Case report

Pembrolizumab-induced autoimmune haemolytic anaemia and cholangitis

Harriet Williams , Robin Aitchison

Haematology Department, Buckinghamshire Healthcare NHS Trust, Aylesbury, UK

Correspondence to
Dr Harriet Williams;
harriet.williams3@nhs.net

Accepted 19 November 2019

SUMMARY

Increasing numbers of patients are now offered immunotherapy as part of their cancer treatment. These treatments, while often very effective, have a wide range of adverse effects that are distinct from those of traditional chemotherapy regimens. Thyroid disease, dermatological disease, colitis and pneumonitis are some of the most commonly reported immune side effects. We present a case of life-threatening de novo autoimmune haemolytic anaemia (AIHA) complicated by immune cholangitis induced by pembrolizumab. An 81-year-old woman with metastatic melanoma completed a two-year course of pembrolizumab in August 2018 and six weeks later presented to hospital with jaundice. Admission haemoglobin (Hb) was 91 g/L, rapidly decreasing to 31 g/L, at which point she required admission to the intensive care unit. AIHA is a rare but potentially life-threatening complication of checkpoint inhibitors and should be considered in patients presenting with anaemia during or after immunotherapy treatment.

BACKGROUND

Immune checkpoint blockade with programmed cell death (PD-1) antibodies (pembrolizumab and nivolumab) has in recent years vastly improved the treatment of metastatic melanoma and is now used increasingly in the treatment of other solid tumours and haematological malignancies.[1–3]

Though undoubtedly a major advance in treatment, these new therapies are increasingly recognised as having a side effect profile quite different from that of standard myelosupressive chemotherapy. We now report a case of life-threatening de novo autoimmune haemolytic anaemia (AIHA) with cholangitis induced by pembrolizumab, a humanised IgG4 monoclonal antibody. This treatment promotes apoptosis of tumour cells by targeting the PD-1 transmembrane protein on cytotoxic T cells, thereby preventing peripheral immune tolerance. Such therapies can have multisystem adverse effects and haematological immune-related adverse events (irAEs) are increasingly recognised and are potentially life threatening. A recent observational study suggested that neutropenia, immune thrombocytopenia and AIHA are the most common types of haematological irAEs.[4]

CASE PRESENTATION

Here, we present a case of de novo pembroluzimab-induced haemolytic anaemia occurring in association with immune cholangitis

An 81-year-old woman was diagnosed with a melanoma on her left arm (pT4a) in 2014. This was initially treated surgically with a wide local excision and lymph node clearance of the left axilla.

She developed in transit metastases in the left axilla two years later and had a repeat excision. Subsequent imaging revealed multiple bilateral pulmonary nodules in keeping with metastatic disease. She commenced pembrolizumab as first-line systemic therapy in August 2016, at a dose of 140 mg every three weeks. This was increased to 150 mg from May 2018. During treatment, she developed asymptomatic radiological cholecystitis which was assumed to be immunotherapy-related but no other obvious adverse effects.

She completed a two-year course of pembrolizumab in August 2018 with imaging at that time showing a minor increase in the size of several retroperitoneal lymph nodes but no evidence of pulmonary, liver or subcutaneous metastases, indicating an almost complete radiological response to treatment.

Six weeks later, she was admitted to hospital with a one-week history of jaundice and lethargy and a three-week history of anorexia, upper abdominal pain and nausea.

INVESTIGATIONS

On arrival, her haemoglobin (Hb) was 91 g/L, with a normal white cell and platelet count. Her alkaline phosphatase (ALP) and total bilirubin levels were both raised. Findings of a CT scan of the chest, abdomen and pelvis were consistent with cholangitis, and she was initially treated with intravenous antibiotics. Imaging also revealed an 8 mm left axillary lymph node and enlarged left supraclavicular, coeliac and para-aortic lymph nodes as well as non-specific lung nodules and a small volume of pelvic-free fluid. Two days after admission, she became acutely hypoxic, requiring high-flow nasal oxygen and admission to the intensive care unit (ICU). A repeat full blood count revealed a Hb of 39 g/L with raised lactate dehydrogenase (LDH) and bilirubin levels.

DIFFERENTIAL DIAGNOSIS

Haemolysis was immediately suspected due to the acute drop in haemoglobin, and initial investigations supported this with an LDH level of 1176 U/L, a bilirubin level of 164 µmol/L and a blood film showing red cell agglutination. The diagnosis was confirmed with a monospecific direct antiglobulin test (DAT) and was positive (4+) both for C3d and IgG. Subsequent reticulocyte count was 8.9%.

To cite: Williams H, Aitchison R. *BMJ Case Rep* 2019;**12**:e232505. doi:10.1136/bcr-2019-232505

Further analysis of the hyperbilirubinaemia showed that there was an increase in both conjugated (335 µmol/L) and unconjugated bilirubin (181 µmol/L), indicating that haemolysis was not the only pathological process causing the rise in bilirubin. MR cholangiopancreatography was suggestive of acalculous cholecystitis and subsequent MRI of the liver showed diffuse gallbladder thickening and intrahepatic and extrahepatic biliary thickening compatible with an additional diagnosis of immunotherapy induced cholangiopathy.

TREATMENT

The patient was started on a four-day course of intravenous methylprednisolone and received six units of red cells over 24 hours, via a blood warmer. Three days after admission to ICU, Hb was 96 g/L, LDH was 392 U/L and bilirubin had risen to 561 µmol/L.

OUTCOME AND FOLLOW-UP

After four days in ICU, the patient was discharged to the haematology ward and continued on a weaning dose of oral prednisolone. In total, she received 12 units of red cells. Her admission was complicated by pseudomonas bacteraemia for which she completed a course of broad-spectrum antibiotics. She was discharged on prednisolone, and three months later was well off steroids with a Hb of 110 g/L although she still had grade one liver dysfunction with an ALP of 180. Four months after discharge, her haemoglobin and liver function tests normalised, and she has been well since then and has returned to a predisease level of functioning. Using the Eastern Cooperative Oncology Group score, her current performance status is zero.[5]

DISCUSSION

PD-1 inhibition has revolutionised the treatment of some malignancies and allowed some patients with metastatic disease to have prolonged periods of progression-free survival.[2 3] Inhibiting the body's immune regulatory mechanisms is a potent cancer therapy but also can result in adverse effects due to the activation of a widespread immune response.[6 7] Predicting which patients will be affected is currently impossible, and the severity of immune adverse effects can vary from minor side effects such as fatigue, pruritus and diarrhoea to life-threatening immune reactions, as described above.

Pembrolizumab has been shown to be an effective treatment for metastatic melanoma, but the vast majority of patients receiving it will experience minor immune-related side effects. In the KEYNOTE-001 phase 1b trial, 86% of patients experienced an adverse effect, with 17% of patients experiencing a grade 3 or 4 adverse effect which may necessitate cessation of treatment.[8]

The number of reported cases of pembrolizumab-induced AIHA is relatively small, but AIHA is an increasingly recognised serious immune haematological effect of checkpoint blockade generally, with some suggestion that it is more commonly associated with PD-1 and PD L1 inhibitors, such as nivolumab and pembrolizumab, than with CTLA4 inhibitors such as ipilimumab.[9]

Patients with immune checkpoint inhibition AIHA may be DAT positive (IgG and/or C3d) or DAT negative,[10] with some cases being reported in patients known to have a positive DAT before initiation of immunotherapy.[11] More research is needed to understand the significance of this and identify whether a positive DAT could be a reliable predictor of the development of AIHA during immunotherapy treatment. In addition, pre-existing immune haemolysis may worsen when cancer is treated with immunotherapy.[12]

The mainstay of treatment of checkpoint inhibition-related AIHA is with glucocorticoids, and the majority of cases require red cell transfusions to correct anaemia initially. Other immune modulatory drugs, such as the anti-CD20 molecule rituximab, have been used to good effect.[13–15]

A recent case series of immune checkpoint inhibitor-associated haemolytic anaemia found that the median time from lowest Hb to partial or complete recovery was 47 days which is comparable to our case. Half of the patients experienced an additional irAE, as was also the case with our patient who also developed immune-related cholangiopathy. Interestingly, 50% of the patients in this case series were rechallenged with immunotherapy with only one experiencing a recurrence of AIHA, suggesting that therapy could be cautiously reintroduced if appropriate.[10]

Hepatotoxicity is a relatively common irAE, affecting 5%–10% of patents treated with checkpoint inhibitors.[16] It most commonly takes the form of hepatocellular damage with a resultant transaminitis rather than cholestasis as described here.[17 18] Diagnosis of immune mediated liver injury may be delayed due to the need to rule out metastatic invasion, biliary obstruction and infective aetiologies before initiating corticosteroids or other immune modulatory drugs.

Checkpoint inhibitor-associated cholangitis may be associated with clinical and pathological features distinct from other infective or immune aetiologies of cholangitis. Typical radiological findings may include extrahepatic and intrahepatic duct dilatation, gallbladder wall thickening and bile duct hypertrophy, with varying stages of bile duct injury and ductopenia. Liver biopsy may show CD8-positive T cell infiltration. Response to corticosteroids has been described in one case series of nivolumab-induced cholangiopathy as poor to moderate.[19]

Learning points

- Educating physicians about immune-related side effects is paramount as both oncologists using these drugs and other specialists including haematologists and hepatologists need to be aware of these serious complications.
- Immune-related side effects may occur during and shortly after the end of immunotherapy treatment.
- Assessing a jaundiced patient on immunotherapy may be difficult as there may be more than one immune mediated cause of hyperbilirubinaemia in these patients.
- Pretreatment direct antiglobulin testing may identify some patients at high risk of developing autoimmune haemolytic anaemia, but additional research is needed.
- Further research should focus on identifying individuals who may be at particularly high risk of experiencing immune adverse effects and optimising treatment strategies for these patients.

Contributors HW and RA both contributed to the design of the work and to the writing and final approval of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Harriet Williams http://orcid.org/0000-0002-8009-9236

REFERENCES

1 Helmink BA, Gaudreau P-O, Wargo JA. Immune checkpoint blockade across the cancer care continuum. *Immunity* 2018;48:1077–80.
2 Ribas A, Puzanov I, Dummer R, *et al*. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol* 2015;16:908–18.
3 Robert C, Schachter J, Long GV, *et al*. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med* 2015;372:2521–32.
4 Delanoy N, Michot J-M, Comont T, *et al*. Haematological immune-related adverse events induced by anti-PD-1 or anti-PD-L1 immunotherapy: a descriptive observational study. *The Lancet Haematology* 2019;6:e48–57.
5 Oken MM, Creech RH, Tormey DC, *et al*. Toxicity and response criteria of the eastern cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–56.
6 Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. *PLoS One* 2016;11:e0160221–15.
7 Michot JM, Bigenwald C, Champiat S, *et al*. Immune-Related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer* 2016;54:139–48.
8 Hamid O, Robert C, Daud A, *et al*. Five-Year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *Ann Oncol* 2019;30:582–8.
9 Tanios GE, Doley PB, Munker R. Autoimmune hemolytic anemia associated with the use of immune checkpoint inhibitors for cancer: 68 cases from the food and drug administration database and review. *Eur J Haematol* 2019;102:157–62.
10 Leaf RK, Ferreri C, Rangachari D, *et al*. Clinical and laboratory features of autoimmune hemolytic anemia associated with immune checkpoint inhibitors. *Am J Hematol* 2019;94:563–74.
11 Kong BY, Micklethwaite KP, Swaminathan S, *et al*. Autoimmune hemolytic anemia induced by anti-PD-1 therapy in metastatic melanoma. *Melanoma Res* 2016;26:202–4.
12 Ogawa K, Ito J, Fujimoto D, *et al*. Exacerbation of autoimmune hemolytic anemia induced by the first dose of programmed death-1 inhibitor pembrolizumab: a case report. *Invest New Drugs* 2018;36:509–12.
13 Sherbeck JP, Hugan S, Novak B, *et al*. Pembrolizumab induced autoimmune hemolytic anemia with possible auto-anti-EN(A)FS specificity. *Transfusion* 2018;58.
14 Khan U, Ali F, Khurram MS, *et al*. Immunotherapy-associated autoimmune hemolytic anemia. *j. immunotherapy cancer* 2017;5.
15 Shaikh H, Daboul N, Albrethsen M, *et al*. A case of autoimmune haemolytic anaemia after 39 cycles of nivolumab. *Case Reports* 2018;2018.
16 Haanen JBAG, 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:iv119–42.
17 Jennings JJ, Mandaliya R, Nakshabandi A, *et al*. Hepatotoxicity induced by immune checkpoint inhibitors: a comprehensive review including current and alternative management strategies. *Expert Opin Drug Metab Toxicol* 2019;15:231–44.
18 Reddy HG, Schneider BJ, Tai AW. Immune checkpoint inhibitor-associated colitis and hepatitis. *Clin Transl Gastroenterol* 2018;19. Erratum in: Clin Transl Gastroenterol 2018;14;9(11):206.
19 Kawakami H, Tanizaki J, Tanaka K, *et al*. Imaging and clinicopathological features of nivolumab-related cholangitis in patients with non-small cell lung cancer. *Invest New Drugs* 2017;35:529–36.