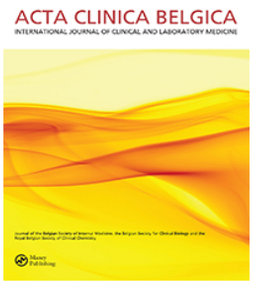

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CASE REPORT

Severe pulmonary infections complicating nivolumab treatment for lung cancer: a report of two cases

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ABSTRACT

Background: Immunotherapy represents a recent milestone in the treatment of lung cancer, particularly with the rapidly expanding development of monoclonal antibodies targeting checkpoint inhibitors in the programmed cell death-1 (PD-1) pathway, such as nivolumab and pembrolizumab. Classical auto-immune side effects of these treatments, often called immune-related adverse events (irAEs), can affect multiple organs, including the lungs in which potentially life-threatening pneumonitis may require rapid treatment with high doses of corticosteroids. Nevertheless, the occurrence of severe infections in cancer patients treated with nivolumab, outside the context of immunosuppressive therapy, is a complication that has rarely been reported in the literature.

Clinical cases: We report two cases of severe pulmonary infection with unusual microbes, Mycobacterium tuberculosis and Aspergillus fumigatus, in patients treated with nivolumab for non-small cell lung cancer.

Conclusion: Ruling out pulmonary infections may require extensive investigation, as these may have an atypical presentation due to immunomodulation. Furthermore, treating the patient with corticosteroids for immune-related pneumonia could lead to a fatal outcome in this context. This report highlights the importance of excluding the presence of opportunistic infections and tuberculosis before considering immune-related pulmonary toxicity with or without a history of prior corticosteroid use. These cases also emphasize the potential value of tuberculosis screening in patients treated with PD-1 checkpoint inhibitors.

KEYWORDS

Non-small cell lung cancer; immune checkpoint blockade; pneumonitis; tuberculosis; aspergillosis

1. Introduction

Immunotherapy represents a recent milestone in the treatment of lung cancer, especially with the rapidly expanding development of monoclonal antibodies targeting the checkpoint inhibitor pathway [1]. In particular, drugs aimed at the programmed cell death-1 (PD-1) axis, such as nivolumab and pembrolizumab, have been approved since 2015 by the United States Food and Drug Administration for the treatment of advanced non-small cell lung cancer.

The use of checkpoint inhibitors is classically associated with several auto-immune side effects, often called immune-related adverse events (irAEs), which are believed to derive from systemic immune enhancement[2]. These toxicities can affect multiple organs, including the lungs in which potentially life-threatening pneumonitis may require rapid treatment with high doses of corticosteroids.

In this report, we discuss 2 cases of severe pulmonary infections caused by atypical pathogens in patients treated with nivolumab for non-small cell lung carcinoma.

2. Case reports

Case 1: A 69-year-old man was diagnosed with a metastatic lung adenocarcinoma of the upper right lobe. He received first-line treatment with 4 cycles of cisplatin-pemetrexed, followed by 4 cycles of maintenance pemetrexed but discontinued due to intolerance. Tumor progression four months later was treated with a second-line regimen of 18 cycles of nivolumab with a good initial response. At follow-up, the patient was diagnosed with bronchopneumonia. No pathogen was identified and he only showed mild improvement after amoxicillin-clavulanic acid treatment. Given the persistence of symptoms and the evidence of pulmonary infiltrate in the upper right lobe on chest radiograph one month later (Figure 1), a bronchoscopy with bronchoalveolar lavage (BAL) was performed and demonstrated positivity for *Mycobacterium tuberculosis* in both cultures and by polymerase chain reaction (PCR) analysis. Antituberculosis treatment was started accordingly.

Case 2: A 57-year woman, followed for a locally advanced squamous cell lung cancer of the upper right lobe, was initially treated with 6 cycles of cisplatin-gemcitabine which resulted in disease control. In the context of cancer progression at follow-up, a second-

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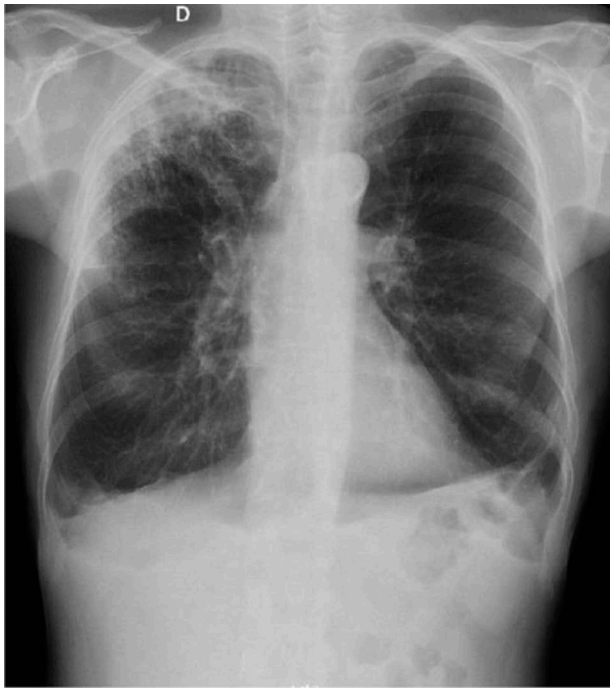

Figure 1. Chest X-ray showing upper right lobe infiltrate.

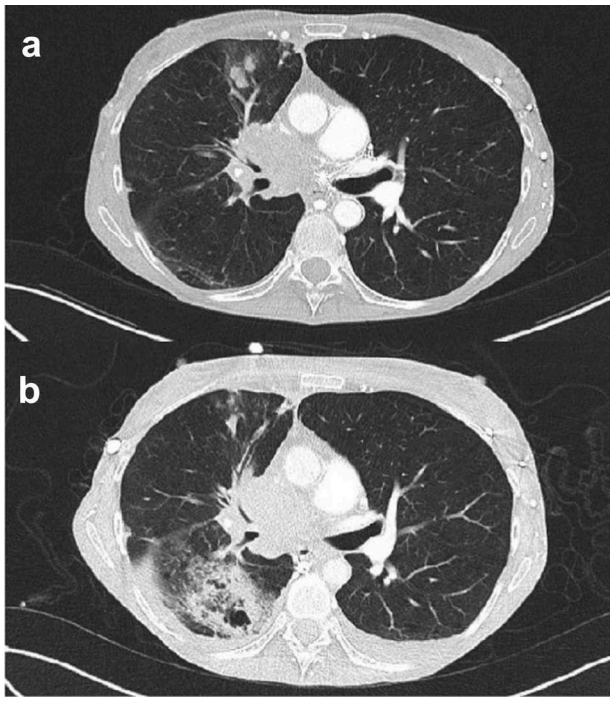

Figure 2. Chest computed tomography (CT) scan before (A) and after (B) the appearance of an excavated lesion in the lower right lobe apical segment.

line treatment with nivolumab was initiated. After the second cycle, the patient presented with fever which was empirically treated with amoxicillin-clavulanate before escalating to piperacillin-tazobactam due to clinical deterioration. Chest computed tomography revealed an excavated infiltrate in the apical segment of the lower right lobe (Figure 2 A and B). A bronchoscopy with BAL detected elevated levels of Aspergillus galactomannan antigen. The patient was then treated with voriconazole for invasive pulmonary aspergillosis with good clinical response.

3. Discussion

It has been shown that anti-PD-1-based therapy plays a major role as a regulator of immune activation by modulating T cell responses. This mechanism could lead to both tumor control in patients with lung cancer as well as trigger a loss of self-tolerance, resulting in immune-related adverse events. Moreover, the PD-1/PD-ligand-1 pathway appears to play an important role in immune control in chronic infections[3].

According to a retrospective study in metastatic melanoma patients, the major risk factor for infection after immune checkpoint blockade is the use of immunosuppressive drugs such as corticosteroids and infliximab in combination with nivolumab[4].

Publications reporting the occurrence of serious infectious complications associated with immunotherapy without the co-administration of immunosuppressive agents are very scarce.

3.1. Mycobacterial infections

After literature review, we found 7 additional cases of *M. tuberculosis* infection associated with anti-PD-1 immunotherapy (nivolumab, pembrolizumab) in patients in whom there was no history of prior corticosteroid use [5–10], and one case of pneumonia caused by *Mycobacterium avium*[11].

Previous studies have shown an increase in PD-1 expression on the cell surface of T lymphocytes in chronic infections such as tuberculosis[12]. Furthermore, in vitro blockade of PD-1 with monoclonal antibodies has been demonstrated to restore *M. tuberculosis* antigen responsiveness of circulating T cells[13], similar to the mechanisms described with tumor cells, and this supports the potential influence of anti-PD-1 therapy in tuberculosis[14]. However, the exact role of PD-1 in the pathophysiology of tuberculosis has yet to be further elucidated[15].

There are two main assumptions that relate anti-PD -1 therapy and the occurrence of active tuberculosis. The first is an immune reactivation of T cells against *M. tuberculosis* provoked by the checkpoint inhibitor blockade, and could be similar to the immune reconstitution inflammatory syndrome (IRIS) described in HIV infection. The second is the occurrence of opportunistic infections resulting from lymphopenia that occurs as a possible side effect of immunotherapy [7,16]. It should be noted that among the few published cases of *M. tuberculosis* infection associated with cancer immunotherapy, one patient suffered from a paradoxical response after anti-tuberculosis treatment, an observation supporting the first hypothesis[9].

3.2. Aspergillosis

We describe the second case of *Aspergillus fumigatus* pulmonary infection occurring in a patient treated with cancer immunotherapy in the absence of immunosuppressive treatment[17], in contrast to the other previously published case reports [18–20].

Paradoxically, starting immunotherapy may also have a favorable effect on the control of fungal infections, as has been shown in mouse models[21], and, therefore, immune modulation may be more complex than expected. Accordingly, one case of intractable mucormycosis has reportedly been treated with amphotericin, posaconazole, nivolumab, and interferon-γ which led to clinical improvement[22].

4. Conclusion

Complications associated with immunotherapy must be cautiously evaluated. Ruling out pulmonary infections may need extensive investigation as these may have an atypical presentation due to immunomodulation. In our cases, treating the patient with corticosteroids for immune-related pneumonia could have led to a fatal outcome. Non-invasive testing for latent tuberculosis should also be considered before initiation of anti-PD-1 immunotherapy.

Disclosure statement

No potential conflict of interest was reported by the authors.

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