CASE STUDY

Immunotherapy induced cerebral vasculitis

Rebecca Busch

ABSTRACT

Immunotherapy has emerged as a powerful therapeutic approach in the fight against certain types of cancers. Immune checkpoint inhibitors (ICI) such as Pembrolizumab (Keytruda) help the immune system recognize and kill cancer cells but can also result in life threating immune-mediated adverse reactions (irAE). Neurologic complications associated with immunotherapy are now recognized more frequently than ever before. Patient X had recently completed a two-year treatment with Pembrolizumab for advanced metastatic melanoma. Six weeks after completion of treatment the patient was admitted into the ED with severe mental confusion. After a steep decline in condition the patient spent a further two months in hospital, including four weeks in ICU, after suffering auto-immune induced cerebral vasculitis which was presumed to be caused by her previous treatment with Pembrolizumab.

Keywords: Immunotherapy, Pembrolizumab, check- point inhibitor, auto-immune

N Z J Med Lab Sci 2022; 76(3): 154-156

INTRODUCTION

Patient X was a 67-year-old woman with a six-year history of melanoma, with the diagnosis of advanced metastatic melanoma being made in 2018 (in an area unsuitable for surgical removal). Given the poor five-year survival rates for advanced metastatic (stage IV) melanoma, less than 20% survived more than one year without treatment (4). The patient was placed on a study with the immune checkpoint inhibitor (ICI) immunotherapeutic agent Pembrolizumab.

ICI are a group of monoclonal antibodies the main aim of which is restoring and boosting the anti-tumour activity of cytotoxic T cells. Pembrolizumab is one such ICI. Checkpoint proteins, such as cell programmed death receptor 1 (PD-1) on T cells and programmed death ligand 1 (PD-L1), help keep immune system responses in check. The binding of PD-L1 to PD-1 keeps T-cells from killing tumour cells in the body. Blocking the binding of PD-L1 to PD-1 with an ICI allows the T-cells to kill tumour cells. The immune system is then able to detect cancer cells and stops them from growing and spreading. For Patient X, immunotherapy treatment worked well, with no further metastasis, and the areas of concern shrinking in size. After two years on the Pembrolizumab treatment the treatment was deemed a success and the treatment was completed. Six weeks after the last treatment the patient lost consciousness suddenly at home and was taken to the ED via ambulance. When she arrived in hospital, she was awake but very confused and agitated.

Table 1. shows patient results (abnormal results in red). Cardiac markers were greatly elevated with hsTnI 5903ng/L (0-10) and CK 912U/L (30-180). Blood cultures taken on this day also came back negative (after day 5) and a urine dipstick showed the presents of protein. Initially the diagnosis was a sepsis due to an infection (as this patient was prone to infections and being on immunotherapy puts patients at a greater risk of infection) and possibly a heart attack/injury. An ECG was conducted and showed a normal rhythm. The patient was placed on antibiotics to combat the infection. Overnight the patient deteriorated quickly becoming unconscious.

Table 1. Patients results (abnormal results in red)

Haematology – CBC			Biochemistry - Venous blood gas		
	Patient	Normal Reference Range		Patient	Normal Reference Range
Hb	119g/L	115 – 155	pH	7.39 U	7.30 – 7.40
Hct	0.36	0.35 – 0.46	PCO_2	35mmHg	40 -50
MCV	0.88fL	80 – 99	PO_2	33mmHg	24 - 40
MCH	29pg	27 – 33	HCO_3	20.9 mmol/L	22.0 -32.0
Platelets	309 x 10^9/L	150 - 400	TCO_2	22.2 mmol/L	25 - 33
WBC	15.5 x 10^9/L	4.0 -11.0	iCa	1.12 mmol/L	1.15 – 1.30
Neutrophils	13.2 x 10^9/L	1.0 – 7.5	Glucose	10.05 mmol/L	3.5 – 7.7
Lymphocytes	1.6 x 10^9/L	1.0 – 4.0	Lactate	8.0 mmol/L	<2.0
Monocytes	0.6 x 10^9/L	0.2 – 1.0			
Eosinophils	0.03 x 10^9/L	0.0 – 0.5			
Basophils	0.03 x 10^9/L	0.0 – 0.2			
Meta/ Myelocytes	0.05 x 10^9/L	0.0 – 0.06			

An MIR, X-ray, CT and electroencephalogram (EEG) were ordered the next day to try to establish if the condition was "query encephalopathy or encephalitis". The X-ray showed no central or lobar pulmonary embolism. Pulmonary arteries beyond the lobar level were unable to be evaluated due to "artefact" and "mild pulmonary oedema" which could "represent an early inflammatory process" (a mild pneumonia was present). The CT scan showed "no acute intracranial abnormality". The results of the MIR showed "large number of tiny foci of diffusion restriction demonstrated through the supratentorial brain. No discrete mass lesion or abnormal enhancement". The conclusion of the Radiologist was that this is "suggestive of a central embolic source". In other words, clots from other areas of the body were moving to the brain causing tiny areas of infarct and reducing the patient consciousness.

The heart was the first area considered due to the elevated troponin (TnI) and creatine kinase (CK). The EEG showed "encephalopathic EEG with features of bifrontal brain dysfunction, there were no features of non-convulsive status".

As the heart was now considered the area of interest, several investigations were carried out on the heart including a Transthoracic Echo, ECG and Transoesophageal Echo. The results showed "normal LV function. No vegetation or thrombus seen" and "no evidence of endocarditis". The substantial increase in TnI and CK were diagnosed as being due to a Type 2 myocardial infarction, which is defined as "myocardial infarction secondary to coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension or hypotension" (9). This ruled out the heart as a cause of the brain damage.

The medical team then began to look for a viral or bacterial cause which has led to encephalitis. Blood serology for CMV, EBV, Hepatitis B/C and HIV were ordered but all came back negative. A CSF sample was also tested for Herpes simplex, varicella zoster, enterovirus, parechovirus, *Neisseria meningitidis* and *Cyptococcus neoformans* but were also negative. The appearance of the CSF was noted to be "clear and colourless" and did have a high protein content, 1.08g/L (reference range -0.15 to 0.4) but the culture showed no growth. Nothing in the results seemed to explain why the patient had such an altered mental state. The doctors described the patient's condition as "a bit of a mystery".

The patient continued to decline in health to the point where she could no longer breath by herself and was moved to ICU and was placed on a ventilator. The patient was prescribed a broad spectrum of antibiotic to treat any infections, as well as systemic corticosteroids therapy while they considered administration of other systemic immunosuppressants.

As other conditions were ruled out the medical team then started investigating the rarer causes for the brain deterioration. As the patient had six weeks earlier finished an ICI immunotherapy with Pembrolizumab they started to investigate autoantibodies causes for the cerebral vasculitis. Anti-neutrophil cytoplasmic autoantibodies (ANCA), were ordered. ANCA came back positive with an "atypical" pattern. Produced by a spectrum of antibodies including myeloperoxidase, elastase, lactoferrin and antinuclear antibodies". Anti-myeloperoxidase antibody, antinuclear antibodies screen (ANA) and anti-proteinase 3 antibodies were then added to this sample to see specifically what this autoantibody was, but all came back within the normal range. NMDA (N-methyl-D-aspartate) Receptor antibody on the CSF and in the blood also came back negative (increasing levels of NMDA within the brain are associated with memory and learning impairment, psychosis ad excitotoxic brain injury) (10).

A tracheal aspirate was taken on day five due to fluid built up in breathing tube, but came back negative for *pneumocystis jirovecil*, a fungal infection of the lungs, as well as all influenza strains, RSV, Parainfluenza, Human Metapneumovirus, rhinovirus, adenovirus and Sars-Cov-19. More specialised immunology results also arrived back from Pathology laboratory, Oxford in the UK. The western blot was negative for anti-Hu, Ri, Yo, Ma2, anti-CV2/CRMP5, Amphiphysin, Sox-1, Zic-4, Tr, Titin and Rocoverin Paraneoplastic antibody markers. Tests for LGT1, CASPR2, AMPA1, AMPA2 and GAB antibodies also all came back negative from the UK laboratory. The immunotherapy drug itself Pembrolizumab was also tested for and came back at 7.0mg/L but no antidrug antibodies were detected. Despite many tests been conducted, at this point no one was able to pinpoint the exact antibody causing the issue, the presumptive diagnosis was listed as "checkpoint inhibitor cerebral vasculitis". This meant that some autoantibody in the patient's body was causing the small veins in the brain to constrict, causing small areas of infarct, leading to the comatose state the patient was now in.

As the patient was not improving on life support and with high dose steroid treatment the diagnostic team decided to try plasma exchange (PE) to remove the circulating immune complexes, immunoglobulins and complement components from the patient's system, in the hope that this would improve the patient's prognosis. During PE therapy small amounts of blood are gradually removed through an intravenous line and circulated through a machine that separates blood into red cells, white cells, platelets and plasma. The plasma portion of the blood is removed and replaced by a plasma substitute (Albumex in this case) and then added back to cells and returned via the intravenous line. The removed plasma is then discarded. One procedure typically removes 65-70% of autoantibodies in plasma (5). Typically, several procedures are needed to lead to a clinical improvement (5). In Patient X's case, after one PE treatment the patient's condition rapidly improved to a point where the patient was opening her eyes and trying to communicate (although still on ventilator). After the second round of PE, two days later, the patient was able to have the ventilator removed and could make some sounds but was still very confused. Two further rounds of PE were completed, again at two-day intervals, and resulted in an improving Glasgow Coma Scale (GCS) 7 (tubed, intubated and comatose) to GSC 15 (extubated and full awake). The patient however was still very confused and weak after almost four weeks in a coma. This rapid improvement really did suggest to the medical team that the antibody mediated immune system is driving this process and seemed to confirm the presumptive diagnosis of Pembrolizumab associated CNS vasculitis. The patient was now awake and breathing but still very confused. To continue the patient's improvement the ICU team, neurologist and oncologist applied for special approval to use the drug rituximab along with reducing doses of oral steroids. Rituximab use was approved. Rituximab is a monoclonal antibody medication and is considered a type of immunotherapy. It works by identifying and labelling B-cells for destruction by the body's immune system and was originally used to treat lymphoma (6). However, it is increasingly used for the treatment of autoimmune conditions including neurological diseases (6).

After five weeks in hospital, four weeks of that being in ICU, the patient was released to the neurology ward where she continued to improve but remained very confused, weak and was still being feed by a nasogastric tube. After further improvements following a second dose of rituximab the patient was moved to the rehabilitation ward at Burwood hospital. The patient spent two weeks learning to eat and walk again as was later released home with a walking frame. The patient still suffers from general muscle weakness, resulting in mobility issues, and has developed a Parkinson-like tremor in her hands but is otherwise well. She will continue to be followed up by neurology and oncology departments.

DISCUSSION

ICI have become the standard of care for treating patients with advanced metastatic melanoma since their approval in 2011 (11). Their use has increased the proportion of patients with unresectable advanced melanoma that have achieved long-term overall survival (11). However, one of the major disadvantages in the use of Immunotherapy is the appearance of inflammatory manifestations – immune-related adverse events (irAE) (2). These reactions are often relatively mild but more severe irAEs have been reported including several forms

of vasculitis (2). Clinically significant neurological irAEs reactions are reported to occur at an incidence of 1% among patients treated with PD-1/PD-L1 inhibitors (e.g., Pembrolizumab) (1). Some analyses have also suggested that neurological irAE are more frequent in patients suffering from melanoma compared to other types of cancer (12,13). Other research has shown that age-associated changes in the body's immune system, including alterations in surface protein expression, are thought to contribute to an increased susceptibility of patients to autoimmune diseases in general (2).

Despite the well-known side effects of ICIs when a patient presents to hospital with neurological symptoms, or mixed symptoms in this case, a thorough work-up needs to be conducted to exclude other underlying conditions. These conditions could include infections, tumour progression, tumour cell spread to the CSF, vascular complications such as ischemia or bleeding, brain parenchyma, metabolic alterations as well as side effects due to previous or ongoing systemic therapies (1). Therefore, appropriate diagnostic measures such as imaging, CSF diagnostic, electrophysiological assessments as well as additional laboratory testing depending on the clinical picture.

The lack of well-stablished diagnostic criteria for immune-related complications also remains a challenge to the diagnostic team (1). Despite the increased use of ICI and more knowledge about the incidence, clinical presentation and severity of irAE there still seems to be no generally accepted approach regarding patient management by medical staff (14). Several guidelines are starting to become available, mainly due to immunotherapy trials, like the one this patient was on (14). Treatment plans mainly often follow the treatment given to this patient - use of intravenous immunoglobulins, plasmapheresis, B-cell-depleting antibody rituximab or other immunosuppressive drugs such as cyclophosphamide or methotrexate (15).

CONCLUSION

Immunotherapeutic strategies have been on the rise in the field of clinical oncology over the last decade especially in the treatment of non-resectable melanomas. As the number of patients undergoing these treatments increases so too does the number affected by neurological irAE. Therefore, patients entering treatment need to be made aware of the possibility of irAE and require close clinical monitoring as early and accurate diagnosis is key to starting the appropriate treatment and avoiding permanent brain damage. More data is also needed about the occurrence of neurological complications and what treatment strategies work most effectively for these patients. More research into possible biomarkers which may help identify patients who may be prone to neurological complication while undergoing ICI treatment may also be beneficial.

Despite all the risks associated with immunotherapy there is no denying how this treatment has improved and extended the lives of so many oncology patients. In fact, statistically speaking, patient X would probably not still be alive at the time of admission if not for the study she was on (ICI therapy with Pembrolizumab).

AUTHOR INFORMATION

Rebecca Busch, BMLSc, Medical Laboratory Scientist, Canterbury Health Laboratories, Ashburton
Correspondence: beck_wilsin23@yahoo.com

REFERENCES

1. Roth P, Winklhoger S, Muller A, et al. Neurological complications of cancer immunotherapy. *Cancer Treat Rev* 2021; 97: 102189.
2. Cadena R, Abdulahad W, Hospers G, et al. Checks and balances in autoimmune vasculitis. *Front Immunol* 2018; 9: 315.
3. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. *Nat Commun* 2020; 11: 3801.
4. Hamid O, Robert C, Daud A, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab. *Ann Oncol* 2019; 30: 582-588.
5. Lehmann HC, Hartung HP. Plasma exchange and intravenous immunoglobulins: mechanism of action in immune-mediated neuropathies. *J Neuroimmunol* 2011; 2311-2): 61-69.
6. Whittam H, Tallantyre E, Jolles S, Huda S. Rituximab in neurological disease: Principles, evidence and practice. *Pract Neurol* 2018; 19: 5-20.
7. Taylor R, Lindorfer M. Drug insight: the mechanism of action of rituximab in autoimmune diseases – the immune complex decoy hypothesis. *Nat Clin Pract Rheumatol* 2007; 3: 86-95.
8. Seyfizaden N, Hasenkamp J. A molecular perspective on rituximab: A monoclonal antibody for B cell non-Hodgkin lymphoma and other affection. *Crit Rev Oncol Haematol* 2016; 97: 275-90.
9. Collinson P, Lindahl B. Diagnosing Type 2 Myocardial Infarction. American College of Cardiology 2016 (*https://www.acc.org/latest-in-cardiology/articles/2016/05/18/13/58/diagnosing-type-2-myocardial-infarction)*
10. Newcomer J, Farber N, Olney J. NMDA receptor function, memory and brain aging. *Dialogues Clin Neurosci* 2000; 2: 219-232
11. Rogiers A, Boekhou A, Schwarze J, et al. Long-term survival, quality of life and psychosocial outcomes in advanced melanoma patients treated with immune checkpoint inhibitors. *J Oncol* 2019; 5269062.
12. Shi S, Jaoube JA, Kanwar R. Neurological adverse effects due to programmed death (PD-1) inhibitors. *J Neurooncol* 2020; 148: 291-297.
13. Kao JC, Liao B, Markovic SN, Klein CJ. Neurological complications associated with anti-programmed Death 1 (PD-1) antibodies. *JAMA Neurol* 2017; 74:1216-1222.
14. Haanan J, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28: 119-142.
15. Anderson D, Beecher G, Nathoo N, et al. Proposed diagnostic and treatment paradigm for high-grade neurological complications of immune checkpoint inhibitors. *Neurooncol Pract* 2019; 6: 340-345.