Immune-mediated diabetes due to pembrolizumab

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Abstract
Melanoma is one of the most commonly occurring skin cancers in the UK. As recommended by NICE, there are a number of drugs available to treat melanoma and immunotherapeutic drugs are widely used to improve survival in metastatic melanoma. Monoclonal antibodies can cause immune-related side effects, including diabetes.

Pembrolizumab, an anti-programmed cell death-1 receptor monoclonal antibody (PD-1 Ab), was given to a 63-year-old woman with metastatic melanoma. She developed osmotic symptoms with tiredness and confusion after pembrolizumab treatment cycles. She was diagnosed with diabetic ketoacidosis; she was treated with intravenous insulin and started on insulin to control her hyperglycaemia.

Endocrine immune-related side effects are common with immunotherapeutic agents, especially anti-cytotoxic T-lymphocyte associated protein-4 monoclonal antibody (anti-CTLA-4) and PD-1 Abs. They mainly affect thyroid, pituitary and adrenal glands. Immune-related diabetes is a rare side effect of immunotherapeutic agents. Therefore, clinical suspicion for immune-related diabetes should be high in patients who are treated with these immunotherapeutic agents. Copyright © 2017 John Wiley & Sons.

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Key words
immunotherapy; diabetes

Introduction
Melanoma is the third most common skin cancer in the UK and accounts for the majority of skin cancer deaths. Anti-cancer drugs are powerful and sometimes have unexpected side effects. NICE has recommended the use of immunotherapeutic drugs for the treatment of metastatic melanoma.1,2 These are pembrolizumab, nivolumab (anti-programmed cell death-1 receptor monoclonal antibodies; PD-1 Abs), and ipilimumab (anti-cytotoxic T-lymphocyte associated protein-4 monoclonal antibody; anti-CTLA-4).3 These agents can induce immune-related adverse effects. These side effects affect various body organs, including endocrine and non-endocrine systems. Here we present the case of a woman who developed immune-related diabetes while on pembrolizumab for the treatment of metastatic melanoma.

Case report
A 63-year-old white Caucasian woman, with no personal or family history of diabetes or other autoimmune disease, had melanoma 20 years ago in the right arm which was treated surgically. She remained well and in remission for a number of years. In 2015, she developed a mass in the right axilla which on biopsy was confirmed to be metastatic melanoma. The mass was removed surgically.

Subsequently, our patient underwent radiotherapy to the axilla. Post radiotherapy, she commenced adjuvant chemotherapy with pembrolizumab for which five cycles were planned. The first cycle was completed uneventfully.

After the second cycle the patient developed dryness of mouth and polydipsia and was prescribed artificial saliva. She was subsequently admitted under the oncology team for tiredness and nausea, but no obvious cause was found. She was discharged home on anti-emetics.

Two weeks following the patient’s second cycle of pembrolizumab, she developed confusion and was referred by her GP to the medical team for further assessment with a differential diagnosis of brain metastasis or an infection of unknown source.

On admission to the department, her Glasgow coma scale was 14/15 with a normal temperature. She had tachycardia with a normal blood pressure. Her systemic examination was unremarkable. Investigations revealed a plasma glucose of 38.7mmol/L with capillary blood ketones of 7.6mmol/L and venous pH of 7.16. Other blood investigations revealed dehydration without any evidence of infection, and normal thyroid function tests. Her radiological investigations were normal.
She was treated for diabetic ketoacidosis (DKA) as per the Joint British Diabetic Society (JBDS) guidelines 2010. After initial intravenous insulin treatment, she was started on subcutaneous insulin therapy. She was started on pre-mixed insulin by the admitting medical team. Unfortunately, the diabetes relevant auto-antibodies were not requested. She was reviewed by the oncology team and pembrolizumab was discontinued. She was reviewed by the diabetes team and her insulin was switched to a basal-bolus regimen. She continues to be followed up by the specialist diabetes service. Her HbA1c was 60mmol/mol at diagnosis. She has been under oncology follow up and no further cycles of pembrolizumab were administered. This decision seems to have been made largely because of the severity of the immune-mediated diabetes that she developed as a result of pembrolizumab administration.

Discussion

Our patient was treated with pembrolizumab and developed symptoms of diabetes after her second cycle. She was admitted under the oncology team who did not consider the diagnosis of diabetes as a possible cause for her presenting symptoms. She was re-admitted with confusion and presented with DKA under the medical team. Such was the severity of diabetes at presentation that we considered our patient may have developed diabetes after her first cycle of pembrolizumab but her diagnosis was delayed, resulting in further decompensation and DKA following her second cycle.

Although pembrolizumab is associated with improved survival in patients with metastatic melanoma, it is also known that these immunotherapy agents cause immune-related side effects. There are very few data available regarding the incidence of immune-related diabetes with these agents although it is well recognised. One published series estimates the incidence to be 0.8%.

The incidence of immune-related diabetes mellitus increases to 1.5% when combination immunotherapy agents are used. Time from drug administration to diabetes manifestation could range from one week to five months. Patients can present with hyperglycaemia or DKA.

The exact pathogenesis of immune-mediated diabetes is not known. The most likely explanation is that the anti-PD-1 receptor ligand blockade by immunotherapy-targeted T-cell regulation not only increases the tumour cell destruction, but also causes them to cross-react with the self-antigens. This immune-mediated destruction could be responsible for the development of auto-immune diabetes. Additionally, mice model PD-1 blockade has been known to cause type 1 diabetes mellitus. Decreased PD-1 expression is also noted in patients suffering from auto-immune type 1 diabetes. Thus, a direct relationship between pembrolizumab and diabetes is plausible. Insulin therapy is the main form of treatment rather than oral hypoglycaemic agents. Although it is thought to be an immune-related process, steroids are not indicated in the treatment.

Following our involvement in the management of this patient’s case, we corresponded with the GP and the oncology and surgical teams who did not consider the diagnosis. She has been under oncology follow up and no further cycles of pembrolizumab were administered.

Key points

- Endocrinopathies are an important side effect of monoclonal antibodies
- Other medical specialties using these drugs should be aware of the signs and symptoms of the various endocrinopathies so that timely diagnosis and treatment are achieved
- Involve the specialist medical teams in managing the endocrinopathies so that these patients can have appropriate follow up

Our patient presented with DKA under the medical team and pembrolizumab was discontinued. She was admitted under the oncology team and pembrolizumab was discontinued. We have a collective responsibility to educate and inform our colleagues managing the endocrinopathies so that timely diagnosis and treatment are achieved.

Conclusion

Pembrolizumab is a humanised monoclonal antibody which acts on the anti-PD-1 immune-checkpoint receptor pathway, blocking its interaction with ligands on the cancer cells. It causes unrestrained T-cell activation and results in anti-tumour activity. Anti-CTLA-4 and anti-PD-1 monoclonal antibodies are well known to cause immune-related side effects, especially endocrine side effects. Immune-related diabetes is also a recognised side effect of these agents, although rare, in addition to the thyroid, pituitary and adrenal manifestations. There is a direct relationship between pembrolizumab and immune-mediated diabetes.

Clinical suspicion of diabetes mellitus should be high when anti-PD-1 Ab is used for metastatic melanoma. Early recognition of hyperglycaemia will prevent emergency admission with DKA and its complications. It is unclear if the immune-related diabetes effects of pembrolizumab are reversible and further cohort-based studies will be needed to confirm the same.

Declaration of interests

There are no conflicts of interest declared.

References