Letter to the Editor (Case report)

Checkpoint inhibitor-induced eosinophilic fasciitis following high eosinophilia associated with complete response

Eosinophilic fasciitis is a rare immune-related adverse event associated with complete responses in melanoma patients.

Sr., Checkpoint inhibitors induce a plethora of immune-related adverse events [1] including rare events. We report on a patient with debilitating eosinophilic fasciitis with accentuated eosinophilia possibly due to a higher risk from local dinitrochlorobenzene treatment prior to checkpoint inhibitor therapy.

A 77-year-old female patient with acral lentiginous melanoma underwent complete right axillary lymph node dissection (0/21). Five months later several cutaneous metastases on the right arm and the thorax were found. Mutation analysis revealed BRAF wildtype, which excluded the possibility of a targeted therapy with BRAF inhibitors. A combined chemoimmunotherapy with dacarbazine and a contact sensitizer to boost the immune reaction against tumour antigens, local dinitrochlorobenzene, was started. However, the disease progressed and immunotherapy with an anti-cytotoxic T-lymphocyte-associated Protein 4 antibody (ipilimumab) was initiated. Two weeks after the second dose of ipilimumab, the patient developed grade 2 autoimmune diarrhoea in the Common Terminology Criteria for Adverse Events, meaning an increase of four to six stools per day over baseline, which was treated with prednisolone. Because of new cutaneous metastases, therapy was switched to an anti-programmed cell death receptor-1 antibody (pembrolizumab). Under pembrolizumab therapy she experienced a histologically confirmed complete response at month 9. After 22 months or a total of 31 infusions with pembrolizumab (three-weekly applied) the patient developed muscular pain and oedema in the upper arms and thighs with an only slightly elevated creatine kinase of 227 U/l (normal range <170 U/l) and considerable eosinophilia of 33% (normal range: 2–4%; absolute: 4092/μl), but clinical symptoms were not suggestive of classical eosinophilic fasciitis as there was no oedema or skin change on careful examination. Additionally, she developed grade 2 Common Terminology Criteria for Adverse Events autoimmune hepatitis with an increase of transaminases higher than three-fold the upper limit of normal. Therefore, pembrolizumab was stopped and treatment with prednisolone started at a starting dose of 1 mg/kg with a slow taper.

Creative kinase, transaminases and eosinophil count were declining, but myalgia and oedema were only slightly improving. About 2 months later the patient was unable to move her arms and pursue the functions of daily living due to severe pain in both forearms. At this time the patient was still on prednisolone (20 mg/day). Clinical examination revealed a symmetric, bilateral woody induration of both forearms from the elbow to the wrist with peau d’orange appearing skin. The groove sign was positive. Leucocytes were elevated (14 200/μl) with relative lymphopaenia, but no elevated eosinophil count. Creatine kinase was in the normal range (56 U/l). CRP was slightly elevated (9.6 mg/l; normal range: <5 mg/l). ANAs were negative and there was no hypergammaglobulinaemia. MRI of both forearms revealed superficial and deep fascial thickening, thickened skin and intra-/subcutaneous oedema (Fig. 1, left). Clinical symptoms and imaging findings were consistent with eosinophilic fasciitis. The dose of prednisolone was raised and MTX at 10 mg per week and then 20 mg s.c. was started. Symptoms were slightly improving and follow-up MRI of the left forearm 9 months later revealed almost complete regression of the signs of eosinophilic fasciitis (Fig. 1, right). The patient is still in complete regression of her melanoma disease.

Eosinophilic fasciitis is a rare connective tissue disorder with variable clinical manifestations that occurs spontaneously [2] or is induced by checkpoint inhibitors [3–7]. Interestingly, of the five other recently reported cases of fasciitis under treatment with checkpoint inhibitors three were in complete remission when the fasciitis started [3, 4, 6]. Only a bladder cancer patient treated with ipilimumab and nivolumab showed tumour progression [5]. In accordance with other rheumatic immune-related adverse events, fasciitis occurred late, between 8–22 months after beginning checkpoint inhibitor therapy [4]. This underlines the question about the required duration of treatment after complete response. In our case histologically confirmed complete response was seen after 9 months, while fasciitis occurred after 22 months of treatment with pembrolizumab. We observed a remarkable temporary increase in the eosinophil count at the beginning of symptoms. Although eosinophilia is associated with better outcome in patients melanoma treated with checkpoint therapy [8], it may also precede or coincide with autoimmune side effects such as eosinophilic fasciitis. Thus, when encountering a patient with complete response and eosinophilia, potentially the decision to cease checkpoint inhibitor therapy could be favoured more easily.

Eosinophilic fasciitis is a rare immune-related adverse event induced by treatment with checkpoint inhibitors with lasting sequelae. For better outcome it is therefore crucial to recognize this side effect and treat patients promptly. Prolonged surveillance of patients is necessary.
since onset can be late in the course of therapy or even after termination of checkpoint inhibitor therapy. Thorough documentation of these rare cases, e.g. in registries, will enable further insights and a better understanding of risk factors.

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**References**


