The Many Faces of Immune Checkpoint Inhibitor-Associated Pneumonitis: 4 Case Reports

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Case series

Patients: 54-year-old • 69-year-old • 73-year-old • 73-year-old
Final Diagnosis: Immune checkpoint inhibitor-associated pneumonitis
Symptoms: Cough • dyspnea • fever • malaise
Medication: —
Clinical Procedure: —
Specialty: Oncology • Pulmonology

Objective: Rare disease

Background: Advanced non-small cell lung cancer has poor prognosis and low survival. Immunotherapy with the use of immune checkpoint inhibitors is a relatively new method of treatment that offers a chance to significantly extend the survival and quality of life of patients over that obtained with conventional chemotherapy. One of the complications of immunotherapy is immune checkpoint inhibitor-related pneumonitis.

Case Reports: We analyzed the available medical data on the treatment of 22 patients with non-small cell lung cancer who were treated in our clinic and qualified for immunotherapy with one of the anti-PD-1/anti-PD-L1 agents: nivolumab, atezolizumab, or pembrolizumab. In this group of patients treated with immune checkpoint inhibitors, 4 patients experienced immune checkpoint inhibitor-related pneumonitis.

Conclusions: Immune checkpoint inhibitor-related pneumonitis is a rare but potentially life-threatening complication of immune therapy. It can manifest in many ways, from asymptomatic to severe cases, which require quick action and treatment. Knowing the spectrum of symptoms and being alert to the possibility of such a complication is an important skill for doctors who use immunotherapy in their patients.

Keywords: Carcinoma, Non-Small-Cell Lung • Immune Checkpoint Inhibitors • Immunotherapy • Lung Diseases, Interstitial

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Background

Advanced lung cancer is characterized by an unfavorable prognosis and low 5-year survival rates, with a 5-year survival rate of 6.3% in the United States. Low survival is caused by late diagnosis and the lack of effective treatment. The response rates of standard, platinum-based chemotherapy regimens in advanced non-small lung cancer range from 20% to 40% [1,2]. The introduction of immune checkpoint inhibitors significantly improved the prognosis of patients with disseminated lung cancer. Among the patients qualified for immunotherapy, a 3-year survival was observed in 20% to 30% of cases [3,4], and 5-year survival in 16% [5], which contributes to the fact that cancer is increasingly considered today to be a chronic disease. Immunotherapy is characterized by a lower incidence of severe adverse effects, but is not entirely devoid of them.

Immune checkpoint inhibitor-related pneumonitis (ICI-P) is one of the complications associated with the use of immune checkpoint inhibitors. We can diagnose ICI-P on the basis of dyspnea or other respiratory symptoms in a patient undergoing immunotherapy, after excluding infection and disease progression [6]. The incidence of ICI-P varies depending on the source. In clinical trials, the incidence of this complication was estimated at 3% to 5% [7,8]; however, the values differ in real-life studies. In a retrospective study involving 203 patients, Suresh et al reported the occurrence of ICI-P in 19% of cases [9]. Despite the significantly higher incidence of serious adverse events in the course of immunotherapy in real-life studies, the overall survival and progression-free survival rates are comparable to those observed in clinical trials [7].

The median time to onset of ICI-P ranges from 5 to 12 weeks after the initiation of immunotherapy; however, cases of ICI-P have been reported to develop even after 24 months [10].

The time of complication occurrence is highly variable, and its manifestation can range from an asymptomatic course, in which abnormalities are found in imaging tests only, to respiratory failure and death. ICI-P severity is assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 classification on a 5-point scale. Grades 3 to 5 are considered a significant severity of disease. Grade 3 includes severe symptoms, which lead to limited self-care and indication of oxygen therapy. Grade 4 is characterized by respiratory compromise, in which urgent interventions such as intubation are needed. Grade 5 is characterized by death related to pneumonitis [11]. The occurrence of severe ICI-P during therapy is associated with the possibility of serious complications and high mortality [12]. The overall mortality associated with the use of PD-1/PD-L1 inhibitors is approximately 0.5%. Although ICI-P is not the most common complication of immunotherapy, severe ICI-P is responsible for the greatest number of fatal complications [13]. Therefore, physicians in charge of such therapy need to be aware of this relatively rare but serious complication of immunotherapy.

Among the 22 patients with non-small cell lung cancer treated with immunotherapy (pembrolizumab, atezolizumab, nivolumab) in our department, ICI-P developed in 4 patients and affected patients receiving second-line immunotherapy with nivolumab or atezolizumab. One of the patients had adenocarcinoma and the remaining 3 had squamous cell carcinoma. So far in our department, we have not found ICI-P cases in patients receiving pembrolizumab.

In this study, we present 4 case reports of patients with diagnosed ICI-P to demonstrate the different manifestations and characteristics of this complication.

Case Reports

Case 1

Patient KK, a 54-year-old patient, had adenocarcinoma of the right lung with metastases to both lungs and the central nervous system. After central nervous system radiotherapy, 6 cycles of chemotherapy using the pemetrexed and cisplatin regimen, and 10 days after the first administration of the drug atezolizumab (Tecentriq 1200 mg), the patient reported fever up to 39°C, cough, and dyspnea at rest. On admission, the patient’s condition was serious and the oxygen saturation was decreased (54%). In laboratory test results, increased C-reactive protein levels and leukocytosis were noticed. Arterial blood gases revealed signs of complete respiratory failure.

Apart from showing the tumor of approximately 80×70 mm in size in the upper and middle field of the right lung, high-resolution computed tomography (HRCT) of the chest revealed fluid in the left pleural cavity, nodules in both lungs (metastases), enlarged mediastinal lymph nodes (present before the treatment), and new previously absent opacities, including numerous macular, confluent parenchymal, and reticular opacities with areas of ground-glass opacities in the left lung, and smaller areas of similar opacities in the superior segment of lower lobe of the right lung (Figures 1, 2).

Case 2

Patient TK, a 69-year-old man with squamous cell carcinoma of the left lung (CS III B) and a history of chemoradiotherapy qualified for atezolizumab immunotherapy due to progression after previous treatment. The patient was admitted to our department after 5 treatment cycles (in the 13th treatment week) to perform a checkpoint examination. On admission, his general
condition was fair, with an Eastern Cooperative Oncology Group performance status scale (ECOG) of 2. The patient reported increased coughing and general weakness. Laboratory test results showed slightly increased inflammatory markers. There were no signs of respiratory failure. CT of the chest showed subpleural areas of crazy-paving pattern and consolidations in the middle fields of the right lung. Within these changes there were irregular areas of consolidation and isolated areas of crazy-paving pattern in the middle and upper lobe of the left lung (Figures 3, 4).

Case 3

Patient ZB, a 73-year-old man, had squamous cell carcinoma of the right lung (CS IIIB) and after 2 cycles of chemotherapy according to the KG regimen, he qualified for immunotherapy with nivolumab owing to progression. On the day following the administration of the 8th cycle, the patient had exercise-induced dyspnea, decreased exercise tolerance, and weakness. The CT revealed (Figure 5) consolidation with a halo sign and ground-glass opacities in the posterior segment of right lower lobe.
Case 4

Patient WK, 73-year-old man, had squamous cell carcinoma of the right lung (CS IIIB). After 4 cycles of chemotherapy according to the KG regimen and palliative radiotherapy of the hilum, he qualified for immunotherapy owing to progression. After 10 cycles of nivolumab treatment and 3 days before the scheduled 11th cycle, a sudden deterioration of health occurred, with fever up to 38.5°C, dyspnea at rest, and dry cough. The patient’s condition was serious, with an ECOG performance status scale score of 3. Laboratory test results revealed increased inflammatory markers, and arterial blood gas analysis showed the features of partial respiratory failure. HRCT revealed reticular, subpleural confluent opacities at the background of ground-glass areas in the dorsal fields of the lower lobes in both lungs (Figure 6).

To exclude infection in each case, sputum was collected for culture, and blood tests for antibodies against atypical bacteria were performed. The test results were negative.

Discussion

All cases described above were confirmed as ICI-P and they present the variety of possible manifestations of the disease. Early diagnosis of this serious complication is crucial, as quick treatment implementation gives the patient the best chance of survival; however, early diagnosis can be difficult to achieve in practice. As presented in Case 1, ICI-P can resemble ordinary severe pneumonia, as it includes fever, cough, and dyspnea at rest. Therefore, it is important that patients who are treated with immune checkpoint inhibitors are alert to their respiratory symptoms and, when there are concerns, are able to contact the treating physician who is familiar with the possibility of ICI-P incidence. An ICI-P diagnosis should always be made in patients receiving immune checkpoint inhibitor therapy who present new inflammatory lesions on chest CT, with or without symptoms. In Case 2, the patient presented with not clearly marked symptoms (grade G2); however, the chest CT showed extensive areas of a paving pattern. It is worth noting that ICI-P was diagnosed during routine follow-up examination, proving the usefulness of examinations in early detection of this complication of immune checkpoint inhibitor treatment. It is important to remember that ICI-P can occur at any time during treatment; however, in Case 3 we can see a direct relationship between the administration of immunotherapy and the appearance of symptoms (grade G2). In doubtful cases, the exclusion of infection and CT scans are useful tools for making a correct diagnosis, even if requiring diagnostics beyond the checkpoint time, as prompt diagnosis and treatment are necessary in these patients. The importance of prompt diagnostics was presented in Case 4, in which the patient developed symptoms of respiratory failure due to ICI-P. Significant deterioration of his general condition was observed (grade G4), as captured during the qualification for the next cycle of immunotherapy. From the CT scan, our attention was drawn to reticular, confluent opacities in the dorsal fields of both lungs.

The final diagnosis of ICI-P should be made after the exclusion of other diseases, such as infectious pneumonia, tumor progression or pseudo-progression, acute exacerbation of

Figure 5. Chest high-resolution computed tomography: consolidation with halo sign and ground-glass opacities around in the posterior segment of right lower lobe (red arrows).

Figure 6. Chest high-resolution computed tomography: reticular, subpleural, confluent opacities at the background of ground glass areas, mainly in the dorsal fields of lower lobes in both lungs (red arrows).
chronic obstructive pulmonary disease (COPD), or radiotherapy-induced lung injury.

Among all patients treated with immune checkpoint inhibitors in our department who developed ICI-P, 2 of them (patient KK after the first cycle of atezolizumab and patient WK after 10 cycles of nivolumab), due to a serious complication of grade G4 (CTCAE 5.0), terminated immune checkpoint inhibitor treatment. The remaining 2 patients (patient TK after 5 cycles of atezolizumab and patient ZB after 8 cycles of nivolumab) continued immunotherapy after treatment with prednisolone. Treatment discontinuation involved both the patients using the anti-PD1 monoclonal antibody (nivolumab) and the anti-PD-L1 antibody (atezolizumab).

According to literature reports, the time of the pneumonitis occurrence can vary. Cho et al [14] from Seoul National University Bundang Hospital in South Korea, who studied a group of 167 patients treated with immunotherapy in a retrospective study, found that pulmonary complications occurred on average about 54.5 days from the initiation of immunocompetent therapy. In other studies, the median duration of ICI-P was diverse, but did not exceed 3 months: 2.3 months, Delaunay et al [15]; 2.8 months, Naidoo et al [7]; and 2.75 months, Suresh et al [9].

Suresh et al [9] reported a higher incidence of ICI-P in patients with squamous cell carcinoma. This is in line with our observation that 3 of 4 patients had squamous cell carcinoma. Suresh et al found that women were not more often affected by IZP than were men. In our observations, all cases of this complication concerned men only.

Naidoo et al [7] showed that ICI-P was more often related to cigarette smoking. This observation was also confirmed by our observations. All of our patients were current long-term smokers.

Moreover, Cho et al [14] reported that pulmonary complications occurred in 13.2% of 167 examined patients (G1-G4). In our observation of a small group of patients, the complication occurred in 18% of treated patients. Statistically insignificant, but worth emphasizing, was the fact that ICI-P was more common in patients with a history of radiation therapy, COPD, and no extrathoracic metastases. In our group, 3 of 4 patients were treated with radiotherapy. Three of them also had COPD. Extrathoracic metastases were present in 1 patient. Our observations were consistent with the conclusions of South Korean researchers, whereby the radiologic manifestations of ICI-P in chest CT were heterogeneous [14]. In the available retrospective studies, researchers described the presence of unilateral or bilateral ground-glass opacities, nodules, reticular opacities, foci of consolidation, and thickening of interlobular septa [9,16].

Suresh et al [9] in their retrospective work on 205 patients at Johns Hopkins University School of Medicine in Baltimore noted that the most common form of radiologic manifestation was the overlapping of ground-glass opacities and consolidation. Moreover, they emphasized that in 14% of cases these changes could be observed in the close proximity of the neoplastic infiltration.

Naidoo et al [7] divided radiological changes in IZP into 5 subtypes: cryptogenic organizing pneumonia, ground-glass opacities, interstitial pneumonia, inflammation of the hypersensitivity type, and pneumonitis not otherwise specified (Table 1). In CT scans of our patients, we observed ground-glass opacities,
reticular opacities, crazy-paving pattern, and consolidations (Figures 1-6). Usually, the abnormalities were located on both sides, most often in the subpleural area, except for 1 patient in whom the area of the ground-glass opacity was strictly limited to the segment of the right lung (Figure 5). The most common abnormality observed in CT in our patients was the ground-glass opacity, which agrees with observations of Suresh et al. [9]. In 1 patient, CT scanning revealed an image of crazy-paving pattern in the subpleural area (Figure 3). Owing to the ongoing COVID-19 epidemic and radiological features that may have suggested an active phase of the disease, the patient was tested for SARS-CoV-2 twice, which allowed for the exclusion of COVID-19. These observations present the diversity of radiologic manifestations of ICI-P and demonstrate that CT alone cannot serve as a diagnostic method of this complication, but serves only as a supplementation of clinical data.

Pharmacological treatment protocols depend on radiological imaging and the severity of pneumonitis. Patients with grade 2 pneumonitis (CTCAE) or higher should receive corticosteroid therapy. Doses typically start at 0.5 to 1 mg/kg/day of prednisone or equivalent for 3 to 6 months. Steroid-refractory disease or patients with respiratory failure can require therapy with intravenous corticosteroids and/or cytotoxic therapies.

In the present study, after treatment with steroids in adequate doses, depending on the severity of the complication (G2 or G4), clinical and radiological improvement was achieved in each patient. The cases of pneumonitis in patient KK (Case 1) and WK (Case 4) were classified as grade G4 due to the severity of symptoms and serious general condition caused by ICI-P. Initially, both of these patients received methylprednisolone intravenously. Additionally, due to rapidly increasing respiratory failure, patient KK was also treated with noninvasive ventilation, and patient WK stayed in the Intensive Care Unit for 4 days. Treatment with immune checkpoint inhibitors was discontinued in these patients.

The incidence of ICI-P in our other 2 patients was classified as grade G2, and after 6 weeks of treatment with prednisone, the patients continued the immunotherapy. None of the patients required infliximab or any other immunosuppressive drugs other than steroids.

The number of patients treated with immunotherapy with checkpoint inhibitors (atezolizumab, nivolumab, and pembrolizumab) in our department was small and was related to the relatively recent introduction of immunotherapy treatment therapies funded by the National Health Fund in Poland. As the number of qualified patients on immunotherapy increases each month, the frequency of complications of immunotherapy will also increase. In our department, pulmonary complications of treatment occurred in 4 patients, with an incidence of ICI-P of 18%. Although our study was conducted on a small group of patients, our results are consistent with those of larger studies.

**Conclusions**

The incidence of ICI-P in our department was comparable to that reported in the available literature. In our observation, ICI-P incidence was comparable in the group of patients treated with nivolumab (2 cases of ICI-P in 13 patients) and atezolizumab (2 cases in 9 patients). ICI-P can manifest in a variety of ways, ranging from asymptomatic cases with abnormalities only on imaging tests to severe respiratory failure leading to death. Radiological manifestations are heterogeneous. Abnormalities can be 1- or 2-sided, often very limited (to 1 segment), or can be diffuse and extensive. Paving in chest CT can also be a manifestation of ICI-P.

**Declaration of Figures’ Authenticity**

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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