, increased levels of preexisting autoantibodies, such as anti-thyroglobulin antibodies, anti-rheumatoid factor antibodies, anti-thyroid peroxidase antibodies and antinuclear antibodies may be also representing an underlying mechanism. Third, increased levels of inflammatory cytokines, such as C-reactive protein and interleukin-6 (IL-6), are also related to the occurrence of pulmonary adverse events.