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Pembrolizumab-induced massive hypereosinophilia associated with mononeuritis multiplex, brain microvascular lesions and intestinal eosinophilic infiltration in a melanoma patient

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Introduction

Immune checkpoint inhibitors (ICPis) such as pembrolizumab have improved the overall survival in melanoma patients. Pembrolizumab is a monoclonal antibody that binds to the programmed cell death protein 1 (PD-1) receptor, thereby releasing PD-1 pathway-mediated inhibition of the immune response. Like other ICPis, pembrolizumab is associated with a significant risk of immune-related adverse events (irAEs) which can affect any organ. Prompt recognition and appropriate management are required, as irAEs can be associated with severe decline in organ function and quality of life, and even be life-threatening. However, this may prove challenging for uncommon and poorly characterized irAEs. Here, we report an unusual case of massive hypereosinophilia associated with disabling neurologic and digestive adverse events after 4 courses of pembrolizumab.

Case report

An 82-year-old man with a long-lasting history of melanoma BRAF negative was treated with pembrolizumab 200 mg i.v. once every 3 weeks following the surgical removal of a lung metastase. His-medical history included otherwise longstanding adrenal insufficiency substituted with hydrocortisone 10 mg daily, asthma controlled with as needed salmeterol and tiotropium, and recurring allergic bronchopulmonary aspergillosis (ABPA) with chronic stable increased total IgE serum level (circa 4000 kU/L) and eosinophilia (circa 1×10^9/L).

After 2 courses of pembrolizumab, the patient complained of unusual fatigue and musculoskeletal pain. After 4 courses, pembrolizumab was stopped at the request of the patient whose general condition was declining.

One month after the last pembrolizumab administration, the patient was hospitalized for acute diarrhea. He also reported new motor and sensory difficulties of the right hand and tingling of the 4 distal extremities. On examination, there was weakness of the intrinsic muscles of the right hand, and sensory loss of all fingers. Of note, a left hand motor deficit had spontaneously resolved within 48 h a few days before admission.

Initial laboratory tests were mostly unremarkable except (normal ranges in parentheses): C-reactive protein 128 mg/L (<10 mg/L); blood absolute leukocyte and eosinophil count (AEC) 48×10^9/L (4–10×10^9/L) and 26×10^9/L (0.05–0.3×10^9/L) respectively, without morphological abnormalities on the blood smear. Of note, AEC gradually increased from the first pembrolizumab course, peaking at 36×10^9/L one week before admission (Fig. 1). There was no clinical or radiological evidence for recurrence of ABPA and total IgE were stable compared to previous values. Except for eosinophilia, the clinical and biological signs typically observed in DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome were not present (no fever, skin rash, organ damage, lymphadenopathy or atypical lymphocytes). Brain magnetic resonance imaging (MRI) showed multiple seemingly vascular acute and subacute lesions in various arterial territories. Many were located in the deep structures (striatum, corpus callosum and deep white matter) and some in the cortical regions (particularly the right parieto-temporal cortex). Some exhibited restriction of diffusion, some small hemorrhages. No lesion was suggestive of metastatic disease (Fig. 2-A, B, C). Although consistent with a vascular process, these findings did neither explain the right upper limb motor deficit, nor had a distinct clinical translation. Precerebral arteries doppler ultrasonography did not reveal any significant hemodynamic abnormalities; electrocardiogram and echocardiography were normal. Antinuclear antibodies and antineutrophil cytoplasmic antibodies were negative. Stool were negative for infectious agents, including parasites and Clostridium difficile. Endoscopy with biopsies revealed signs of colitis and a severe duodenitis with marked eosinophilic infiltration.

IrAEs associated with pembrolizumab were suspected. One week after hospital admission, the patient was initiated on methylprednisolone 50 mg i.v. daily for 3 days, then given oral prednisone 20 mg daily with a subsequent taper over 10 weeks. There was a dramatic response to

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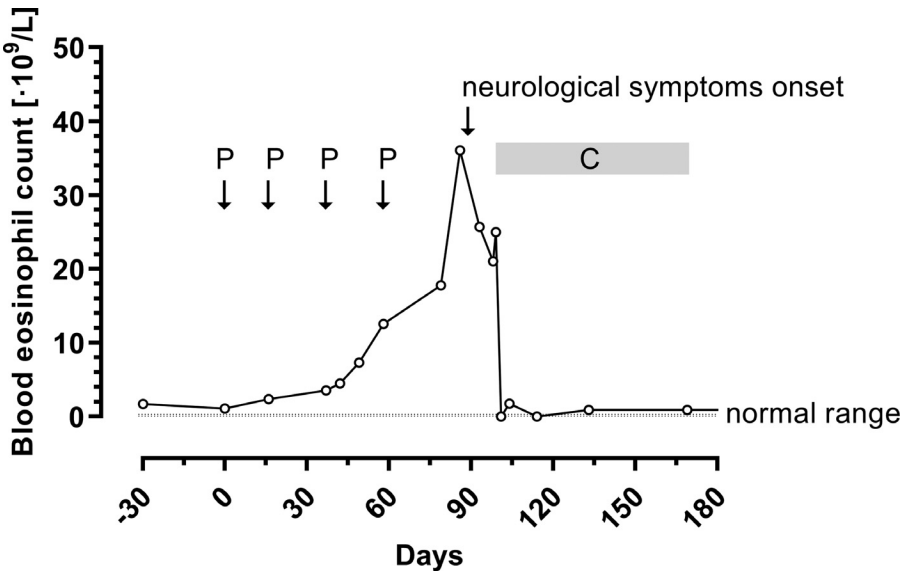

Fig. 1. Blood eosinophil count before and after starting pembrolizumab. Pembrolizumab dose administrations are represented by P and downward arrows, and corticosteroids by C. The onset of neurological symptoms is represented by a downward arrow.

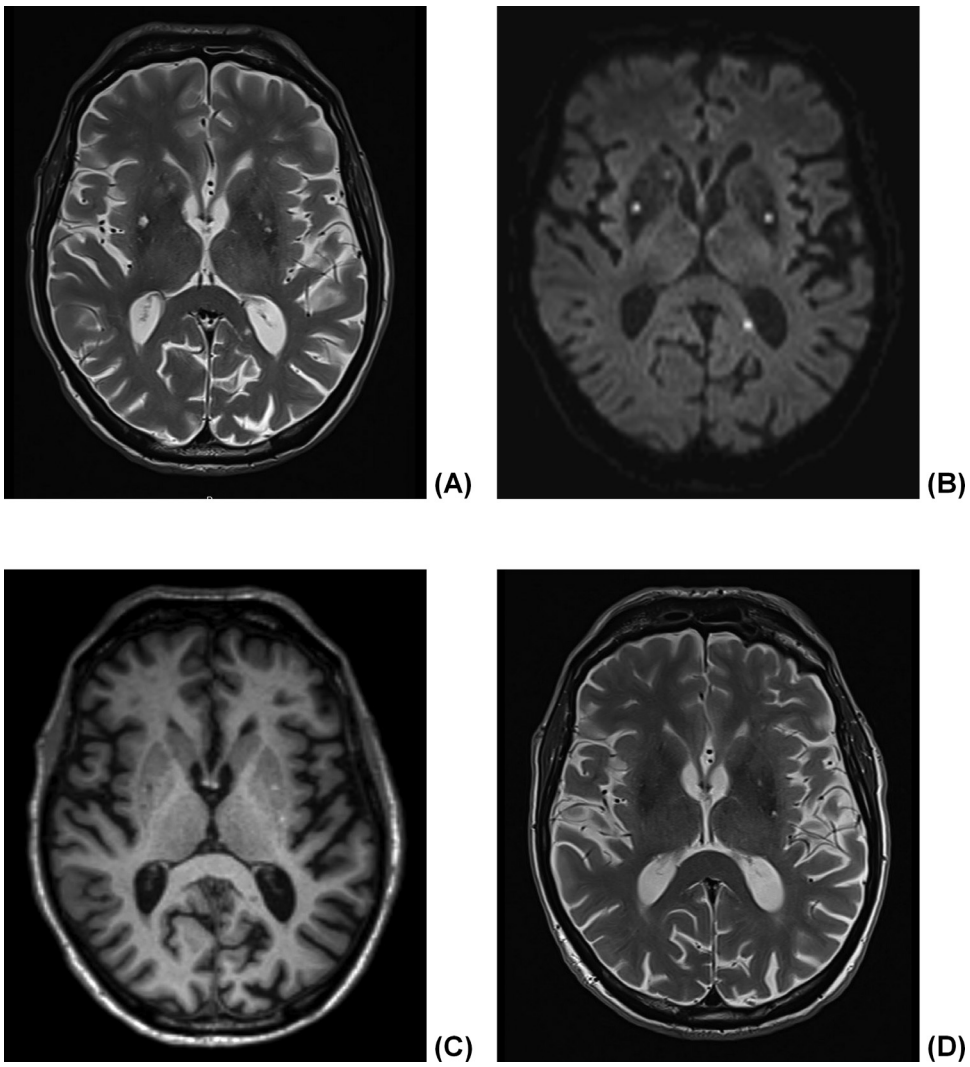

Fig. 2. Brain imaging (MRI) revealed multiple acute and subacute lesions in the striatum (A), some with restriction of diffusion (B), some with small hemorrhages (C). Lesions were also visible in the right parieto-temporal cortex and periventricular regions (not shown). Evolution at 11 months showed regression of the lesions with minimal scarring (D).

glucocorticoids with a quick drop in AEC to baseline values after 3 days (Fig. 1). Diarrhea resolved concomitantly without any anti-infectious treatment. A follow-up brain MRI showed regression of most of the lesions with minimal scarring (Fig. 2-D). Unfortunately the neurological deficits of the right hand persisted. Electroneuromyography performed later (at 8 months) revealed inexcitability of the right median, right ulnar and left fibular nerves by motor and sensory stimulation.

The oncological course was marked by the occurrence of a lymph node metastasis at 3 months from the last pembrolizumab administration, which was treated with radiotherapy. Later on additional metastases developed; immunotherapy was not resumed considering the past irAEs, and the patient eventually died 32 months after the last dose of pembrolizumab.

Discussion

This patient presented concomitantly hypereosinophilia, mononeuritis multiplex, microvascular lesions in the brain, eosinophilic duodenitis and colitis one month after the last pembrolizumab administration.

Eosinophilia has been associated with immunotherapies, including pembrolizumab, most likely via overproduction of eosinophilopoietic cytokines such as IL-5 [Singh et al., 2020, Bernard-Tessier et al., 2017, Occhipinti et al., 2018]. Eosinophilia may be predictive of a good treatment response in melanoma [Gaba et al., 2015, Krishnan et al., 2020]. However, in this case, the AEC were unusually high. In a case series of 37 patients with eosinophilia induced by ICPis, the median peak of AEC was 2.7×10^9/L and only 2 patients had peak values above 9×10^9/L [Scanvion et al., 2020]. Although stable ABPA could not by itself explain such a massive AEC increase, it might have been a predisposing condition as the patient had slightly elevated AEC on a chronic basis. Considering the plausible time relation to drug exposure, with a steady increase of AEC starting shortly after pembrolizumab initiation (Fig. 1), a causal relationship was considered highly probable.

Sustained hypereosinophilia may cause damage to various organs, including the nervous system, via eosinophilic infiltration, mediators' release, hypercoagulability and thrombosis [Lee et al., 2008, Lee and Ahn, 2014]. A duodenitis with marked eosinophilic infiltration was actually demonstrated in this patient [Yang et al., 2019]. Mononeuritis multiplex is a known irAEs, however in this case pembrolizumab-induced hypereosinophilia itself could have been the trigger. Finally, the brain microvascular lesions could correspond to small arterial thrombosis, as an embolic origin was ruled out by a cardiac workup and the localization of the lesions were atypical for vasculitis [Khoja et al., 2016]. In this case, the various clinical disorders appeared concomitantly with the eosinophilia peak, which strongly suggests a causal link.

Conclusion

Atypical adverse drug reactions can be difficult to recognize. In this case, hypereosinophilia was not immediately recognized as an irAE, furthermore there was a lack of awareness of its potential for organ damage. Clinicians should systematically consider an adverse drug reaction in the differential diagnosis and promptly set up a multidisciplinary approach in case of a diagnostic challenge.

Consent

An informed consent form was signed by the patient.

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.

CRediT authorship contribution statement

Kim Dao: Writing – original draft, Visualization. **Thierry Kuntzer:** Writing – review & editing. **Philippe Maeder:** Visualization, Writing – review & editing. **Valerie Frossard:** Writing – review & editing. **Francoise Livio:** Writing – original draft, Writing – review & editing.

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