CASE REPORT

Rare side effect of adjuvant ipilimumab after surgical resection of melanoma: Guillain-Barré syndrome

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Accepted 28 November 2017

SUMMARY

Guillain-Barré syndrome is a life-threatening neurological disorder that presents with rapid ascending paralysis and areflexia. Guillain-Barré syndrome is traditionally associated with infections from a gastrointestinal or respiratory tract source. We report the case of a 71-year-old man with melanoma who was treated with ipilimumab as adjuvant immunotherapy and subsequently developed Guillain-Barré syndrome. The diagnosis was made clinically through physical exam findings. He was successfully treated with a combination of intravenous immunoglobulin therapy and corticosteroids.

BACKGROUND

According to the National Institutes of Health and National Cancer Institute, the estimated 2017 incidence of melanoma of the skin in the USA is 87 110.[1] Standard treatment of primary melanoma is with wide local excision, with possible sentinel lymph node biopsy (SLNB) depending on tumour depth, and complete lymph node dissection if SLNB is positive. Patients then receive either surveillance or adjuvant immunotherapy based on the results and degree of lymph node involvement.[2] Adjuvant treatment is encouraged when the tumour characteristics include increased thickness, mitotic rate or ulceration, or lymph node involvement, and extranodal extension.[2]

Standard adjuvant immunotherapy after melanoma excision for stage III disease is with ipilimumab, based off the results of the European Organisation for Research and Treatment of Cancer 18071 trial.[3–5] In this randomised controlled trial, overall survival was significantly prolonged in those who were treated with ipilimumab.[3–5]

Ipilimumab is a monoclonal antibody that binds to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). This produces a signal that inhibits CTLA-4 and therefore allows cytotoxic T lymphocytes to destroy any malignant cells. The most commonly reported side effects of ipilimumab treatment are fatigue, headache, pruritus, skin rash, weight loss, diarrhoea and nausea.[6] Current black box warnings for ipilimumab use include fatal immune-mediated adverse reactions, such as hepatitis, dermatitis, neuropathy, enterocolitis and endocrinopathy.[7] One of the rarest immune-related complications is Guillain-Barré syndrome, with only five reported cases.[8–12] Recent studies emphasised rare neurological toxicities among immune checkpoint inhibitors, with the most commonly reported types including headaches, radiculopathies and encephalitis.[13–15]

We present a case of a patient who underwent wide local excision for a left postauricular melanoma and received three doses of adjuvant ipilimumab, with subsequent development of Guillain-Barré syndrome.

CASE PRESENTATION

A 71-year-old man was first diagnosed with a left postauricular melanoma in August of 2013. At the time, the tumour was 5.5 mm thick and there was no sentinel lymph node involvement. The patient was placed on surveillance without adjuvant treatment after excision. In September 2016, the patient was diagnosed with a local recurrence of his melanoma—a left preauricular melanoma. The melanoma was excised with a left cervical lymph node dissection, and pathology demonstrated extranodal extension. Therefore, the patient was started on adjuvant ipilimumab on 2 March 2017.

In April 2017, 7 days after he received his third cycle of ipilimumab, he started experiencing difficulty with getting up from a seated position and walking. He had also fallen several times due to progressive lower extremity weakness. On physical exam in the clinic, he was found to have profound weakness and was directly admitted to hospital. He denied shortness of breath, chest pain, vision changes, dysphagia, change in sensation or alterations in mental status. He also denied a history of respiratory tract or gastrointestinal infection, immunisation, surgery or trauma.

INVESTIGATIONS

Based on the above clinical presentation, possible differentials were evaluated with lab results, including a complete metabolic panel, complete blood count, lactate dehydrogenase, thyroid-stimulating hormone, adrenocorticotropic level and cosyntropin stimulation test, cortisol level, creatine kinase, digoxin level, and urinalysis. We also ordered a protein electrophoresis, acetylcholine receptor antibody assay and voltage-gated calcium channel antibody. Lab results were within normal limits, besides a slightly elevated lactate dehydrogenase of 288 IU/L. Ganglioside (GM) antibodies were also ordered but had not been drawn by the patient in outpatient.

Neurology was consulted and CT cervical spine, thoracic spine and lumbar spine with contrast were

To cite: Patel RJ, Liu MA, Amaraneni A, *et al*. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2017-221318

ordered to rule out metastatic disease. The CT cervical spine revealed advanced vertebral degenerative changes, but no signs of malignancy. CT thoracic spine and lumbar spine indicated degenerative changes and a neurostimulator device at L3 for pain relief for osteoarthritis, with no signs of malignancy. Due to the mechanical device, we did not perform an MRI of the spine. A non-contrast MRI of the brain was obtained and showed no evidence of hypophysitis.

On hospital day 3, the patient was found to have progressive and ascending muscle weakness. His strength was 2/5 in the proximal muscles and 3/5 in the distal muscles of both the lower and upper extremities. Deep tendon reflexes were absent in the brachioradialis, triceps, patellar and Achilles, and the biceps reflex was diminished at 1+ bilaterally. As a precaution, vital capacity and negative inspiratory force were monitored every 4 hours to ensure the patient was able to maintain his airway.

Due to increasing weakness and high clinical suspicion on Guillain-Barré syndrome, a lumbar puncture under fluoroscopy was performed. The lumbar puncture cerebrospinal fluid (CSF) results did not show any evidence of cytoalbuminological dissociation based on a total protein of 39, the upper limit of normal. However, autoimmune side effects often do not have the same lab presentation as classical autoimmune diseases. Further testing with an electromyography found the lower extremity peroneal and tibial motor response to be of low amplitude and prolonged latency. Additionally, there was evidence of an acute sensorimotor polyradiculopathy with mixed axonal/demyelinating features. There was no indication of a presynaptic or postsynaptic neuromuscular junction disorder; thus, our clinical suspicion for Guillain-Barré syndrome was high enough that we decided to initiate treatment.

TREATMENT

Treatment was started on hospital day 4. The patient was treated with intravenous immunoglobulin, dosed at 0.4 g/kg of ideal body weight (75 kg) for a total of 30 g each day for five consecutive days. Our patient received 5 days of intravenous immunoglobulin treatment and was found to have marked improvement on treatment day 5, hospital day 8.

OUTCOME AND FOLLOW-UP

On neurological exam, the patient had regained most of his strength and was 4/5 on all lower and upper extremity tests, besides bilateral deltoid, hip flexion and dorsiflexion (2/5). On discharge, we started the patient on a 1-month course of steroids to help him progress to baseline function. The patient was discharged to an inpatient rehabilitation facility to continue working on his strength. Since discharge from the hospital, the patient has been slowly improving muscle strength and regaining function.

DISCUSSION

The significance of this case is the development of atypical Guillain-Barré syndrome after the administration of ipilimumab, which was successfully managed with immediate intravenous immunoglobulin and subsequent steroids several weeks later. Ipilimumab is a checkpoint inhibitor that modulates a patient's immune system. A meta-analysis of 22 clinical trials found that 72% of individuals on anti-CTLA-4 antibodies experienced some type of immune-related adverse event.[16]

The treatment of autoimmune side effects of ipilimumab is primarily with corticosteroids. Standard treatment for Guillan-Barré is with intravenous immunoglobulin or plasma exchange.[17 18] Few cases demonstrating the management of Guillain-Barré related to ipilimumab have been reported. While one case showed success in treating Guillan-Barré with immediate high-dose steroids,[8] it was not successful in another case of ipilimumab-induced Guillan-Barré revealed by an occlusive enteric neuropathy.[10] Gaudy-Marqueste *et al* suggested that the high-dose steroids usually used for ipilimumab colitis may be less effective in preventing neuronal degeneration in Guillan-Barré, as shown in a 2006 Cochrane review which found corticosteroids ineffective for classical Guillan-Barré. Other studies have used immediate intravenous immunoglobulin (IVIG), with one case demonstrating success[12] and another case[9] where the patient died in 3 days from respiratory insufficiency; however, this patient declined artificial respiration. Based on these outcomes from the literature and after consultation with the neurological service, we decided to evaluate the patient's response to IVIG and stop ipilimumab before administering steroids. As his base functional status was not completely normal at his discharge several weeks later, we started the patient on a 1-month steroid course with gradual taper.

While rare, it is critically important to recognise and treat the neurological side effects of anti-PD-1 therapy such as ipilimumab as they can lead to life-threatening consequences.[19] Besides polyneuropathy, additional neurological side effects demonstrated in other studies on immune checkpoint inhibitors include ataxia, paraesthesia, dysarthria, tremor, paresis/paralysis, aseptic meningitis and transverse myelitis.[9 20–22] Prompt steroid administration has been shown to be effective for the resolution of many of the above side effects in these studies. As the acute onset of lower extremity weakness and clinical deficits typically peak at 2–4 weeks, early treatment with intravenous immunoglobulin is of paramount importance.[23 24]

In conclusion, our patient experienced a rare and adverse event after the use of adjuvant ipilimumab for melanoma. After his third cycle of treatment, he rapidly developed ascending weakness, paralysis and areflexia, which improved after intravenous immunoglobulin therapy. He continued to progress towards baseline during his hospital stay, but did not recover completely in strength. He was subsequently discharged to an inpatient rehabilitation centre for further treatment. This case is meant to create awareness about a rare adverse event of ipilimumab treatment and the effectiveness of immediate intervention. It is important to be aware of Guillain-Barré syndrome as a potential side effect of ipilimumab therapy due to its rapid onset and high risk of respiratory compromise.

Learning points

- Ipilimumab treatment as adjuvant therapy for melanoma can cause rare neurological side effects such as Guillain-Barré syndrome, which may lead to life-threatening consequences.
- Early detection of Guillain-Barré syndrome is essential in order to prevent the life-threatening complication of respiratory failure.
- Guillain-Barré syndrome must be identified based on clinical suspicion because cerebrospinal fluid confirmation may be falsely negative.
- Guillain-Barré syndrome resulting from ipilimumab therapy should be treated promptly with intravenous immunoglobulin±corticosteroids.

Contributors RJP: analysis of current literature as it relates to case, drafting manuscript, critical revision of manuscript, final approval of version to be published.

MAL: critical revision of manuscript, final approval of version to be published. AA: designed treatment plan and clinical recommendations, critical revision of manuscript, final approval of version to be published. SKS: designed treatment plan and clinical recommendations, analysis of current literature as it relates to case, drafting manuscript, critical revision of manuscript, final approval of version to be published.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Howlader N, Noone AM, Krapcho M *et al*eds, . *SEER CancerStatistics Review, National Cancer Institute,1975-2014*. Bethesda, MD: National Cancer Institute. based on November 2016 SEER data submission, posted to the SEER web site, April 2017. https://seer.cancer.gov/csr/1975_2014/
2 Kauffmann RM, Chen SL. Workup and staging of malignant melanoma. *Surg Clin North Am* 2014;94:963–72.
3 Eggermont AM, Chiarion-Sileni V, Grob JJ, *et al*. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2015;16:522–30.
4 Eggermont AM, Chiarion-Sileni V, Grob JJ, *et al*. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. *N Engl J Med* 2016;375:1845–55.
5 Coens C, Suciu S, Chiarion-Sileni V, *et al*. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2017;18:393–403.
6 Hodi FS, O'Day SJ, McDermott DF, *et al*. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711–23.
7 Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 2012;30:2691–7.
8 Wilgenhof S, Neyns B. Anti-CTLA-4 antibody-induced guillain-barré syndrome in a melanoma patient. *Ann Oncol* 2011;22:991–3.
9 Bot I, Blank CU, Boogerd W, *et al*. Neurological immune-related adverse events of ipilimumab. *Pract Neurol* 2013;13:278–80.
10 Gaudy-Marqueste C, Monestier S, Franques J, *et al*. A severe case of ipilimumab-induced guillain-barré syndrome revealed by an occlusive enteric neuropathy: a differential diagnosis for ipilimumab-induced colitis. *J Immunother* 2013;36:77–8.
11 Mukherjee V, Postelnicu R, Esaian D, *et al*. An unusual cause of acute respiratory failure. *Am J Respir Crit Care Med* 2014;189:A6185.
12 Kelly Wu W, Broman KK, Brownie ER, *et al*. Ipilimumab-induced Guillain-Barré syndrome presenting as dysautonomia: an unusual presentation of a rare complication of immunotherapy. *J Immunother* 2017;40:196–9.
13 Touat M, Talmasov D, Ricard D, *et al*. Neurological toxicities associated with immune-checkpoint inhibitors. *Curr Opin Neurol* 2017;30:659–68.
14 Larkin J, Chmielowski B, Lao CD, *et al*. Neurologic serious adverse events associated with nivolumab plus ipilimumab or nivolumab alone in advanced melanoma, including a case series of encephalitis. *Oncologist* 2017;22:709–18.
15 Hottinger AF. Neurologic complications of immune checkpoint inhibitors. *Curr Opin Neurol* 2016;29:806–12.
16 Bertrand A, Kostine M, Barnetche T, *et al*. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. *BMC Med* 2015;13:211.
17 Wijdicks EF, Klein CJ, Syndrome G-B*Mayo Clin Proc* 2017;92:467–79.
18 Hughes RA. Swan AV, and van Doorn PA. Intravenous immunoglobulin for Guillain-Barre syndrome. *Cochrane Database Syst Rev* 2014;19:CD002063.
19 Zimmer L, Goldinger SM, Hofmann L, *et al*. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer* 2016;60:210–25.
20 Liao B, Shroff S, Kamiya-Matsuoka C, *et al*. Atypical neurological complications of ipilimumab therapy in patients with metastatic melanoma. *Neuro Oncol* 2014;16:589–93.
21 Mandel JJ, Olar A, Aldape KD, *et al*. Lambrolizumab induced central nervous system (CNS) toxicity. *J Neurol Sci* 2014;344:229–31.
22 Voskens CJ, Goldinger SM, Loquai C, *et al*. The price of tumor control: an analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the ipilimumab network. *PLoS One* 2013;8:e53745.
23 Fokke C, van den Berg B, Drenthen J, *et al*. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. *Brain* 2014;137:33–43.
24 Hughes RA. Swan AV, and van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Databse Syst Rev* 2014;9:CD002063.