Case Report

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Unleashing the tiger – iatrogenic autoimmunity from cancer immunotherapy drugs

Queenie Luu[1] and Gabor Major[1,2]

[1]Department of Rheumatology, Bone and Joint Institute, Royal Newcastle Centre, Locked Bag 1, HRMC (Hunter Regional Mail Centre), NSW 2310, Australia

[2]Faculty of Medicine, University of Newcastle, Newcastle 2305, Australia

Corresponding author: Queenie Luu. Email: queenie.luu@gmail.com

Lesson

Immune checkpoint inhibitors can lead to the development of organ and non-organ specific immune related adverse events.

Keywords

drugs, musculoskeletal and joint diseases, endocrinology, oncology, pharmacology and therapeutics, rheumatology, unwanted effects/adverse reactions

Case report

We report the case of a 72-year-old man who was visiting family from another state and whose medical history was therefore not readily available. He presented with collapse and a three-day history of an acutely swollen and tender right knee on a background of right knee osteoarthritis, diabetes, hypertension, ischaemic heart disease and melanoma requiring amputation of the left index finger and axillary lymph node clearance. At the time of presentation, he was hypotensive with a systolic blood pressure in the 80s, heart rate 70 and febrile with a temperature of 39. With aggressive fluid resuscitation, his blood pressure improved to 91/59. He was empirically commenced on intravenous flucloxacillin for the treatment of presumed septic arthritis and septicaemia. Blood cultures and a knee aspirate were obtained. The knee aspirate was inflammatory with a white cell count of 12,850 cells/cm^3. Gram stain was negative and there were no crystals seen. His C-reactive protein was 43. He was seen by the orthopaedic service and the right knee was washed out. Over the next four days, he remained on intravenous flucloxacillin and maintenance intravenous fluids. On day 5 of admission, he developed a persistent erythema on his cheeks and forehead. Drug rash was suspected and the flucloxacillin was changed to cephazolin. He continued to deteriorate. When we saw him in consultation on day 7, he had ongoing fevers up to 39 and he looked peripherally shut down with cyanotic fingers and toes. He complained of general weakness, pain in the shoulders and right knee which remained warm, swollen and tender. Creatinine, electrolytes and liver function tests were normal. Blood count showed a mild eosinophilia and CRP had risen to 158. He asserted that he had been essentially well prior to this presentation, but was vague about details of his medical history and medications. Allowing for his delirium, we contacted his wife in his home state and obtained collateral history, subsequently corroborated by his treating oncologist of stage III metastatic melanoma that had been treated with pembrolizumab, followed by ipilimumab. The treatment was complicated by life-threatening autoimmune hepatitis, which was controlled with high-dose prednisone and cessation of the immune check point inhibitor therapy. Prednisone was continued for at least four months before presentation, when he started to wean down to 2.5 mg and had been off prednisone for the two weeks before this presentation. We started him on intravenous hydrocortisone 100 mg six hourly. The cortisol level in the blood sample collected the day before he started hydrocortisone was undetectable. There was a dramatic improvement following hydrocortisone. He felt symptomatic improvement after the first dose and within 24 h the fever, right knee arthritis and facial erythema had resolved. He was changed to prednisone 50 mg daily and within 72 h he asked to be discharged. He declined further bloods including testing for adrenocorticotropic hormone and magnetic resonance imaging brain that had been booked to look for suggestion of autoimmune hypophysitis. A panel of autoantibodies including hepatitis-related antibodies and other pituitary hormones were normal.

The cortisol deficiency is likely to be secondary to persistent suppression of the hypothalamic pituitary axis in the context of recent cessation of prednisone that had been taken for several months, or autoimmune hypophysitis from the checkpoint inhibitors, in particular ipilimumab. Normal pituitary

hormones, except for the hypothalamic pituitary axis, make hypophysitis less likely.

Discussion

Cancer immunotherapy has changed the therapeutic landscape for advanced neoplasias. Immune checkpoint inhibitors, cytotoxic T lymphocyte-associated protein 4 and programmed death 1 axis inhibitors, are now available for metastatic melanoma and are being tested for an increasing range of malignancies.

Ipilimumab is a cytotoxic T lymphocyte-associated protein 4 inhibitor. Pembrolizumab and nivolumab are programmed death 1 axes inhibitors. The loss of this inhibition allows for cytotoxic response to tumour antigens, but creates the risk of loss of tolerance to self-antigens and development of autoimmunity.

Up to 85% of patients treated with an immune checkpoint inhibitor are reported to develop an immune-related adverse event.[1] Most immune-related adverse events are mild and do not require treatment or are controlled with low-dose prednisone.

Clinician awareness and suspicion are critical when managing patients exposed to these drugs. Skin and gastrointestinal events are most common.[2] Endocrine toxicities may be asymptomatic or life threatening. They can occur from the sixth week up to several years after start of treatment. The thyroid is most frequently affected, but type I diabetes and, particularly with ipilimumab, hypophysitis can also occur.[2,3] Endocrine toxicity usually causes permanent gland damage requiring lifelong hormone replacement.

Adrenal crisis should be suspected if shock develops and cannot be explained by sepsis. In our patient, clues included persistent hypotension despite aggressive fluid resuscitation, eosinophilia and facial erythema. All these clinical features and the fevers failed to respond to antibiotics, but promptly resolved with the commencement of hydrocortisone.

Overall survival and time to malignancy progression are not affected by the occurrence of immune-related adverse events or the need for glucocorticoids.[4]

Learning points

- If available history does not fit the clinical picture, secondary sources should be explored.
- Up to 85% of patients treated with an immune checkpoint inhibitor experience an immune-related adverse event. These can occur several years after the initiation of immunotherapy and may be life threatening.
- Consider the possibility of adrenal crisis if there is persistent hypotension despite aggressive fluid resuscitation.

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