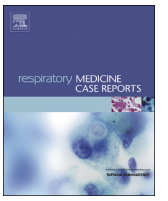
Respiratory Medicine Case Reports 45 (2023) 101898

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

Long-term complete remission after severe pembrolizumab-induced immune-related encephalitis in metastatic lung adeno-squamous carcinoma: A case report

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ARTICLE INFO

Handling Editor: DR AC Amit Chopra

Keywords:
Non-small-cell lung cancer
Immune checkpoint inhibitor
Immune-mediated neurological adverse event
Complete remission

ABSTRACT

Immune checkpoint inhibitors became the treatment of choice, in monotherapy or in association with platinum-based doublet chemotherapy, in first-line therapy for advanced-stage non-small-cell lung cancer without oncogenic driver. Nevertheless, it can be associated with diverse immune-related adverse events; several immune-related adverse events can also follow each other involving multiple organ systems, leading to immune checkpoint inhibitors discontinuation and immunosuppressive therapy that could compromise the prognosis of patients, with the exception of rare situations such as this clinical case.

This case report illustrates a succession of immune-related adverse events including a rare and severe pembrolizumab-induced immune-related encephalitis in a patient with metastatic lung adeno-squamous carcinoma in whom we could observe a long-term and complete remission despite discontinuation of treatment and high-dose corticosteroids.

In metastatic non-small-cell lung cancer, a disease with a poor initial prognosis, some patients can benefit from immune checkpoint inhibitors and can even now present a long-term and complete remission and this despite severe and rare immune-related adverse events, high-dose corticosteroids and an early discontinuation of treatment.

Abbreviations

ICIs	immune checkpoint inhibitors
NSCLC	non-small-cell lung cancer
irAES	immune-related adverse events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
PD-1	programmed cell death protein 1
MRI	magnetic resonance imaging
ctDNA	Circulating Tumor DNA
MRD	Minimal Residual Disease

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https://doi.org/10.1016/j.rmcr.2023.101898
Received 12 February 2023; Accepted 18 July 2023
Available online 24 July 2023

1. Introduction

These last years, immune checkpoint inhibitors (ICIs) have been widely used as treatment for patients with malignant tumors, revolutionizing their management. Tumor cells can interfere with the anti-tumor response of T lymphocytes, through activation of the proteins CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 (programmed cell death protein 1) on the surface of T lymphocytes [1]. The ICIs are monoclonal antibodies allowing a T-lymphocyte-mediated immune response against tumor cells, by targeting the proteins CTLA-4, PD-1 or its ligand PD-L1 [2]. Although effective, these treatments can nevertheless be responsible for a wide range of immune-related adverse events (irAEs), with different degrees of severity, requiring in severe irAES discontinuation of treatment and sometimes high-dose corticosteroids that could affect the prognosis of patients. It is not clearly proven but there could be an association between the occurrence of these side effects and the response to ICPIs.

2. Case presentation

A 71-year-old man was diagnosed with lung adeno-squamous carcinoma in May 2019 by supraclavicular lymph node biopsy. His main antecedents were non-insulin-dependent (type II) diabetes, high blood pressure, right humeral osteosynthesis and appendectomy.

Thoracic assessment showed the appearance of right hilar infiltration, encompassing the right upper pulmonary artery and the main bronchus, bilateral mediastinal and cervical lymph nodes enlargement (especially right supraclavicular and cervical lymph nodes enlargement, diameter of 40 mm). At the abdominal level, a nodule was observed in the left adrenal gland. There was no suspicious brain lesion based on magnetic resonance imaging (MRI). Therefore, in the absence of a formally identified primary tumor, we retained the diagnosis of cIVB adeno-squamous carcinoma (cTx cN3 cM1c, 8th TNM classification).

The patient was an active smoker accumulating 45 pack-year units, with no obvious impact on lung function tests. There was no environmental exposure. Given the absence of oncogenic driver and an expression of PD-L1 by the tumor cells evaluated between 90 and 100%, a pembrolizumab-based immunotherapy was started in June 2019 and continued until October 2019 (total of 7 cycles), allowing a partial response.

In October 2019, due to asthenia and diffuse pain, an endocrine assessment was performed and identified central adrenocortical insufficiency which was substituted by hydrocortisone.

Two weeks later, the patient was taken to the Emergency Department for mild confusion, responsible for a low-velocity car accident. The anamnesis was not helpful due to neurological conditions. Blood tests revealed a moderate inflammatory syndrome (CRP at 43.81 mg/L), hyponatremia (127 mmol/L) and hypokalemia (3.3 mmol/L). Other blood parameters were normal. The clinical neurological examination, apart from the mentioned confusion (characterized by a spatial-temporal disorientation), was without particularity, as well as the imaging assessment (by brain CT scan and MRI). The confusion persisted. The electroencephalograms were compatible with encephalopathy, without epileptiform activity. Lumbar puncture showed cellularity at 5 elements/μL, including 30.5% lymphocytes and 68.6% macrophages. The IgG concentration in the cerebrospinal fluid was 2.4 mg/dL. Glucose, lactate and protein analyses were normal. The search for viral pathogens, autoimmune and paraneoplastic serologies came back negative. Pending the results of PCR tests and the infectious serologies, empirical treatment with aciclovir was initiated and continued for 48 hours.

In the meantime, the patient's neurological condition deteriorated alarmingly, the latter being in a state of severe confusion with complete mutism. Several phases of confusion succeeded until a state of extreme agitation, associated with probable multisensory hallucinations. Subsequently, high-dose intravenous corticosteroids therapy (1.75 mg/kg) was introduced in the hypothesis of grade 3 immune-mediated encephalitis and we observed a very quick clinical improvement. The patient was discharged twelve days later, with a full recovery (ECOG performance status scale of 0). Oral corticosteroid treatment was continued on a tapered schedule for a total of 5 weeks. Immunotherapy was permanently discontinued.

A PET-CT was performed in April 2020 with a complete metabolic response. To date, the patient is still in oncological remission, the last radiological assessment dating from August 2022.

3. Discussion

Although ICIs have radically changed the management of lung cancer, they can be responsible for multiple irAEs of varying intensity.

To date, due to the lower incidence of neurological irAEs, data available on it in clinical trials of non-small-cell lung cancer (NSCLC) are limited, and most of these adverse effects are documented in case reports. Although neurological irAEs are relatively rare, approximately accounting for 1%–3% of all irAEs in monotherapies, they may strongly affect the prognosis and even lead to patients' death with cancers [3]. Neurological irAEs can occur particularly in case of immunotherapy combination (anti-PD(L)-1 and anti-CTLA-4) [4]. However, the incidence of grade 3 and 4 irAEs is $<1\%$ in all ICIs.

The precise pathophysiology of irAEs remains unclear. Some potential mechanisms include increased T-cell activity against antigens on both neoplastic and healthy tissues, thereby increasing levels of pre-existing antibodies, inflammatory cytokines, as well as activating complement-mediated inflammation, via the binding of these antibodies to the cytotoxic T lymphocyte antigen 4, which can also be expressed in healthy tissues [5].

In case of immune-related encephalitis, pleocytosis and high protein level in the cerebrospinal fluid are common [6]. Most often, we find leptomeningeal enhancements or brain lesions on MRI, with the exception of rare cases, as in ours [7]. To date, the only definitive test for a diagnosis of autoimmune encephalitis is the presence of antineuronal antibodies. In case of immune-mediated encephalitis, these are rarely present.

Although their management is not always obvious, response to corticosteroids is often good [8]. However, the prognosis seems to be reduced in case of lacunar response within 48–72h, requiring rapid identification of these patients and adaptation of therapy [9]. It is important to exclude anemia, aseptic meningitis, autoimmune syndrome, and thrombotic thrombocytopenic purpura as etiologies of encephalitis. In some cases described in literature, additional treatments have been performed, such as intravenous immunoglobulin, plasmapheresis or Rituximab [10,11]. In case of severe neurological irAES, current recommendations advise against resumption of immunotherapy [12].

As in the present case, some data from the literature suggest that the development of irAEs could be a prognostic factor in oncology and notably in certain cancer types (NSCLC and melanoma) and organ-specific irAEs (skin and endocrine) [13,14]. In 2017, Spain et al. reported a response rate in melanoma of nearly 70% in treated patients who developed neurological irAEs (compared to an overall response rate of 20–30% in phase 3 trials), and a median survival of 45.7 months versus 11.2 months in patients without neurological irAEs [15]. Similarly, other data suggest that 40–50% of patients with neurological irAEs achieve a partial or complete response, despite early discontinuation of ICPIs and administration of high-dose corticosteroids [16].

Moreover, NSCLC treated with ICI-monotherapy may develop multisystem irAEs as was the case in our experience. Shankar et al. identified an association between multisystem irAEs and improved survival in NSCLC, which persists after adjustment for treatment duration [17]. In this study, 9% of the patients developed multisystem irAEs.

Furthermore, taking steroids under treatment with ICI seems to increase risk of death and progression compared to patients treated with ICI not using steroids [18]. In subgroup in this meta-analysis, the greatest negative effect on prognosis was evident in patients taking steroids for supportive care. Conversely, the effect of steroids administered to reduce irAEs did not seem to negatively affect overall survival; this finding was similar in NSCLC and melanoma.

Therefore, further clinical trials are still necessary to better understand the complex mechanisms involved in these different events. Some biomarkers such as Circulating Tumor DNA (ctDNA) could in the future offer the possibility of detecting patients without Minimal Residual Disease (MRD) in whom we could earlier stop ICIs with greater safety.

4. Conclusion

This case demonstrates that irAEs can follow each other and patients can develop multisystem irAEs. However, a complete and long-term remission is possible despite high-dose corticosteroids for severe irAEs and early discontinuation of ICIs.

Immune-mediated neurological toxicity is rare and can be fatal, but can also respond to high-dose corticosteroids with a good prognosis.

Even if there is no clear evidence of a correlation between the cancer prognosis and the severity of the irAEs, the fact remains that some patients experience a prolonged response and a complete remission.

Ethics approval and consent to participate

Written informed consent to participate in this case report was obtained from the patient. In this context, our local ethics committee considered that this case report did not require complementary ethical approval.

Consent for publication

Written informed consent for publication was obtained from the patient for publication of this case report.

Funding

This case report did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

Rémy Quirynen and Lionel Pirard contributed to the acquisition of data and to the draft manuscript preparation. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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