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Diabetic ketoacidosis following immunotherapy for lung cancer

SHORT CASE REPORT

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A man in his sixties was treated with pembrolizumab for non-small cell lung cancer and developed diabetic ketoacidosis. Pembrolizumab is a monoclonal antibody approved for treating several types of cancer. Diabetes mellitus type 1 is a rare adverse reaction to immunotherapy for cancer, and in the following we describe the first case reported in Norway of diabetic ketoacidosis resulting from this treatment.

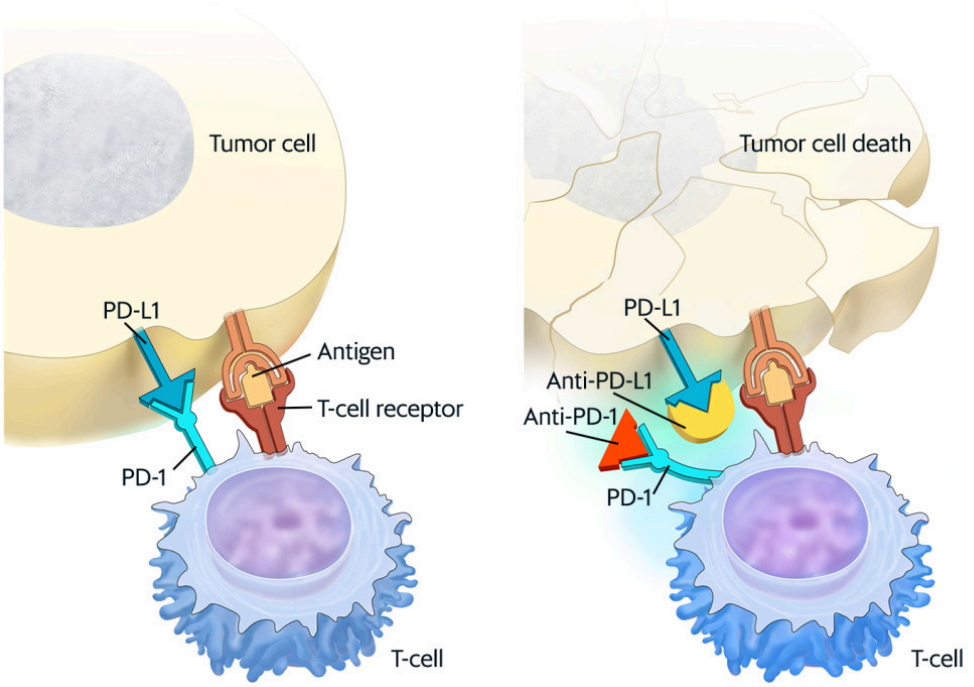

Figure 1 When PD-L1 (programmed cell death ligand 1) on the tumour cell binds to the PD-1 receptor (programmed cell death 1 receptor) on the T-cell, the apoptotic mechanisms of the T-cell are inhibited and prevent the immune system from attacking the tumour cell. Blocking PD-L1 or PD-1 enables the T-cell to attack the tumour cell after antigen binding. Reproduced with permission: © Terese Winslow LLC, U.S. Govt has certain rights.

A man in his sixties was admitted to the Medical Department with suspected sepsis after being found with altered consciousness and tachypnoea with a respiratory rate of 33 breaths/min. On admission he was confused and had Kussmaul respiration with ketone odour and a blood sugar concentration of 69.7 mmol/l. His blood pressure was 172/97 mm Hg, pulse 99 beats/min. and rectal temperature 36.8 °C. Laboratory tests showed pH 7.18 (reference range 7.37–7.45), pCO_2 2.5 kPa (4.7–6.0 kPa), bicarbonate 7 mmol/l (22–27 mmol/l), sodium 118 mmol/l (136–146 mmol/l), potassium 8.2 mmol/l (3.5–5.0 mmol/l), creatinine 141 µmol/l (60–105 µmol/l), CRP 33 (< 5), Hb 12.3 g/dl (13.4–17 g/dl) and leukocytes 17.5 · 10^9/l (3.5–11 · 10^9/l). His pancreatic amylase level was normal (45 U/l, reference range 10–65 U/l), while his lipase level was elevated (749 U/l, < 300). Urine dipsticks showed 3+ for ketones. In light of clinical examinations and supplementary tests, we concluded that the most probable diagnosis was ketoacidosis, and not sepsis. Blood cultures were therefore not ordered.

The patient was treated with fluids and an insulin drip in accordance with the department's procedure for treating ketoacidosis. His blood sugar concentration fell nicely with satisfactory correction of the acidosis. A switch to subcutaneous insulin treatment was possible after a while. On discharge the patient was taking 55 U insulin degludec once a day and 15 U insulin aspart with meals. Three months after the hospitalisation in question, the patient was well regulated on one dose of insulin degludec daily and insulin aspart with meals.

Tests associated with type 1 diabetes, such as s-anti-GAD, s-anti-IA2 and s-insulin antibody, were all negative. C-peptide level measured five weeks after hospitalisation was under 7 pmol/l (370–1 470 pmol/l). HbA1c on admission was 8.4 %. Thyroid tests were normal.

It emerged that the patient had received a diagnosis of adenocarcinoma in the right lung about two months earlier. PET-CT had showed signs of several metastases, and a lung biopsy had detected PD-L1 expression in 95 % of the cells. He had no known diabetes and HbAlc% was 5.7 % at the time. Treatment with pembrolizumab 200 mg had started. The first dose had been administered a month earlier, and the second dose 16 days before the hospitalisation in question with ketoacidosis. After radiotherapy for the lung tumour he will continue on pembrolizumab.

Discussion

Pembrolizumab is a humanised monoclonal antibody that binds to programmed cell death-1 receptors (PD-1 receptors) and blocks interaction with the ligands PD-L1 and PD-L2. PD-1 receptor is a negative regulator of T-cell activity. The drug is indicated for patients with non-small cell lung cancer who express PD-L1 with a tumour proportion score of over 50 %.

Immune-related adverse reactions occur relatively often in patients treated with monoclonal antibodies. Severe adverse reactions are reported for up to 10 % of patients (1). Most conditions – for example immune-related pneumonitis, colitis, hepatitis and nephritis – are treated with corticosteroids. Type 1 diabetes mellitus is a rare adverse reaction, and steroid therapy has not proved effective in the few reported attempts (2–4).

The lipase elevation in our patient was viewed as non-specific, and he did not meet the criteria for a diagnosis of pancreatitis. It is recommended not measuring amylase and lipase in patients undergoing immunotherapy if there is no clinical suspicion of pancreatitis (5).

In a review of all published cases of diabetes after PD-1 receptor therapy, 42 cases were found, 12 of whom had been treated with pembrolizumab, and 30 had been hospitalised with ketoacidosis (2).

Our patient had not received cytostatics or treatment other than pembrolizumab after his cancer had been diagnosed. He had a normal HbA1c% ten weeks prior to hospitalisation with ketoacidosis, and we have concluded that the development of diabetes mellitus is definitely related to treatment with the antibody.

Steroid therapy has been attempted in vain to save beta cell function in patients with diabetes triggered by immunotherapy, and it was concluded in a case study that the treatment had no effect on the immune-related reaction (3). Steroids combined with glucagon-like peptide-1-analogue (GLP-1-analogue) have also been attempted but failed to save beta cell function (4). In 2016, the Japanese Diabetes Organisation announced that steroid therapy is not recommended for treating diabetes secondary to PD-1 antibody therapy (4).

Most reported cases of type 1 diabetes mellitus following treatment with PD-1 antibody are individual case studies. Many describe dramatic courses with ketoacidosis, as in the case of our patient. Ketoacidosis is a life-threatening condition, and patients treated with PD-1 antibodies must be given thorough information on diabetes symptoms so that, in the event, treatment can start as early as possible.

Some have chosen to continue therapy with monoclonal antibody after blood sugar has been normalised with insulin (4, 6), while others have chosen to discontinue it (7).

Our patient is scheduled for further treatment with pembrolizumab.

Conclusion

Immunotherapy for cancer has different side effects from chemotherapy. Doctors who use immunotherapy to treat patients must be on the watch for immune-related endocrinopathies. These will usually require permanent hormone substitution treatment. Serious complications such as diabetic ketoacidosis occur, and patients must be informed of a broad range of possible adverse reactions.

The patient has consented to the publication of the article.

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