CASE REPORT

Limbic encephalitis following immunotherapy against metastatic malignant melanoma

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SUMMARY

Novel immunotherapies are increasingly being used to treat malignant melanoma. The use of such agents has been associated with triggering autoimmunity. However, there has been a paucity in reports of limbic encephalitis associated with these immunotherapies. Pembrolizumab, a monoclonal antibody against programmed cell death antigen (PD-1), is currently being trialled in the UK to treat malignant melanoma. We report a unique case of antibody-negative limbic encephalitis presenting 1 year after starting pembrolizumab, in the context of malignant melanoma. The patient presented with progressive cognitive decline. MRI of the brain revealed signal change within the limbic structures. Cerebrospinal fluid studies confirmed evidence of inflammation with raised white cell count and protein. We were able to prevent further progression of symptoms by stopping pembrolizumab and treating the patient instead with steroids. We advocate considering autoimmune neuroinflammation as a differential for neurological disorders presenting in patients receiving PD-1 antagonist treatment and immunotherapy in general.

BACKGROUND

We present a case of limbic encephalitis associated with pembrolizumab use in melanoma; we are unaware of any previous reports. Pembrolizumab is currently Food and Drug Administration (FDA) approved for the treatment of unresectable malignant melanoma. The use of such immunotherapies pioneered in melanoma are likely to become more widely used across other tumour sites. Autoimmune reactions associated with such treatments are recognised and neuroinflammatory syndromes are likely to occur more frequently. They may mimic classic paraneoplastic syndromes such as limbic encephalitis, as described in our case. It is important that physicians gain an increased understanding of these newer therapies and their effects on the nervous system.

CASE PRESENTATION

A 64-year-old man with stage metastatic melanoma (stage 4 M1a) presented to the neurology department, with worsening confusion, in 2015. The primary tumour, on his calf, had been treated surgically with curative intent in 2005. The patient was noted to have lymphatic spread in 2010. He relapsed after 2 years of bevacizumab (a monoclonal antibody against vascular endothelial growth factor), with metastases on staging CT. He was started on vemurafenib (BRAF kinase inhibitor), as he was positive for the BRAF mutation in 2012.

After a year, he was switched to the third-line PD-1 antagonist, pembrolizumab, as part of a clinical trial (MERCK) in 2013.

In December 2014, after 12 months of therapy with pembrolizumab, his family had reported progressive decline in memory since treatment initiation and he was referred to a local memory clinic. His Mini Mental State Examination (MMSE) at that time was 24/30. CT imaging of the head excluded evidence of brain metastases. Treatment with pembrolizumab therapy was omitted for 1 month, and then restarted. By January 2015, the patient's cognition had significantly declined.

He was admitted under the care of the neurology department in February 2015, and his oncological treatment was stopped. Further history revealed that he was forgetting important hospital appointments and recent conversations. He had stopped driving due to getting lost. He had difficulties using his razor. He had become obsessive over certain tasks; though no other significant personality change had been noted. He could still identify objects. There was no hallucinosis. He had not been noted to have any seizures. The rest of his neurological enquiry was unremarkable. His family had not noted any change in his speech content or fluency. He did not drink alcohol to excess. Systems enquiry was unremarkable.

Neurological examination did not display any focal deficits. Cognitive testing revealed MMSE

Figure 1 Axial and coronal MR T2 images showing high signal affecting bilateral temporal structures, worse on the left. Progression of changes seen between November 2014 (A, B) and February 2015 (C, D) while on pembrolizumab.

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Table 1 Serial CSF studies in 2015

	February	March	April	May	July
White cell count	17	9	3	1	1
Glucose	3.0	3.1	2.3	2.8	2.8
Serum Glucose	6.5	5.0	4.7	6.9	5.6
Protein	0.53	0.36	0.52	0.57	0.37
Bacterial culture	Negative	Negative	Negative	Negative	Negative
Other tests	Viral PCRs negative (EBV, CMV, HS1+2, VZV, enterovirus, parechovirus, HHV6+7, JC/BK viruses) CSF: ACE 0.64 Oligoclonal bands in CSF and Serum negative Cytology: hypercellular CSF. Mainly T-lymphocytes	Cytology: mainly lymphocytes			Viral PCRs negative: (HSV1+2, parechovirus, VZV, enterovirus)

CMV, cytomegalovirus; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; HHV6, human herpesvirus 6; HSV1+2, Herpes simplex virus 1+2; VZV, Varicella-zoster virus.

22/30 and ACE III 64/100, and his deficits predominantly in memory, fluency and language.

INVESTIGATIONS

MRI of the brain revealed bilateral symmetrical T2 signal change with atrophy within the hippocampi extending into the anterior temporal lobe and insula. This was more extensive on the left, with significant volume loss ([figure 1](#)). Previous MRI performed at the referring hospital in November 2014, was reviewed and this showed bilateral high T2 signal affecting the limbic structures, again predominantly on the left, though without volume loss.

Cerebrospinal fluid (CSF) analysis showed evidence of inflammation with a raised protein of 0.53 and a lymphocytosis of 17. Extensive viral PCR was negative ([table 1](#)). Cytology revealed increased cellularity with mainly T-lymphocytes, there were no malignant cells seen. EEG did not show any epileptiform discharges.

The patient had a paraneoplastic panel sent, including other serological tests, to exclude differentials of cognitive decline ([table 2](#)). The following tests were in the normal range or negative: vitamin B₁₂, thyroid function tests, C reactive protein, HIV serology, syphilis serology, paraneoplastic antibodies, anti-voltage-gated potassium channel antibodies and anti-N-methyl-D-aspartate receptor antibodies.

TREATMENT

The patient was started on a course of intravenous methylprednisolone followed by oral prednisolone taper. There was no improvement in his cognition, though we prevented further decline. Given the extensive inflammatory changes seen on imaging, significant improvement was felt to be unlikely. Over a course of 5 months, the patient had serial lumbar punctures to monitor degree of central nervous system (CNS) inflammation. Repeat MRI in June 2015 displayed stable pathology but no further changes.

OUTCOME AND FOLLOW-UP

We postulate that the patient developed an antibody-negative limbic encephalitis triggered by pembrolizumab in the context of metastatic melanoma.

Unfortunately, no further treatment for his melanoma was available, he deteriorated physically and died in January 2016.

DISCUSSION

This case describes limbic encephalitis in a patient with melanoma on pembrolizumab and previous immunotherapy. The onset of symptoms was temporally associated with the use of pembrolizumab. Therefore, we postulate that this was a trigger for this encephalitis, given PD-1 antagonists have been previously described to induce other autoimmune phenomena.

Paraneoplastic disorders associated with melanoma

Paraneoplastic syndromes associated with melanoma are uncommon. Melanoma-associated retinopathy (MAR) and melanoma-associated chronic inflammatory demyelination polyneuropathy (CIDP) are well-described syndromes with the former associated with antibodies against cells of the retina.^{1–3} Other paraneoplastic syndromes are sparse in the literature; we identified a case of anti-Yo positive paraneoplastic cerebellar ataxia syndrome described by Valpione *et al*,⁴ reported with uveal melanoma. Limbic encephalitis is an autoimmune phenomenon that has been described in association with malignancy and in the absence of malignancy.⁵ Limbic encephalitis, however, has not been commonly associated with melanoma in the past. There has been a single report of possible limbic encephalitis with melanoma.⁶ Becquart *et al* described a rapid

Table 2 Serological tests in February 2015

Tests	Result
B ₁₂	Normal level
Folate	Normal level
HIV screen	Negative
Syphilis screen	Negative
Anti-CV2/CRMP5 antibody	Negative
Anti-amphiphysin antibody	Negative
Anti-Ma1/2	Negative
Anti-Hu antibody	Negative
Anti-NMDA antibody	Negative
Anti-VGKC antibody	Negative
Anti-To antibody	Negative
Anti-Ri antibody	Negative

CV2/CRMP-5; collapsin response mediator protein 5; NMDA, N-methyl-D-aspartate receptor; VGKC, voltage-gated potassium channel.

cognitive decline in a patient from a similar age group to our patient. The patient had prolonged survival, developing limbic encephalitis 4 years from point of diagnosis.⁶

Immunotherapy in melanoma causing neuroinflammation

The cytogenetic profile of the melanoma cells is important when deciding on therapy delivered. Our patient was found to be BRAF mutation positive and was started on anti-BRAF therapy with vemurafenib when he developed disease recurrence. The BRAF mutation upregulates tumour proliferation via the MAP kinase pathway.⁷ However, only 50% of melanomas are BRAF-positive.⁸ Furthermore, not all BRAF-positive melanomas are fully amenable to BRAF inhibitors, for example, in the presence of tumour resistance.⁷ Therefore, there has been a shift to target other pathways, with alternative immunotherapies, for individuals such as our patient. Similar drugs (and targets) in melanoma that are being trialled include ipilimumab (CTLA-4 monoclonal antibody) and pembrolizumab or nivolumab (PD-1 monoclonal antibodies).^{7,9}

Autoimmunity following immunotherapy in patients with melanoma has been reported in the literature. There have been reports of CIDP and a single report of paraneoplastic cerebellar syndrome in melanoma after treatment with interferon α .^{10–12} Newer immunotherapies have also been shown to induce autoimmune phenomena in melanoma. Audemard *et al*¹³ reported a case where the use of ipilimumab promoted MAR. There have been cases of autoimmune hypophysitis with the treatment. Interestingly, Chodakiewicz *et al*¹⁴ reported both symptomatic and radiological resolution after stopping ipilimumab treatment. Inflammatory polyradiculoneuropathies have been reported with the use of ipilimumab.^{15,16} Manousakis *et al*¹⁶ reported that immunomodulation and cessation of ipilimumab provided slow recovery.

There is a paucity of limbic encephalitis described in the context of concurrent immunotherapy in malignancy. A case of limbic encephalitis has been described with the use of tocilizumab, a monoclonal antibody against interleukin-6 (IL-6).¹⁷ Yamaguchi *et al*¹⁷ described cognitive decline, limb weakness and seizures after the use of tocilizumab in rheumatoid arthritis. CSF and serum was positive for antibodies against N-termini and C-termini of NMDA typeGluR2.

Pembrolizumab is currently FDA licensed for use in patients with melanoma not amenable to surgery and failed to response to ipilimumab or BRAF inhibitors.¹⁸ PD-1 is an immune-inhibitory receptor expressed on cells of the immune system including B-lymphocytes and T-lymphocytes.^{9,18} PD-1 binds to either of its two ligands, PDL-1 or PDL-2. Binding of the ligands induces apoptosis offering protection from the immune surveillance and autoimmunity.¹⁸ This upregulation of PDL-1/PDL-2 on cancer cells prevents tumour clearance; pembrolizumab therefore inhibits this evasion by cancer cells.⁹ Side effects commonly reported with pembrolizumab include fatigue, nausea and pruritus.¹⁹ Autoimmune phenomena have been reported with pembrolizumab including myocarditis, tenosynovitis, hypothyroidism and adrenal failure.^{18,20,21} A single case of CNS toxicity has been reported by Mandel *et al*.²² They describe an encephalopathy with seizures and raised CSF protein. This toxicity was thought to be immune mediated. Pittet *et al*²³ were able to demonstrate that PDL-2 is expressed on human brain endothelial cells (HBECs). The basal expression of PDL-1 was minimal. Increased migration of CD4 and CD8 T-lymphocytes was observed after blockade of PDL-1/PDL-2. Interestingly, PDL-2 expression was shown reduced on HBECs from multiple sclerosis (MS) lesions. Furthermore,

polymorphisms in the PD-1 gene have been associated with MS.²⁴ Therefore, it could be postulated that blocking PD-1 could have precipitated autoimmunity and transmigration of lymphocytes into the CNS in our patient.

Learning points

- ▶ Programmed cell death antigen blockade may induce neurological autoinflammation.
- ▶ Immunotherapies have a predilection to induce autoimmunity. It is important to consider if immunotherapy has been given in cases of limbic encephalitis and other forms of neuroinflammation. It may mimic paraneoplastic limbic encephalitis.
- ▶ Cessation of the immunotherapy, prompt investigation and immunosuppression may help prevent irreversible neurological deficit.

Contributors SS was responsible for writing the article, revision of drafts and contributed to conception. TL supervised writing and contributed to conception. AT was the attending neurologist involved in the patient's care.

Competing interests None declared.

Patient consent Obtained.

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