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Case Report

Treatment of Checkpoint Inhibitor Induced Eosinophilic Fasciitis with Benralizumab and Intravenous Immunoglobulin

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Abstract

Lung cancer is the leading cause of cancer-associated death as it is one of the most common malignancies worldwide [1,2]. Metastatic lung cancer has historically been associated with a poor outcome under chemotherapy treatment, however, the development of Immune Checkpoint Inhibitor (ICI) and targeted therapies have improved patients' outcome. The role of ICI in treating solid tumors has been broadened in recent years and they are now considered to be the first line therapy for many entities. ICI can cause significant side effects, named immune-related adverse events (irAE). These side effects are due to the mechanism of action of ICI as they block crucial pathways for the regulation of immune responses [3]. The most frequent adverse events are colitis, pneumonitis, hepatitis, adrenocorticotropic hormone insufficiency and hypothyroidism [4]. The treatment of choice for the majority of these side effects include the cessation of ICI, initiation of glucocorticoids and supportive therapy [4]. In refractory cases the utilization of additional immunosuppressive treatments such as biologicals can be necessary [5]. In some cases, rare side effects might occur and guidelines for such cases are lacking. Herein, we present the case of ICI associated eosinophilic fasciitis, which showed a remarkable response to interleukin 5 (IL-5) receptor blockage with Benralizumab in combination with Intravenous Immunoglobulin (IVIG) therapy.

Case presentation

A 68-year-old male was diagnosed with relapsed NSCLC with a PD-L1 expression of >50% on tumor cells. The patient was treated with the Programmed Death cell protein 1 (PD1) inhibitor Pembrolizumab. Under this treatment a complete remission was reached. After 15 months on treatment the patient complained about muscle pain, which was initially interpreted as muscle tensions in context with a change of Co-Medication (T0, Figure 1.). Myositis was ruled out based on normal Creatine Kinase (CK) values. Due to worsening of the symptoms, including swollen ankles, the patient received diuretics with partial improvement of peripheral oedema. At this time point, further laboratory evaluation was performed including microscopic blood analysis and evaluation of chemical values. Here (T1, Figure 1), the absolute count of eosinophils in the peripheral blood increased compared to normal values (2.82 G/l; normal range: 0.00- 0.70 G/l). Due to further persistence of symptoms with additionally a maculopapular exanthema at the extremities (Figure 2A), the treatment with Pembrolizumab was stopped at this time point (T2 Figure 1), the absolute count of eosinophils in the peripheral blood had risen to 4.27 G/l. Furthermore, the C-Reactive Protein (CRP) and the Erythrocyte Sedimentation Rate (ESR) were above norm. With suspicion of irAE to skin and muscles, treatment with Prednisone (PDN) (total 100 mg/day/p.o.) was started for 3 days with dose tapering. The muscular pain and the exanthema were partially regressive and the absolute count of eosinophils in the peripheral blood normalized (T3, Figure 1). Due to a persisting exanthema with tender upper arms and lower legs, PDN therapy was reinitiated (50 mg absolute per day) and a punch biopsy of the skin was performed, which showed signs of actinic elastosis but no signs of active inflammation. At cessation of PDN, due to persisting symptoms under therapy, the eosinophils values rose again to 1.34 G/l (T4, Figure 1). The patient was referred to the rheumatologists for further evaluation of his myalgias in the extremities. At clinical examination, a diffuse and symmetrical thickening of the skin and induration of the underlying soft tissues of the upper and lower extremities was found, which appeared hide-bound, woody, with a peau d'orange texture (Figure 2B). Based on these findings, Eosinophilic Fasciitis (EF) was suspected, and a whole body MRI was performed. The MRI (Figure 3) showed hyper intense alterations of signal along the fascia of the thigh muscles and the muscles of the lower legs as well as along the thoracic wall, compatible with a fasciitis. A PET-CT scan, which was performed at the same to re-stage the tumor response, also showed an increased FDG uptake along the fasciae of the lower extremities and a complete response of the lung cancer. For further differential diagnosis, an immunofixation showed no abnormalities indicative for skleromyxedema. A nephrogenic systemic fibrosis was also an unlikely differential diagnosis as the renal parameters were normal. In addition, there were no signs of a peripheral sclerosis and therefore, a systemic sclerosis was excluded. In order to confirm the suspected diagnosis of an eosinophilic fasciitis, a full skin-to-muscle biopsy of the right thigh was performed, which showed signs of inflammation in the deep subcutaneous tissue with infiltration of eosinophilic granulocytes. Based on this new diagnosis and in order to offer the patient a personalized treatment [6] a therapy with an anti- IL-5 receptor antibody (Benralizumab) was initiated. The patient received 30 mg every 4 weeks. At start of Benralizumab therapy, the eosinophil count in the peripheral blood was 1.45 G/l (T5, Figure 1). Already 10 days after the first application of Benralizumab the eosinophil count in the peripheral blood dropped to 0.0 G/l (T6, Figure 1) and the patient reported a major improvement of the symptoms. To assess the improvement, we established a questionnaire containing four questions on the most prominent symptoms (Stiffness, itching, muscle pain, muscle function/force). During the following three months, the patient reported significant clinical improvement under continued therapy with Benralizumab. The skin showed less oedema and redness and got softer. In the peripheral blood, eosinophil numbers stayed low. After 4 months of monotherapy with Benralizumab the symptoms of the fasciitis appeared to stagnate, with a stationary skin thickness and redness of the skin. Another deep skin biopsy showed a persisting lymphocytic infiltration. In order to further potentiate our immunosuppressive therapy without negatively impacting anti-tumor response, we decided to add monthly Intravenous Immunoglobulin (IVIG) therapy (2 g/kg Bodyweight d1-3, q4w) based on data in non-ICI associated eosinophilic fasciitis (T7, Figure 1) [7,8]. Under the combination of Benralizumab and IVIG the symptoms further improved, with diminished pruritus and decreased local contractures and tensions of the extremities. After six months of dual therapy the patient had only minimal symptoms of the ICI associated eosinophilic fasciitis. The response to therapy was also evident in the regression of IL-5, Neopterin and the CRP (Figure 1B, 1C). Pembrolizumab therapy was reinitiated, but a PET-CT scan >12 months after cessation of the ICI showed new metabolic activity in 2 mediastinal lymph nodes, therefore, a local radiotherapy was performed.

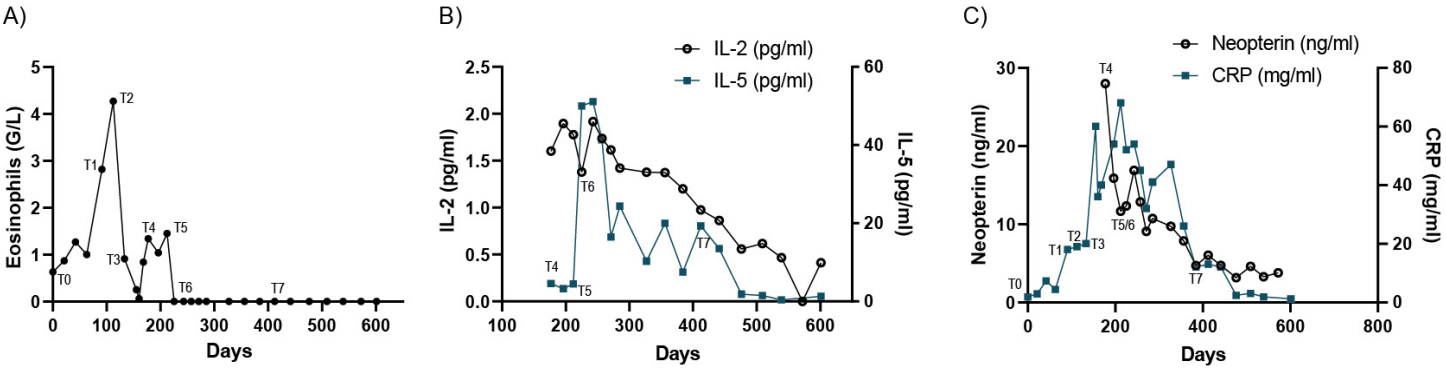

Figure 1: Blood analysis of A) Eosinophils B) IL-5, IL-2 and C) Neopterin and CRP overtime: At the beginning of symptoms (T0), further laboratory evaluation (T1), stopping of ICI (T2), after first PDN therapy (T3), after cessation of PDN therapy (T4), at start of Benralizumab therapy (T5), 10 days after first application of Benralizumab (T6), at start of therapy with IVIG (T7).

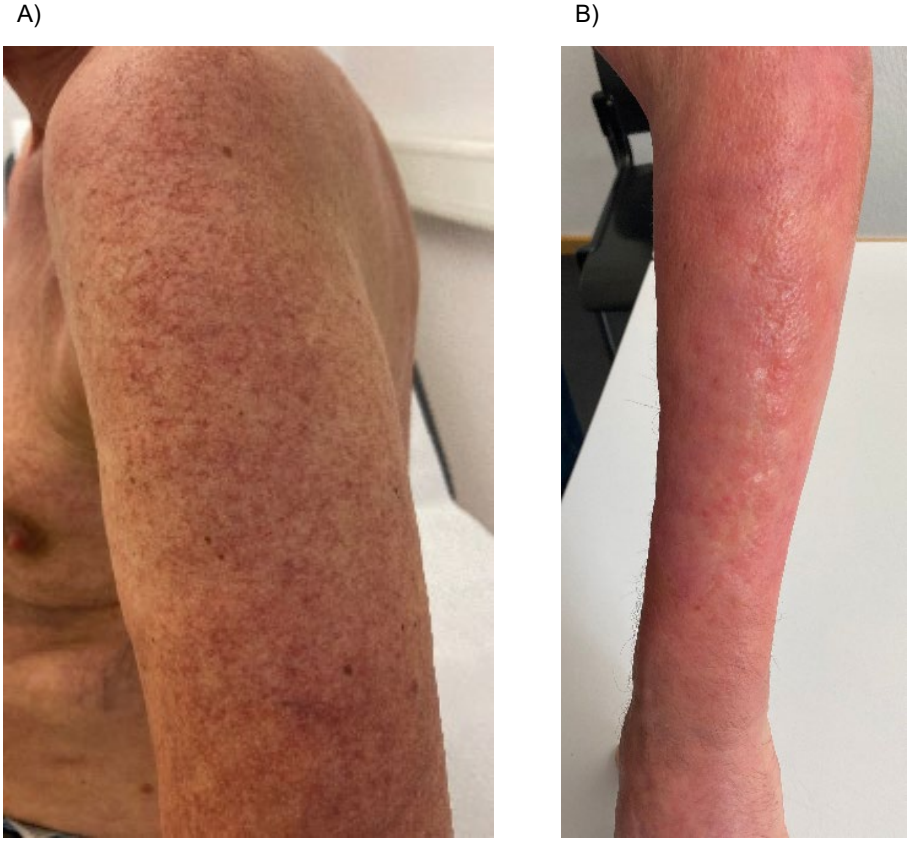

Figure 2: Clinical features: A) maculopapular exanthema B) peau d'organe.

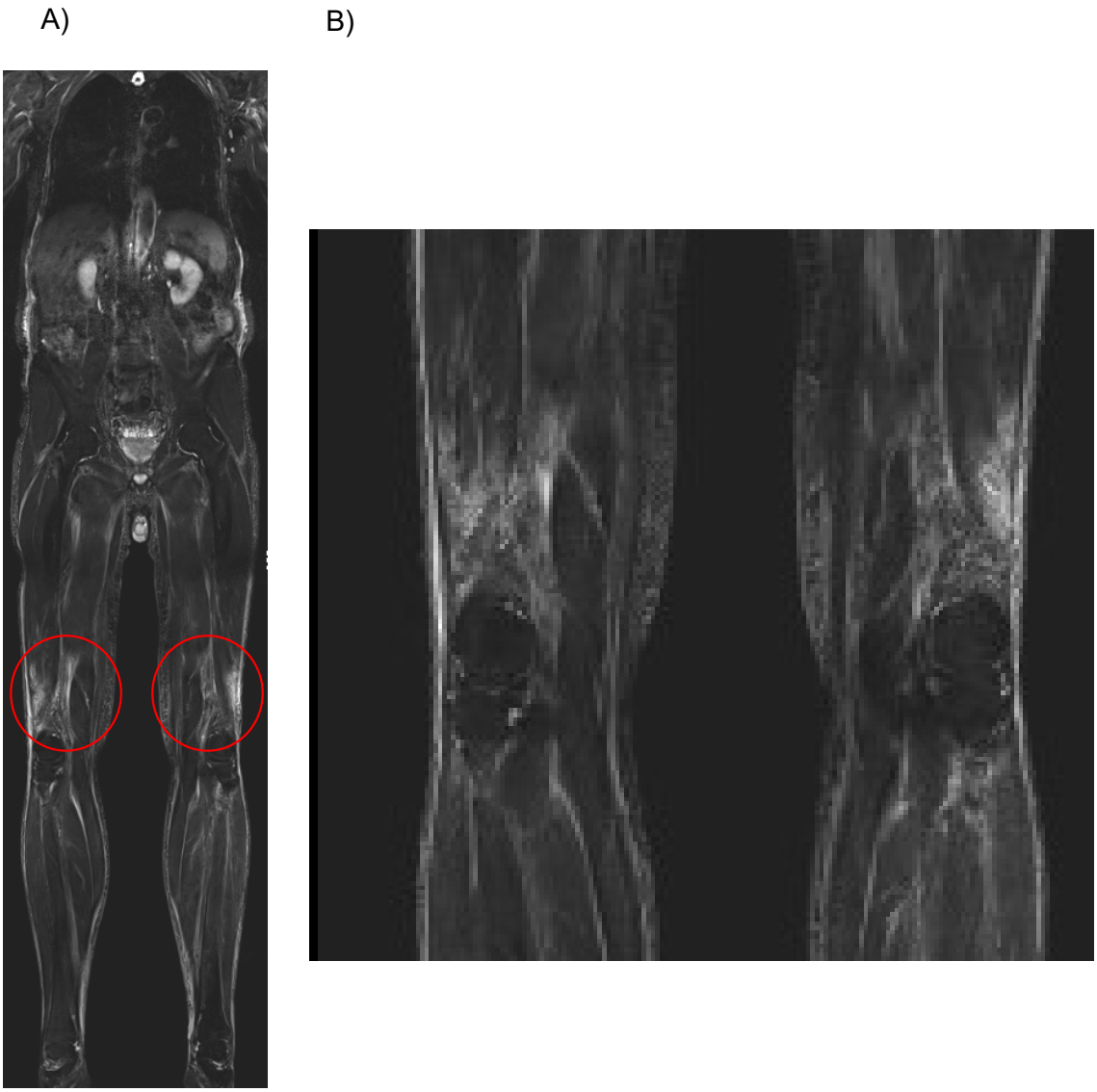

Figure 3: Imaging tests: A) whole body MRI showing hyper intense signal alterations along the fascia of the thigh muscles and the muscles of the lower legs, as well as along the thoracic wall B) MRI image of the upper thigh with increased signal intensities along the fasciae.

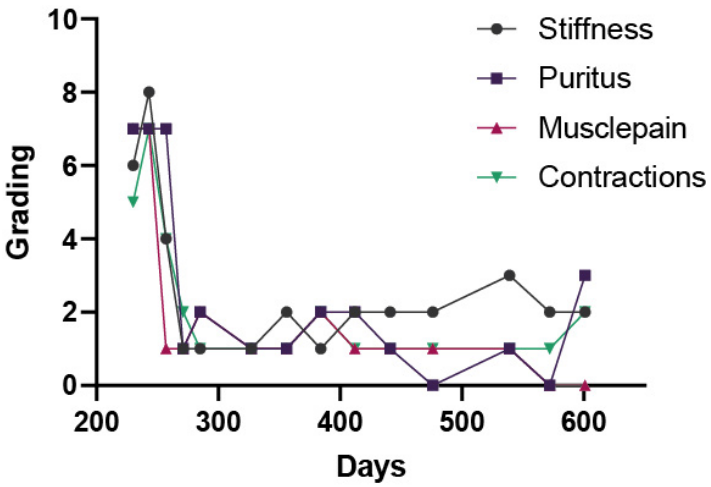

Figure 4: Assessment of the therapy response according to four clinically relevant symptoms: Stiffness (black), pruritus (purple), muscle pain (red) and muscle contractions (green). Assessed weekly with a self-established Likert-Scale questionnaire (0 = no symptoms; 10 = maximum of symptoms).

Discussion

Eosinophilic fasciitis or Shulman Syndrome is a rare scleroderma-like condition, which was first described in 1974. The etiology and pathogenesis remains still unclear [9]. Clinically affected patients present with a symmetric swelling of soft tissues, a peau d'orange appearance (Figure 2B), indurations and thickening of the skin. A groove sign may appear along the course of the veins [10]. Typical laboratory findings are hypereosinophilia, hypergammoglobinemia, elevated ESR and elevated serum aldolase levels [9-11]. MRI is considered to be the best imaging modality in the diagnosis of eosinophilic fasciitis. It often shows increased signal intensities along the fasciae and can be used for determining the best location to perform a muscle biopsy for a histopathologic diagnosis [9]. However, as reported by Narvaez, et al., signal alterations in FDG uptake in the fasciae can also be shown in the FDG PET-CT of patients with eosinophilic fasciitis [12]. In 2013, Pinal-Fernandez, et al. described two major and five minor criteria important in the diagnosis of an eosinophilic fasciitis: swelling, induration and thickening of the skin and the histopathologic verification of a fascial thickening with accumulation of lymphocytes or macrophages, with or without eosinophilic infiltration, were considered the Major criteria; hypereosinophilia, hypergammaglobinemia, groove sign and/or peau d'organe, hyperintense signal alterations of the fascia in the MRI and muscle weakness and/or elevated aldolase levels were included as minor criteria. An exclusion criterion was the diagnosis of a systemic sclerosis. They suggested that the presence of both major criteria, or one major and at least 2 minor criteria verify the diagnosis of an eosinophilic fasciitis [9]. Jinnin, et al. published a guideline for the diagnosis and therapy of eosinophilic fasciitis based on major and minor criteria In their approach a diagnosis was made when one major criterion and at least one minor criterion were fulfilled [11]. So far, no randomized trials on the treatment of eosinophilic fasciitis have been carried out. Treatment with 1 mg/kg Prednisone equivalent per day has been reported which was commonly associated with a rapid normalization of the peripheral hypereosinophilia and the initially elevated ESR. A softening of the skin requires several weeks for improvement under Prednisone treatment. As relapses may occur, higher doses of glucocorticoids or the addition of other immunosuppressive or immunomodulatory agents might be necessary [13-17]. Here, Benralizumab was chosen, because it can resolve eosinophilic inflammation without having a predicted negative impact on the ongoing anti-tumor immune response.

In consideration of these recommendations, one might argue that, in our Case, the prednisone dose was too low and the tapering was performed too early. Therefore, the early relapse could be related to the inconsistent use of steroids in the beginning. As the diagnosis of eosinophilic fasciitis was not suspected at that time, the therapy was not adapted to the current recommendations. Later, after confirmed diagnosis and a prednisone refractory course, we chose Benralizumab as a glucocorticoid- sparing option. We aimed to avoid immunosuppression that could interfere with the anti-tumor response, as previous data suggested a negative effect of glucocorticoids on immunotherapy efficacy [18,19]. For the same reasons we also deemed methotrexate to be a less suitable treatment option. The introduction of ICI has revolutionized the treatment of many malignancies. Nevertheless, a broad range of irAE may occur and can affect almost every organ of the body [4]. Rheumatologic adverse events such as arthralgia, myalgia, arthritis and myositis are common and well described in the current literature. However only few cases of eosinophilic fasciitis or scleroderma have been described so far [10]. Concerning steroid refractory immune related eosinophilic fasciitis there is even less experience [20]. To date, in 14 cases the diagnosis of an eosinophilic fasciitis upon ICI treatment have been described. In additional 10 cases different labels (Myofasciitis, Lymphocytic fasiitis, Skleroderma like Syndrome) were given. In the table below (Table 1) we show a summary of the currently published reports and outcomes. In these cases, previous to development of symptoms related to eosinophilic fasciitis, the patients had been under therapy with PD-1, PD-L1, CTLA-4 inhibitors (Pembrolizumab, Nivolumab, Avelumab, Ipilimumab, Cemiplimab and Atezolizumab). Pembrolizumab and Nivolumab monotherapy were the most common drugs (9 cases each), which might be explained by the approval of Nivolumab und Pembrolizumab for a broad range of indications. There were 2 case reports of eosinophilic fasciitis with the administration of Atezolizumab and one case report each with prior administration of Avelumab, Ipilimumab, Cemiplimab and the dual therapy with Ipilimumab/Nivolumab with subsequent Nivolumab monotherapy.

It seems surprising that only one case of EF has been previously associated with Ipilimumab/Nivolumab even though a higher toxicity of this combination has been reported [21]. As described before, EF was frequently seen in patients with reported remission [22-25]. It is notable that the response rate is especially high in the subgroup of patients with metastatic melanoma. Chan et al suggested the occurrence of EF might be a prognostic marker for improved outcome in advanced melanoma patients, as it occurred exclusively in cases with partial or complete response to therapy [26].The relatively high proportion of overall response might be associated with a higher immune modulatory response in these patients. It has already been shown that patients with irAE have a higher response rate to ICI therapy than patients without irAE [27-29]. In fact, peripheral eosinophilia have been described to be prognostic for response to ICI [30]. In metastatic melanoma patients a high eosinophilic count were associated with a better overall survival upon ICI treatment, unfortunately this was also associated with a higher incidence in irAE [26,31-34]. For NSCLC, a high absolute eosinophil count was also shown to be independently associated with a better progression free and overall survival in a cohort of 134 Patients treated with Nivolumab [35]. For the treatment of advanced NSCLC with Pembrolizumab, no data on the association of these prognostic markers with efficacy of ICI have been described so far. The onset of eosinophilic fasciitis was reported between 1, 5 and 24 months after therapy start with a median onset after 13, 5 months of therapy. The treatment of choice was the cessation of the ICI, and the initiation of a systemic therapy with glucocorticoids and methotrexate. This treatment schedule was reported in the majority of reported cases [20,23,25,26,36-41]. Only a few cases recovered without the initiation of a systemic therapy. In 2 cases an improvement was detected solely by discontinuation of ICI therapy [42,43]. In 1 case topical therapy was successfully conducted and ICI therapy could even be continued [44]. Other cases reported of an improvement of the side effects with a combination of glucocorticoids and other immunosuppressive or immunomodulating agents, such as mycofenolate mofentil, IVIG, sirolimus or Hydroxychloroqiune and Sulfasalazine. However, the field is lacking standardization or response assessment to irAE treatment. Therefore, it is difficult to compare different reports.

Therefore, we established a Likert-scale based questionnaire in order to document the response to therapy. We chose 4 clinically relevant symptoms: stiffness of the extremities, pruritus, muscle pain and contractions which the patient reported once weekly to assess the response to our therapy (Figure 4). In order to avoid prolonged treatment with corticosteroids, we have detected IL-5 as a possible target of treatment to block eosinophils activation in analogy to treatment of allergic diseases [45,46]. One case report described the use of such approach with the anti-IL5 antibody Reslizumab for the treatment of non-immunotherapy related eosinophilic fasciitis. Herein a patient with steroid-refractory eosinophilic fasciitis was described, who had already received methotrexate as well as mycofenolate mofentil, and showed an impressive improvement of symptoms under Reslizumab, which made the cessation of glucocorticoids possible [47]. Our case is the first to report the effects of IL-5 receptor blockage and intravenous immunoglobulin for immunotherapy-related EF with improvement of patient outcome.

I D	Reference	Sex	Age	Malignancy	CPI	Onset (months)	Treatment	Cancer status	CPI stopp	Biopsy	Other irAE	EF
1	Chan et al 2020 [26]	M	48	NSCLC St.IV	Atezolizumab	6	PDN + MTX	PD	Yes	Yes	Not rep.	Yes
2	Chan et al 2020 [26]	F	71	Metastatic melanoma	Nivolumab	3	PDN + MTX	CR	Yes	Yes	Not rep.	Yes
3	Chan et al 2020 [26]	M	43	Metastatic melanoma	Pembrolizumab	15	PDN + MMF	CR	Yes	No	Not rep.	No

4	Chan et al 2020 [26]	M	70	Metastatic melanoma	Pembrolizumab	8	PDN + MTX + anti IgE	PR	Yes	No	Not rep.	No
5	Khoja et al 2016 [22]	F	51	Metastatic melanoma	Pembrolizumab	18	PDN	CR	Yes	Yes	Cerebral vasculitis	Yes
6	Lidar et al, 2018 [23]	F	53	Melanoma	Pembrolizumab	8	PDN + MTX	CR	Yes	Yes	None	Yes
7	Le Tallec et al, 2019/ 2020 [20,38]	F	56	NSCLC St. IV	Nivolumab	9	PDN + MTX; DW; Sirolimus	SD	Not rep.	Yes	Cholangitis	Yes
8	Andres - Lencin a et al, 2018 [36]	M	65	Bladder cancer St. IV	Ipilimumab / Nivolumab x3 Mo., then Nivolumab Mono	16	PDN + MTX (Ciclosporin ineffective)	PD	Yes	Yes	Lichen sclerosus	Yes
9	Toussaint et al, 2019 [25]	F	77	Metastatic melanoma	Pembrolizumab	22	PDN + MTX	CR	Yes	No	Hepatitis	Yes
10	Rischin et al, 2018 [41]	M	55	Metastatic melanoma	Nivolumab	24	PDN + MTX	CR	Yes	Yes	Not rep.	No – lymphocytic fasciitis
11	Daoussis et al, 2017 [48]	M	64	Renal cell carcinoma	Nivolumab	10	PDN	Not rep.	Not rep	No	Not rep.	No
12	Narvaez et al, 2018 [42]	F	67	Renal cell carcinoma	Pembrolizumab	2	NSAID + Colchicine, DW	PD	Not rep.	No	Virtiligo	No– fasziitis
13	Parker et al, 2018 [24]	F	43	Metastatic melanoma	Nivolumab	15	PDN + IVIG	CR	Not rep.	Yes	hypothyroidism	No
14	Narvaez et al, 2018 [42]	M	56	Metastatic urothelial carcinoma	Avelumab	1,5	DW	PD	Yes bc PD	No	No	No – fasziitis

15	Bronstein et al2011 [21]	F	74	Melanoma	Ipilimumab	14	Not rep.	CR	Not rep.	No	Not rep.	No
16	Salamanki etal, 2020 [10]	M	81	NSCLC	Pembrolizumab	18	PDN + (MMF); DW	CR	Yes (temporary)	Yes	Not rep.	No– Skleroderma like syndrome
17	Pabon-Cartagena et al, 2020 [40]	F	61	Met. Nasopharyngeal squamous carcinoma	Nivolumab	12 (2 Mo. Off therpay)	PDN + MTX	CR	Yes prior toEF	Yes	Not rep.	Yes
18	Bui etal, 2020 [44]	M	59	Met. Neuroendocrine carcinoma	Nivolumab	24	Topical therapy, natural UV exposure, physiotherapy	PR	No	Yes	Not rep.	Yes
19	Kobak et al,2019 [49]	M	73	NSCLC	Pembrolizumab	2	PDN	Notrep.	Not rep.	No	Not rep.	No – fasciitis
20	Ollier etal, 2020 [39]	M	64	MetastaticMelanoma	Nivolumab	13	PDN, MTX,IVIG,	CR	Yes	Yes	Not rep.	Yes
21	Wissam et al,2020 [43]	F	48	Met. TNBC	Atezolizumab	15	DW, Physio	PR	Yes	Yes	No	Yes
22	Kruschе et al,2021 [37]	F	73	MetastaticMelanoma	Nivolumab	15	MTX, PDN	CR	Yes (before Diagnosis of EF)	Yes	Diarrhea,Arthralgia	Yes
23	Boppana et al,2021 [50]	F	72	Met. Cutaneous squamouscell Carcinoma	Cemiplimab	12 + 0,5	Hydroxychloroquine, sulfalazine, PDN	Notrep.	No but Dose reduction	Yes	Osteoarthritis	Yes
24	Current paper	M	68	NSCLC St.IV	Pembrolizumab	19	PDN, Benralizumab, IVIG	CR/ PD	Yes	Yes	Virtiligo	Yes

Abbreviations: DW: Drug Withdrawal; PDN: Corticosteroid; MTX: Methotrexate; MMF: Mycofenolate Mofentil; IVIg: Intravenous Immunoglobulin g; PD: Progressive Disease; CR: Complete Response; Not rep: Not reported; Mo: Months, TNBC: Triple Negative Breast Cancer

Table 1: Overview of Cases with immune-related (eosinophilic) fasciitis.

Conclusion

Eosinophilic fasciitis as an adverse event of ICI is a very rare condition where most cases are diagnosed after a prolonged disease course. The management and diagnosis of eosinophilic fasciitis benefits from an interdisciplinary approach with involvement of oncologists, rheumatologists, dermatologists and immunologists.

This case report shows a promising response of ICI related eosinophilic fasciitis treated with the IL-5 receptor antibody Benralizumab in combination with IVIG. This treatment has the potential of inhibiting the eosinophilic inflammation without negatively interfering with ongoing ICI induced anti-tumour immune responses. Our review of literature show that there is still limited experience with this rare irAE and further studies are needed to define optimal therapy.

Consent

Written informed consent was obtained from the patient for publication of this report and any accompanying images.

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