Diarrhea and generalized weakness in a patient with metastatic melanoma and a lumbosacral mass, after initiation of therapy with a checkpoint inhibitor: A case report

Marija Cauchi, Nikitas Nikitas

ABSTRACT

Introduction: Checkpoint inhibitors are immunomodulatory antibodies against cytotoxic T-lymphocyte-associated antigen [Ipilimumab] and Programmed cell death-1 receptor [nivolumab, pembrolizumab] that have improved the prognosis of patients with melanoma and non-squamous cell lung carcinoma. Despite their clinical benefit, these agents are associated with the development of immune-related adverse events (irAEs) of varying morbidity. These irAEs are clinically challenging to be diagnosed and to be treated, as described in this case report.

Case Report: A 58-year old male presented with radicular pain, weakness and loss of sensation in his right leg, eleven years after treatment for cutaneous melanoma. A large lumbosacral mass found on spinal MRI and patient underwent local palliative radiotherapy and he was initiated on systemic monotherapy with ipilimumab. Two doses of 3 mg/kg ipilimumab were administered intravenously within a 21-day interval. After ipilimumab administration, patient developed subsequently diarrhea and generalized weakness and treatment with corticosteroids initiated. Despite treatment, patient developed type 2 respiratory failure, intubated and admitted in general intensive care unit. Diagnostic workup suggested the presence of both ipilimumab associated severe colitis and Guillain-Barre syndrome (GBS). Ipilimumab was permanently discontinued and patient underwent treatment with infliximab and intravenous immunoglobulin for colitis and Guillain-Barre syndrome respectively. Prolonged recovery followed.

Conclusion: To our knowledge, this is the first case report of concomitant development of both ipilimumab-induced severe colitis and life-threatening GBS, in the same patient. The choice of the optimal agent for treatment of these adverse events seems to be system and severity-specific.

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CASE REPORT

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palliative radiotherapy and he was initiated on systemic monotherapy with ipilimumab. Two doses of 3 mg/kg ipilimumab were administered intravenously within a 21-day interval. After ipilimumab administration, patient developed subsequently diarrhea and generalized weakness and treatment with corticosteroids initiated. Despite treatment, patient developed type 2 respiratory failure, intubated and admitted in general intensive care unit. Diagnostic workup suggested the presence of both ipilimumab associated severe colitis and Guillain-Barre syndrome (GBS). Ipilimumab was permanently discontinued and patient underwent treatment with infliximab and intravenous immunoglobulin for colitis and Guillain-Barre syndrome respectively. Prolonged recovery followed. **Conclusion:** To our knowledge, this is the first case report of concomitant development of both ipilimumab-induced severe colitis and life-threatening GBS, in the same patient. The choice of the optimal agent for treatment of these adverse events seems to be system and severity-specific.

Keywords: Colitis, Guillain-Barre syndrome, Ipilimumab, Melanoma

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INTRODUCTION

Immunotherapy is the primary systemic treatment for metastatic melanoma. Checkpoint inhibition with ipilimumab, is the preferred treatment option for most patients. Treatment with ipilimumab—an IgG1 monoclonal antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)—has correlated with significantly improved progression-free survival and overall survival. However, treatment with ipilimumab is associated with a variety of clinically significant autoimmune side effects, which sometimes may be clinically challenging to be diagnosed and to be treated [1, 2].

CASE REPORT

A 58-year old male presented with radicular pain, weakness and loss of sensation in his right leg, 11 years after treatment for cutaneous melanoma. Spinal MRI scan revealed of a large lumbosacral mass (L5-S1 level), compressing the cauda equina, suggested the diagnosis of recurrent metastatic melanoma and 5 cycles of vemurafenib chemotherapy followed after histological confirmation. Despite chemotherapy, the mass increased in size and lower back pain worsened. At this stage, the patient underwent local palliative radiotherapy to improve his lower back pain and two months later he was initiated on monotherapy with ipilimumab (Yervoy®, Bristol-Myers Squibb Co., IMAGE study, NCT0511913). Two doses of 3 mg/kg ipilimumab were administered intravenously within a 21-day interval.

Two days after the second dose of ipilimumab, bloody diarrhea and fever developed. After exclusion of infectious causes of hemorrhagic colitis, the diagnosis of ipilimumab-induced colitis was considered as the most probable and treatment with 1 mg/kg intravenous prednisolone daily was commenced. After remission of symptoms within two days, the patient was discharged home on steroids.

However, thirteen days after the second ipilimumab dose, the patient was re-admitted with acute-onset weakness and paraesthesia in the left lower limb and a tingling sensation in his upper limbs. A new course of palliative radiotherapy was applied at the sacral mass but over the next 2 days he developed further neurologic deterioration with paraesthesia and weakness in all four limbs. Three days later, the patient's voice became hoarse and he failed a swallow test. He was found to have a power of 2 on the MRC grading score in all four limbs, with relative proximal sparing and absence of deep tendon reflexes. Ultimately, 19 days after the last ipilimumab administration, type 2 respiratory failure developed secondary to established airway compromise and deteriorating generalized muscle weakness. The patient was intubated and transferred to general intensive care unit (ICU) for mechanical ventilation. Autonomic

dysfunction was also present initially. An urgent diagnostic workup for the cause of neurologic deterioration and acute respiratory failure was undertaken.

Computed tomography scan of the head was unremarkable. MRI scan showed no ascending infiltration of the spinal cord from the lumbosacral mass. A lumbar puncture, though necessary, could not be performed due to the large mass in the lumbar spine. Nerve conduction studies demonstrated severe sensory and motor polyneuropathy, with no recordable motor potentials. Furthermore, needle electromyography showed an acute inflammatory neuropathy with conduction block, consistent with an acute inflammatory demyelinating polyneuropathy (AIDP). There was no axonal loss. Stool cultures were negative and campylobacter was not detected. An electro-encephalogram was normal. A paraneoplastic screen was negative. Based on clinical presentation and the results of neuro-physiological studies the diagnosis of Guillain-Barre syndrome (GBS) was established. After exclusion of all other possible causes, this GBS case was considered as directly related to the previous ipilimumab administration. Ipilimumab was permanently discontinued.

Given that GBS developed whilst the patient was on a high dose of prednisolone (1 mg/kg daily), a 5-day course of intravenous immunoglobulin (IVIg) was commenced at the recommended dose of 400 mg daily. Steroids were gradually tapered down. After completion of IVIg treatment, the patient's neurologic symptoms and muscular strength gradually improved over the course of the next 4 weeks. Due to prolonged weaning from mechanical ventilation and one failed extubation attempt, the patient underwent a tracheostomy.

During his ICU stay the patient experienced a recurrence of ipilimumab-induced colitis, confirmed on serial endoscopic studies and biopsies. Prednisolone tapering was held and high-dose treatment re-started but colitis proved resistant to steroid treatment. Infliximab treatment was therefore initiated, with satisfactory response and recovery starting within the next 72 hours.

After 26 days of treatment, the patient was decannulated and he was discharged from the ICU. Motor strength gradually improved. A minor swallowing defect remained present without, however, compromising his airway.

DISCUSSION

Ipilimumab is a new therapeutic human recombinant IgG1 antibody, currently used as second-line therapy in metastatic melanoma. It has been shown to result in sustained remission [1] of disease, with significantly improved overall survival rates demonstrated in two large phase III trials [2, 3]. Apart from its therapeutic effectiveness, ipilimumab has also been demonstrated to result in severe immune-related adverse events (irAEs), such as enterocolitis, hepatitis, dermatitis, neuropathy and endocrinopathy [4–6].

To our knowledge, this is the first case report of concomitant development of both ipilimumab-induced severe colitis and life-threatening GBS in the same patient, after treatment for metastatic melanoma. Both required intensive immunomodulatory treatment and permanent discontinuation of the drug. In phase III clinical trials, severe colitis was found to occur in 5% and life-threatening GBS in less than 1% of treated cases [4, 7, 8].

A previous case report of ipilimumab-induced GBS has some notable similarities and differences in comparison with our case [9]. Similarly to this case, the irAEs occurred after more than one dose of ipilimumab and progressed rapidly. However, our patient developed GBS four weeks after treatment initiation whilst the previously reported case occurred after 7 weeks. The two cases demonstrate a variable time onset of development and variable severity of the same irAE. In contrast to the previous case report, the case we present developed more severe GBS, with cranial nerve involvement and abolishment of swallowing and cough reflex for a prolonged period of time which led to patient's intubation, mechanical ventilation and prolonged ICU stay.

Our patient also developed severe colitis early after ipilimumab administration (day 2) and had already been on treatment with 1 mg/kg of prednisolone for 11 days prior to GBS onset. In view of that fact, GBS was treated with a 5-day course of IVIg instead of high-dose corticosteroids, with adequate and sustained response. Also, our patient finally required the addition of infliximab (as used in previous reports, i.e. 5 mg/kg once every two weeks [10]) due to the recurrence of colitis three weeks after his initial response. Despite the previously reported responsiveness of GBS [9] and colitis [11] to high dose corticosteroid treatment, in our case, GBS developed and colitis recurred whilst the patient was on high doses of prednisolone, and required treatment with IVIg and infliximab respectively for remission. That treatment response could be related to the severity of presentation and may indicate a refractoriness of ipilimumab-induced irAEs to corticosteroid treatment. Furthermore, our case would suggest that corticosteroid treatment is not protective against the development of ipilimumab-induced GBS and the established recommended therapies (IVIg and plasma-exchange) should be the first-line or mainstay of treatment of this life-threatening irAE.

Our case could be considered as clinically challenging for two reasons: first, the pre-existence of a large lumbosacral mass and right lower limb weakness was confusing and misled the diagnosis initially, until the involvement of upper limbs and cranial nerves became clinically evident. Second, in our case, lumbar puncture was deferred due to the existence of the metastatic mass in the lumbar spine. Thus, the typical cerebrospinal fluid (CSF) albuminocytologic dissociation seen in GBS could not be demonstrated, and the exclusion of malignant CSF infiltration was not possible. However, the main diagnostic clinical features of GBS were met.

CONCLUSION

This case report showed that despite its therapeutic potential, ipilimumab may be associated with the development of more than one severe and life-threatening immune-related adverse events in the same patient. Therefore, physicians should have a low threshold for the suspicion and diagnosis of potentially severe or life-threatening ipilimumab-related adverse events. Early commencement of potent immunomodulatory therapies, along with the permanent discontinuation of ipilimumab, are necessary to halt their progression and treat them effectively. The choice of the optimal first-line and second-line immunomodulatory agent seems to be system and severity-specific, but further case-studies and clinical trials are warranted to clarify this clinically challenging decision.

Author Contributions

Marija Cauchi – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Nikitas Nikitas – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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