Immunome Research
ISSN: 1745-7580

Boyd et al., Immunome Res 2015, 11:2
DOI: 10.4172/1745-7580.1000092

Case Report Open Access

# Ipilimumab Induced Encephalitis: A Case Report

**Karen Boyd**[1*#], **Dheeraj Kalladka**[2#], **James Overell**[2], **Ashita Waterston**[1]

[1]*Department of Medical Oncology, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom*

[2]*Department of Neurology, Institute of Neurological Sciences, South Glasgow University Hospital, Glasgow, United Kingdom*

[#]*Both authors contributed equally.*

[*]**Corresponding author:** Karen Boyd, Department of Medical Oncology, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom, Email: boyka01@googlemail.com

**Received date:** March 30, 2015; **Accepted date:** June 18, 2015; **Published date:** June 23, 2015



## Abstract

**Background:** Cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) is a helper T cell protein receptor that down regulates the immune system when bound to antigen presenting cells. Ipilimumab selectively binds to CTLA-4 inhibiting the immune tolerance to tumour cells and has recently been approved for the treatment of metastatic melanoma. Autoimmune sequelae are side-effects of such immunomodulatory therapies. We describe the first case of ipilimumab induced delayed onset encephalitis.

**Case:** A 71 year-old man with BRAF wild-type metastatic melanoma received ipilimumab as first-line therapy. He presented with generalised weakness and headache following cycle 2 of ipilimumab. Blood analyses confirmed pan-hypopituitarism and MRI showed lymphocytic infiltration of pituitary gland, confirming autoimmune hypophysitis. Hormone replacement and a course of dexamethasone resolved the initial symptoms. Two months later he developed myoclonic jerks, drowsiness and mood elevation. CSF protein was raised with normal white and no malignant cells. Ipilimumab was stopped and high dose methylprednisolone was intiated resulting in improvement within 24hours. Post methylprednisolone electroencephalogram showed normal background activity with no seizures.

**Discussion:** Gastrointestinal (colitis, nausea), skin (pruritis, rash) and fatigue are the most common (30-40%) ipilimumab induced side effects. Endocrinopathies are reported in 1-2% of patients. CTLA-4 is expressed by pituitary gland thereby being susceptible for lymphocytic hypophysitis following ipilimumab. Neurological side effects are even rarer yet (<1%). Autoimmune encephalitis can be a delayed response and in our case was around 2 months after second dose of ipilimumab therapy. No cases of delayed onset ipilimumab induced encephalitis have been described as yet, but with increasing use of immune therapies which up-regulate T cells, rarer immune sequelae are likely to be on the rise.

**Conclusion**: Ipilimumab caused delayed onset autoimmune encephalitis and hypophysitis that was steroid responsive. Multi-specialty approach with early intervention of a neurologist and endocrinologist is a must for improved identification, treatment and outcomes.

**Keywords:** Metastatic melanoma; Ipilimumab; Encephalitis; CTLA-4; Hypophysitis; Auto-immune

## Introduction

Immunomodulatory therapy in the oncological setting has gained interest in recent years and its efficacy is established with improved overall survival in metastatic melanoma [1]. This therapeutic approach is being assessed in a wide variety of tumour types [2]. Ipilimumab is a monoclonal antibody that selectively inhibits CTLA-4 receptor found on helper T-cells and down-regulates the immune tolerance to tumour cells, aiding the cytotoxic T lymphocytes to recognise and destroy tumour cells. Ipilimumab is now licensed in the first-line setting in the treatment of metastatic melanoma (BRAF mutated or wild-type). By up-regulating T-cell action, it has been recognised that ipilimumab can cause a wide sequelae of unwanted autoimmune side effects in addition to the desired anti-tumour effect. More commonly recognised autoimmune side effects of treatment include colitis and dermatitis. This case describes a gentleman who developed delayed onset autoimmune encephalitis in addition to autoimmune hypophysitis secondary to ipilimumab.

## Case

A 71 year old retired engineer with a past medical history of paroxysmal atrial fibrillation, hypertension, diverticular disease, and an episode of electrical shock induced cardiac arrest that was successfully direct current cardioverted, presented with increasing breathlessness on exertion. Pulmonary function was normal. Computed tomography (CT) scan of Chest/Abdomen/Pelvis demonstrated three intrapulmonary masses (two in the right middle lobe and one in the left lower lobe, largest 13 mm) and a CT-guided biopsy confirmed metastatic melanoma. BrafV600 testing was wild-type. The primary lesion was not identified with none disease burden elsewhere. He was commenced on Ipilimumab 3 mg/kg with a plan for four cycles every three weeks. Following his second cycle, he presented with extreme fatigue, headaches and altered sensation in his occipital and neck region. Blood investigations revealed a suppressed hormonal

profile including morning cortisol<30 nmol/L (240-600), thyroid stimulating hormone 0.17 mU/L (0.35-5.0), free T4 8.5 pmol/L (9-21), testosterone 1.0 nmol/L (10-36), free testosterone 21 pmol/L (>200) and LH 0.6 U/L (1.0-12.0). Prolactin (64 mU/L), FSH (2 U/L) and IGF-1 (142 µg/L) were normal. Magnetic Resonance Imaging of Head and Spine with contrast identified no metastases or leptomeningeal disease process. Bilateral sub cortical infarcts remained unchanged over 4 years from a previous scan. Widespread degenerative changes in cervical and lumbar region with non compressive L3/L4, L4/L5 central disc bulge were identified.

Based on local guidelines, Dexamethasone 16 mg/day for ipilimumab induced grade 3 endocrinopathy was initiated that resulted in quick resolution of headache, paraesthesias and fatigue. As per endocrine specialist advice, thyroxine 75 µg/day and transdermal testosterone were initiated. MRI pituitary demonstrated a normal sized pituitary with an abnormal pattern of heterogeneous enhancement and slightly thickened stalk with moderate enhancement consistent with lymphocytic hypophysitis (Figure 1). He made a good recovery and was discharged home on a 4 week reducing course of dexamethasone with a view to commence hydrocortisone at 30 mg and 20 mg when the dexamethasone had stopped.

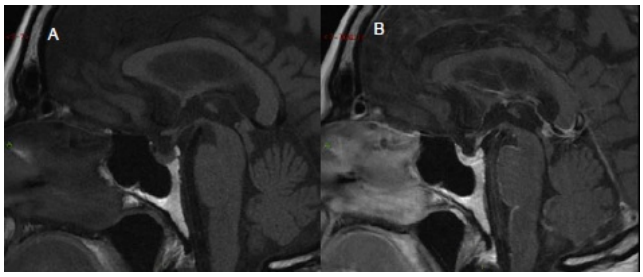


**Figure 1:** A) Pre-contrast T1w image showing normal sized pituitary. B) Post-contrast images showing heterogeneous enhancement with slightly thickened and moderately enhanced pituitary stalk.

After an initial recovery, at a 2 week post-discharge out-patient review he reported increasing fatigue and generalised headaches with no features to suggest raised intracranial pressure. Given the circumstances and uncertain nature of the body's usual cortisol response after anti-CTLA4 treatment, his hydrocortisone was doubled to mimic a stress response and this resulted in a transient resolution of symptoms. Two weeks later he presented again with recurrent increasing headaches, confusion, myoclonic jerks and a one off raised temperature (38 deg Celsius). General physical and neurological examinations were unremarkable. Blood analyses were unremarkable, including normal calcium and C-reactive protein. Cortisol remained <30 nmol/L when measured pre morning replacement dose, and TSH undetectable with a normal T4 due to replacement. Empirical antibiotic Augmentin (amoxicillin and clavulunate) were initiated despite no infective foci identified. Dexamethasone was commenced in case autoimmune pituitary swelling was causing his headaches. His behaviour became increasingly erratic after only 2 doses dexamethasone; his sleep was disturbed and he expressed grandiose delusions. While awaiting EEG, dexamethasone was switched to hydrocortisone, empirical thiamine; ibuprofen and oral morphine were prescribed. MRI head and C-spine were unchanged from previous. CT Chest & Abdomen showed stable disease with no new metastases. He subsequently became increasingly drowsy despite stopping morphine. Cerebro-spinal fluid (CSF) showed a raised protein 1.37 g/L (<0.5) with normal cells and no organisms identified. Cytology showed no malignant melanoma cells. CSF viral and bacterial polymerase chain reactions were negative. Autoimmune encephalitis was diagnosed and he was commenced on 3 days of intravenous Methylprednisolone 1 gm/day. The fluctuating drowsiness was presumed non-convulsive seizures. Intravenous methylprednisolone resulted in quick resolution of symptoms within 24 hours and suggested that the erratic behaviour on dexamethasone was secondary to encephalitis as opposed to steroids. EEG was performed but this was post resolution of symptoms and was normal. Anti-voltage-gated-potassium-channel, anti-NMDA receptor, anti-neuronal and anti-thyroid peroxidase antibodies were negative. Pituitary antibodies were not tested.

He went home on a 4 week reducing course of oral methylprednisolone with a view to restart hydrocortisone. At a 3 month out-patient follow-up review his symptoms have not recurred and was back to independent living. He will not recommence Ipilimumab given the severity of his symptoms.

## Discussion

Melanoma is an immunogenic cancer that can mount an immune response in the host. Metastatic melanoma therapy is based on immunotherapy and ipilimumab, a human monoclonal antibody is designed to selectively block CTLA-4 receptor found on helper T-cells thereby down-regulating the immune tolerance to tumour cells and aiding the cytotoxic T lymphocytes to recognise and destroy tumour cells. This approach can cause immune related adverse events (irAEs). In a phase II trial of ipilimumab alone in 61 patients with metastatic renal cancer, a highly significant association between irAEs and tumour regression was observed [3].

In both phase II4 and phase III3 trials of ipilimumab around 80% of patients reported irAEs of which 12-25% had severe events. Interestingly when combined with gp100 vaccine only 8% irAEs were noted as reported in a recent phase III trial [4,5]. The most common gastrointestinal side effect was diarrhoea followed by skin rash and pruritis. Endocrinopathies, such as our patient's autoimmune hypophysitis, are less common and according to the MDX010-20 trial, occurred in 1.5% of patients [5]. Secondary hypophysitis have been induced in mice models to study the mechanisms by injecting anti-CTLA4 drugs. In a subset of prolactin- and thyrotropin-secreting cells within the pituitary gland, CTLA-4 is expressed at both RNA and protein levels. These sites have been involved in complement activation with deposition identified on pathological specimens from sacrificed mice [6].

Neurological toxicity is even rarer and estimated at <1% with a varied spectrum including central (posterior reversible encephalopathy syndrome [7] (PRES), splenial lesion [8], myelopathy [9] and peripheral (Guillain-Barre syndrome [10], inflammatory myopathy [11], myasthenia gravis type syndrome [12], sensorimotor neuropathy [13] nervous system involvement. Melanocytes and Schwann cells are derived from neural crest cells with similar antigenic properties and hence some degree of molecular mimicry could exist to explain these side effects. With increasing therapeutic use of newer selective monoclonal antibodies, it is likely we will see the emergence of further immune-related complications that we are as yet unaware of.

The onset of these side effects has mostly been early during induction or a few cycles of therapy with median times of 5-6 weeks [14]. This is in contrast to our patient who had an early hypophysitis but then went on to develop encephalitis almost 8 weeks after stopping ipilimumab, that were both steroid responsive. The irAEs have been thought to be dose related from early dose-escalation studies which needs further confirmation from other studies [4]. Severe neurological irAEs are managed with stopping the inciting agent ipilimumab and initiating high dose intravenous methylprednisolone followed by 1-2 mg/kg tapering over a 4 week period. Our patient showed a rapid response to high dose methylprednisolone and has remained stable during 3 month follow-up. Bristol-Myers-Squibb, the manufacturers of ipilimumab have developed a risk evaluation and mitigation strategic plan to address irAEs based on organ systems [15].

Unlike traditional chemotherapy regimens where side effects can be predicted to peak and resolve at specific time frames according to the drug's pharmacokinetics and pharmacodynamics, it appears that up-regulation of the body's own T-cells through therapy such as ipilimumab results in much more unpredictable timing and class of side effects. The average elimination half-life of Ipilimumab is 14.7 days with steady state achieved by the 3rd dose [16], but the up-regulatory T-cell effects caused by inhibiting the negative checkpoint seems to last much longer. In a recent pooled analysis of 1861 patients on ipilimumab,17 improved survival of 26% at 3 years follow-up, suggests, with ever improving survival rates there may yet be a possibility in some it can 'reboot' the immune system and expand the possibility of irAEs.

## Conclusion

The side effect spectrum of Ipilimumab is expanding. To our knowledge, this is the first report of ipilimumab induced encephalitis. Multi-specialty approach is needed and early discussion with neurology team is a must when confronted with neurological presentation, for quick identification, treatment and prevention of neurological sequelae. With newer immunomodulatory oncological therapeutic options, it is likely we will confront an increasing incidence of previously rare autoimmune conditions.

## Disclosures

All authors have no disclosures relevant to this report.

## References

1. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, et al. (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363: 711-723.
2. Tomasini P (2012) Ipilimumab: it's potential in non-small cell lung cancer. Ther Adv Med Oncol 4: 43-50.
3. Yang JC, Hughes M, Kammula U, Royal R, Sherry RM, et al. (2007) Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. J Immunother 30: 825-830.
4. Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, et al. (2010) Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 11: 155-164.
5. McDermott D, Haanen J, Chen TT, Lorigan P, O'Day S (2013) Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20). Ann Oncol 24: 2694-2698.
6. Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, et al. (2014) Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med 6: 230ra45.
7. Maur M, Tomasello C, Frassoldati A, Dieci MV, Barbieri E, et al. (2012) Posterior reversible encephalopathy syndrome during ipilimumab therapy for malignant melanoma. J Clin Oncol 30: e76-e78.
8. Conry RM, Sullivan JC, Nabors LB (2015) Ipilimumab- induced encephalopathy with a reversible splenial lesion. Cancer Immunol Res 3: 598-601.
9. Abdallah AO, Herlopian A, Ravilla R, Bansal M, Chandra-Reddy S, et al. (2015) Ipilimumab-induced necrotic myelopathy in a patient with metastatic melanoma: A case report and review of literature. J Oncol Pharm Pract pii: 1078155215572932.
10. Gaudy-Marqueste C, Monestier S, Franques J, Cantais E, Richard MA, et al. (2013) A severe case of ipilimumab-induced guillain-barré syndrome revealed by an occlusive enteric neuropathy: a differential diagnosis for ipilimumab-induced colitis. J Immunother 36: 77-78.
11. Sheik Ali S, Goddard AL, Luke JJ, Donahue H, Todd DJ, et al. (2015) Drug-associated dermatomyositis following ipilimumab therapy: a novel immune-mediated adverse event associated with cytotoxic T-lymphocyte antigen 4 blockade. JAMA Dermatol 151: 195-199.
12. Loochtan AI, Nickolich MS, Hobson-Webb LD (2015) Myasthenia gravis associated with ipilimumab and nivolumab in the treatment of small cell lung cancer. Muscle Nerve.
13. Thaipisuttikul I, Chapman P, Avila EK (2015) Peripheral neuropathy associated with ipilimumab: a report of 2 cases. J Immunother 38: 77-79.
14. Liao B, Shroff S, Kamiya-Matsuoka C, Tummala S (2014) Atypical neurological complications of ipilimumab therapy in patients with metastatic melanoma. Neuro-Oncology 16: 589-593.
15. (2015) Immune-mediated Adverse Reaction Management Guide. FDA-approved REMS.
16. Trinh VA, Hagen B (2013) Ipilimumab for advanced melanoma: a pharmacologic perspective. J Oncol Pharm Pract 19: 195-201.
17. Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, et al. (2015) Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol.