Eosinophilic fasciitis and acute encephalopathy toxicity from pembrolizumab treatment of a patient with metastatic melanoma.

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Key words: melanoma, pembrolizumab, eosinophilic fasciitis, encephalopathy, anti-PD1 treatment

Funding: Leila Khoja was supported by grants from CIHR and the Guglietti Family Fellowship fund.

Disclosures: D. Hogg has served as a consultant or on the advisory boards of BMS, Merck, and Roche. M.O. Butler has received honoraria from Merck Canada and BMS Canada, and has served as a consultant for or on the advisory boards of Merck and BMS.

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Word count: 1858

Tables/figures: 1 table, 1 figure

DISCLAIMER: N. Al-Faraidy was not available to confirm coauthorship, but the corresponding author, D. Hogg, affirms that N. Al-Faraidy contributed to the article and thus confirms her coauthorship status.”
Abstract

Anti-PD1 inhibitors have significant activity in metastatic melanoma. Responses often occur early and may be sustained. The optimal duration of treatment with these agents is unknown.

Here we report the case of a 51-year-old woman treated with pembrolizumab, as part of the Keynote-001 trial, as first line treatment for metastatic disease. She experienced a complete response after 13.8 months of treatment with no adverse events. One month after the last drug infusion and 18 months from starting treatment, the patient presented with eosinophilic fasciitis. She then developed acute confusion and weakness, thought to be secondary to intracranial vasculitis. High dose steroids were initiated with resolution of the fasciitis. Aspirin was commenced for presumed vasculitis with resolution of the neurological symptoms.

To our knowledge, there are no previous reports of eosinophilic fasciitis or cerebral vasculitis due to anit-PD-1 agents. This case demonstrates that toxicity may occur in association with pembrolizumab treatment after a prolonged period of treatment without toxicity. Future trials should explore the optimal duration of treatment with pembrolizumab.
Background

Checkpoint inhibitors have significantly improved survival outcomes in metastatic melanoma. Ipilimumab was FDA approved in 2010 and has shown durable responses beyond three years in a subset of patients[1]. More recently the PD1 antibodies pembrolizumab and nivolumab were both approved for treatment refractory metastatic melanoma after ipilimumab failure[2-5]. Emerging data from the Keynote 006 comparative study of ipilimumab (a CTLA-4 inhibitor) and pembrolizumab have shown superiority of first line pembrolizumab in response rates and survival[5]. However the optimal duration of treatment with anti-PD1 agents is unknown. The majority of toxicities, particularly immune related adverse events (IrAE), appear to occur in the first 6 months of treatment, but toxicity may occur later with ongoing therapy. [6]

Here we report the case of a 51-year-old woman with M1c metastatic melanoma whom we treated with pembrolizumab as first line treatment for metastatic disease. This patient had a complete radiological response to pembrolizumab with no adverse events during 18 months of treatment. One month after discontinuation of treatment she presented with eosinophilic fasciitis, and went on to develop acute confusion presumed to be secondary to cerebral vasculitis.

Case presentation

A 51-year-old woman presented with a right calf mass. She had a background of hypertension, eczema and depression. She had smoked 1½ packs per day for 30 years. Initial biopsy was suggestive of a clear cell sarcoma and she received neoadjuvant radiotherapy (50 Gy in 25 fractions) to be followed by surgery. Pre-operative review of the initial biopsy revealed S100, microphthalmia-associated transcription factor (MITF) and vimentin positivity, human melanoma black antigen (HMB45) and melanoma antigen recognized by T-cells (MART-1) negativity by immunohistochemistry. Molecular analysis was negative for known diagnostic chromosomal translocations consistent with a sarcoma. The lesion was determined to be a primary melanoma and she proceeded with surgical excision and sentinel lymph node biopsy (SLN).

The mass was completely excised and final pathology showed a primary melanoma measuring 4.5x2.8x2.2 (involving the neurovascular bundle), with a mitotic rate of 2 per 10 high power fields, no lymphovascular invasion and a negative SLN (0/1). The tumor was BRAF negative. Pre-operative radiological staging had shown a number of non-specific lung nodules, one of which, in the left upper
lobe, showed growth during active radiological surveillance post-operatively. This lesion measured 1cm in and a wedge resection of the lung was performed in a second surgery. Pathology showed completely excised metastatic melanoma and the patient continued active surveillance.

A mass in the right lower lobe was noted 15 months after lung surgery along with other multiple lung nodules, and biopsy was consistent with metastatic melanoma. The patient was enrolled onto the Keynote-001 Phase I trial of pembrolizumab and assigned to the treatment naïve cohort on a 10mg/kg every 2 weeks schedule. Her treatment proceeded uneventfully with no drug-related toxicities. Her response was early, with an 84% reduction by immune related response criteria (irRC) on the first assessment scan at 2.8 months (after 6 infusions). A complete response (CR) was achieved after 13.8 months of treatment or 27 infusions. Treatment was later discontinued (after a total of 36 infusions) as a CR had been achieved and maintained (allowed on the Keynote 001 protocol)

A month after treatment was discontinued the patient complained of muscle aches and heaviness in the limbs that were generalized and fluctuated in severity to become painful at times. Episodes were self-limiting and lasted minutes. There was no functional deficit at that time and creatinine kinase concentrations and other elements of the blood screen—including electrolytes, hormone profile (thyroid function, ACTH, cortisol), full blood count, and liver screen—were normal. The symptoms progressed over the next 6 weeks so that she went on to report headaches accompanied by floaters in her visual fields. No deficits were found on neurological examination, although she moved with apparent difficulty. Blood tests (normal ranges given in brackets) showed an erythrocyte sedimentation rate (ESR) of 20 (0-20), creatinine kinase (CK) 28 (0-149), and eosinophil count of 1.8 (0.04-0.4 x10^9/L); magnetic resonance imaging (MRI) of the brain was normal. By 12 weeks after discontinuation of treatment, she had visible puffiness of the face and thickened and tethered waxy skin on all limbs and abdomen. No rash was evident and muscle power was normal. The muscles were not tender but she described them as painful and heavy or stiff. A further increase in eosinophil count to 5.24 at that time prompted a clinical diagnosis of eosinophilic fasciitis. An MRI of the right upper limb revealed marked fascial edema associated with the musculature of the arm and the right chest wall involving the latissimus dorsi, serratus anterior and pectoralis muscles (Fig. 1). A full thickness biopsy of skin and subcutaneous tissue performed 2 weeks later showed infiltration of the dermis with a lymphoedosinophilic infiltrate with scattered eosinophils in the interstitium. The fascia contained a denser infiltrate of eosinophils, plasma cells, and lymphocytes, findings consistent with a diagnosis of eosinophilic fasciitis (Fig. 1).
Just prior to the muscle biopsy, her husband reported that the patient was confused. Confusion progressed over 3 days and she experienced episodes of urinary and fecal incontinence prompting admission to her local hospital. Screening blood tests and CT scan of the brain were reported as normal. She was transferred to our institution for further management. At the time of transfer she was not oriented to time or place, had gait disturbance with distal weakness, and demonstrated marked confabulation. It was feared that she had a progressive autoimmune condition affecting her central nervous system. Methylprednisone was commenced at 2mg/kg i.v. dose (total of 170mg) on the day of transfer. Brain MRI showed hyperintense white matter foci in both subcortical (enhancing on FLAIR) and periventricular areas (non-enhancing). There were ovoid lesions perpendicular to the ventricles and lesions involving the corpus callosum (Fig. 1). All lesions showed restricted diffusion. The findings were consistent with either demyelination or an ischemic process.

The methylprednisone dose was increased to 1 g per day and further investigations performed. Lumbar puncture revealed no evidence of viral, fungal, or mycobacterial infection. Cytology showed no malignant cells, and cerebrospinal fluid (CSF) protein (0.27 g/l) and glucose (4.4 mmol) were normal. Oligoclonal bands were detected in the CSF, with an IgG concentration of 0.033 g/l (albumin 0.160 g/l and IgG/albumin ratio 0.208), but a similar pattern was seen in the serum, and a normal IgG index was detected. These results suggested a systemic immune response, rather than one originating in the central nervous system. A repeat brain MRI after 10 days of steroid treatment showed increased enhancement in the previously noted lesions and lesions involving the cortex, changes more suggestive of multiple infarctions and possibly a vascular process.

A steroid taper of 5 mg/week was initiated, starting with 60 mg prednisone and aspirin (81 mg; in view of the infarcts) was commenced. Subsequent transthoracic echocardiogram was normal and computed tomography (CT) angiography did not reveal large or medium vessel vasculitis or any evidence of intracranial hemorrhage. The eosinophil count was 1.7 on day of transfer to our institution and returned to normal 6 days later. Table 1 details results of serial blood investigations during investigative workup. The confusion and fasciitis resolved within 20 days of transfer to our institution; weakness, and deficits in proprioception and gait improved more slowly. At the time of this report the patient was improving in active rehabilitation prior to discharge home. Mild contractures of the elbows to 10 degrees, and the fingers of the right hand are present, her performance status is 1 (compared to a performance status of 0 at baseline).
Discussion and Conclusions

Eosinophilic fasciitis (EF) is a rare disorder of unknown etiology characterized by painful symmetrical swelling and thickening of the skin in the distal extremities and rarely the trunk and neck[7]. Progression causing induration of the skin and fibrosis of fascia gives rise to contractures and, in extreme cases, restriction of the chest wall musculature; visceral involvement is usually absent. Prior to presentation, patients may have myalgia, weight loss, inflammatory polyarthritis or a history of a change in medication or intense physical exercise preceding infection. There may be an underlying diagnosis of a hematological disorder, solid tumor, or autoimmune disease. Full skin to muscle biopsy is required for diagnosis, with characteristic findings being an inflammatory infiltrate of lymphocytes (CD8+ T cells predominate with macrophages) and or eosinophils in the fascia but complete or relative sparing of the epidermis and dermis. Blood tests may not be informative: ESR is often normal or only mildly elevated. High dose steroid treatment typically results in complete resolution in the majority of cases. Eosinophilic fasciitis is a distinct entity unrelated to eosinophilic vasculitis. However, there are reports of associated small vessel vasculitis with digital gangrene occurring in EF, suggesting some overlap with connective tissue disorders such as scleroderma[8, 9]. Cerebral vasculitic changes on angiography have been described in a patient with EF, causing a hemorrhagic stroke[10]. We were unable to assign a definite diagnosis to the patient’s neurologic disorder. Having ruled out a demyelinating process and embolism from the heart or large vessels, the clinical and radiologic findings were suggestive enough of cerebral vasculitis that we continued steroid treatment on which she had shown improvement. It is possible that the initial EF in our patient progressed to small vessel vasculitis of the brain.

Pembrolizumab has significant activity in metastatic melanoma. Responses often occur as early as the first assessment scan, with incremental decreases in tumor measurements thereafter. Late responses are rare[2, 3, 11, 12]. In this patient maximum response or CR was achieved after 13.8 months of treatment, and has been durable to date. However, there is no defined optimal duration of treatment with pembrolizumab. The Keynote-001 phase I trial used an indefinite schedule[2-4] whilst the first line Keynote-006 trial assesses a treatment schedule of two years[11].

Reported toxicity with pembrolizumab has been lower than with ipilimumab. The majority of adverse events have been grade 2 or less, and reversible. The incidence of grade 3-5 toxicity across different cohorts in Keynote-001[2-4, 13] and Keynote-006[11] was 13%. These ranged from pneumonitis (<1%), fatigue (<1%), colitis (<1-3%), diarrhea (<1-3%), hypophysitis (<1%), hypothyroidism (<1%), nausea (<1%)
and arthralgia (<1%). Rare toxicities in individual patients of type 1 diabetes[14] or myocarditis and cardiac failure[15] secondary to pembrolizumab have also been reported. 

Our case is, to our knowledge, the first reported case of eosinophilic fasciitis with an antibody to PD1. The timing of this side effect in our patient occurred after 18 months of treatment, during which no toxicity occurred. Eosinophilic fasciitis is an immune-related condition and in this context is an IrAE. Although we did not biopsy the patient’s brain lesions or subject her to invasive 4 vessel angiography, these were possibly immune mediated, as well. The rapid response to steroids is reassuring, although she has yet to make a full recovery.

The durability of pembrolizumab responses is unknown. Future trials must explore different schedules of treatment to determine the optimal duration of treatment. Continued monitoring of patients on anti-PD1 inhibitors will determine the risk of delayed toxicity, its severity, and reversibility.
References


Table 1: Blood and cerebrospinal fluid investigations of interest during management of late toxicity in our patient (normal ranges: eosinophil count 0.04-0.4 x10^9/l, ESR 0-20, CK ≤149, lactate dehydrogenase (LDH) 125-220, CSF protein 0.15-0.45, CSF glucose 2.2-4.4, CSF IgG 0.005-0.06, CSF albumin 0.134-0.237, IgG/albumin ratio ≤0.249)

<table>
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<th>Time in weeks from discontinuation of treatment</th>
<th>Investigation</th>
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<th>ESR (mm/h)</th>
<th>Creatinine Kinase</th>
<th>LDH</th>
<th>CSF protein/glucose (g/l)</th>
<th>CSF IgG/albumin/ratio (g/l)</th>
<th>CSF Cytology/infection screen</th>
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<td>0.27/4.4</td>
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Figure 1. (A) Full thickness muscle biopsy from the right upper arm demonstrating eosinophilic fasciitis. The dermis is infiltrated with a superficial and deep lymphoeosinophilic infiltrate. A denser infiltrate of eosinophils is seen in the fascia along with plasma cells and lymphocytes. These changes were mirrored in the subcutaneous tissue (eosinophils (Eos) are arrowed). (B) MRI of the right upper arm depicts marked fascial edema involving the deltoid, rotator cuff musculature, biceps and triceps. This edema tracks into the right chest wall musculature. (C) Axial MRI images of the brain during the acute presentation of confusion (arrows highlight changes described) i. T2/FLAIR sequence showing subcortical lesions involving the periventricular white matter and the splenium of the corpus callosum. Such changes are often seen in demyelination but may also be compatible with a vascular etiology. ii. Axial T1 post gadolinium sequence showing multiple small scattered lesions throughout bilateral cerebral hemispheres. The superficial lesions enhance while the deep lesions do not. This picture focuses on the superficial lesions only. iii. Axial diffusion sequence demonstrating several small lesions restricting diffusion in bilateral cerebral hemispheres, predominantly affecting the white matter, compatible with a vascular process. iv. Apparent diffusion coefficient (ADC) sequence showing decreased signal at the emplacement of the lesions, most commonly seen with lesions of vascular etiology.
Figure 1
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