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CASE REPORT

Diabetic Ketoacidosis after Pembrolizumab Treatment in a Patient with Thymic Carcinoma and No Known Diabetes Mellitus: A Case Report

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CASE PRESENTATION

A 64-year-old Chinese man presented in December 2020 with a 3-month history of neck pain. Contrast-enhanced magnetic resonance imaging of the cervical spine revealed a large mass at the C6 vertebra (Figure 1). Computed tomography (CT)–guided biopsy of the mass revealed poorly differentiated carcinoma, with immunohistochemistry tests positive for p40, cytokeratin, CD5, PAX8 and c-kit, and negative for thyroid transcription factor 1, CDX2, leukocyte common antigen, S100 protein, desmin, synaptophysin and CD56. These results were suggestive of thymic squamous cell carcinoma. Positron emission tomography–CT showed a hypermetabolic thymic mass and multiple bone metastases, confirming the diagnosis of metastatic thymic carcinoma (Figure 2). No metastases were observed in the pancreas or adrenal glands. He had a past medical history of hypertension well controlled on amlodipine 5 mg daily. His cell counts, organ function, fasting glucose level and lipid profile were normal 1 month before the diagnosis of malignancy. He had no family history of diabetes mellitus.

The patient received palliative radiotherapy to the painful cervical and thoracic spine bone metastases at a dose of 22.5 Gy in five daily fractions over 1 week with anterior-posterior opposing fields. The thymic tumour was covered in the radiation portal (Figure 3). Subsequently, he was started on palliative chemotherapy with etoposide and cisplatin (etoposide 100 mg/m^2 and cisplatin 30 mg/m^2 daily from day 1 to day 3 every 3 weeks) in January 2021. Regular zoledronic acid

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Ethics Approval: This study was approved by the Kowloon West Cluster Research Ethics Committee of Hospital Authority, Hong Kong [Ref No.: KW/EX-22-065(175-04)]. The requirement for patient consent was waived by the Committee as the patient had passed away at the time of writing.

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every 4 weeks was also given. He developed grade 4 neutropenia requiring granulocyte colony-stimulating factor support, treatment deferrals, and dose reduction. After six cycles of etoposide and cisplatin, CT showed mixed response with stable bone metastases but enlarging thymic tumour. As the patient was asymptomatic, he opted for a drug holiday.

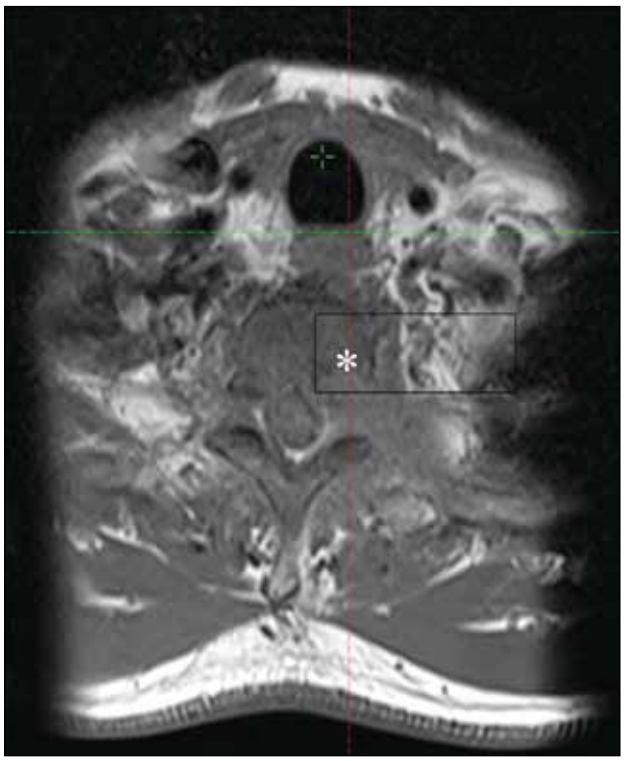

Figure 1. C6 bone metastases (asterisk) on T1-weighted magnetic resonance imaging.

Six months later, the patient complained of increasing lower back pain, and CT confirmed disease progression. He was started on pembrolizumab 200 mg every 3 weeks in November 2021. His fasting glucose level before treatment was 5.8 mmol/L. Baseline morning cortisol level was low at 36 nmol/L (normal: 133-537) while thyroid function was normal (thyroid-stimulating hormone level: 3.67 mIU/L [normal: 0.27-4.20], thyroxine level: 16.9 pmol/L [normal: 12.0-22.0]). He was given hydrocortisone replacement of 10 mg twice daily before starting immunotherapy. No significant side-effects were observed during the first three cycles.

The patient was admitted to the hospital for coma in January 2022, 3 days after the fourth cycle. Blood results showed severe hyperglycaemia (blood glucose level: 55.7 mmol/L) and metabolic acidosis (pH value: 7.22, bicarbonate level: 9.6 mmol/L). Multistix urine test revealed large amounts of ketones. Coupled with an elevated beta-hydroxybutyrate level, the clinical diagnosis of diabetic ketoacidosis (DKA) was suggested. He was treated with insulin infusion and fluid resuscitation. Subsequent investigations after stabilisation showed glycated haemoglobin level of 10.8% and low C-peptide (0.06 nmol/L; normal: 0.30-2.40) and insulin (1.6 mIU/L; normal 2.6-24.9) levels. Anti-GAD65 and anti-IA2 antibodies were negative. Insulin infusion was weaned off and switched to subcutaneous insulin glargine.

The oncology team decided to stop pembrolizumab as the severe hyperglycaemia and DKA could be related

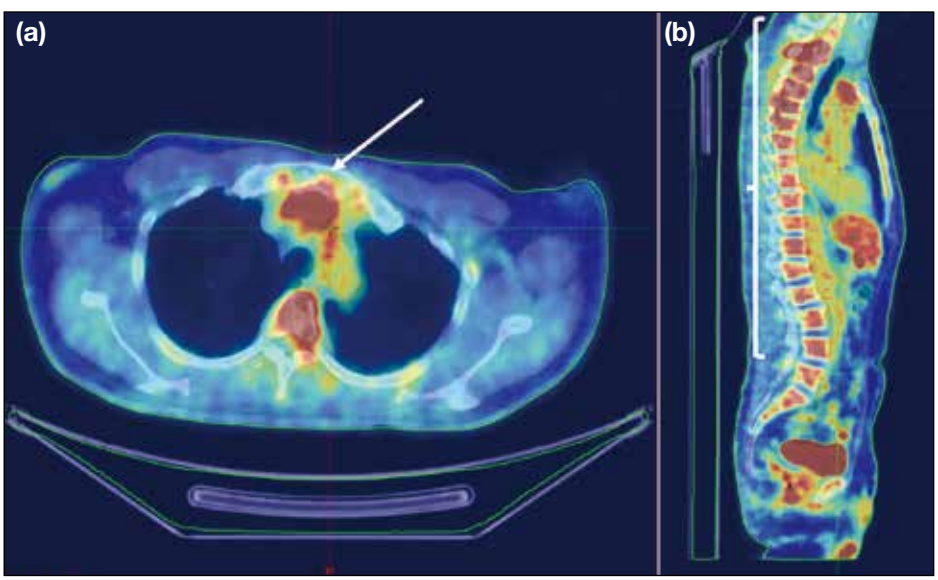

Figure 2. Positron emission tomography–computed tomography images of the thymic tumour (a) [arrow] and extensive bone metastases (b) [square bracket].

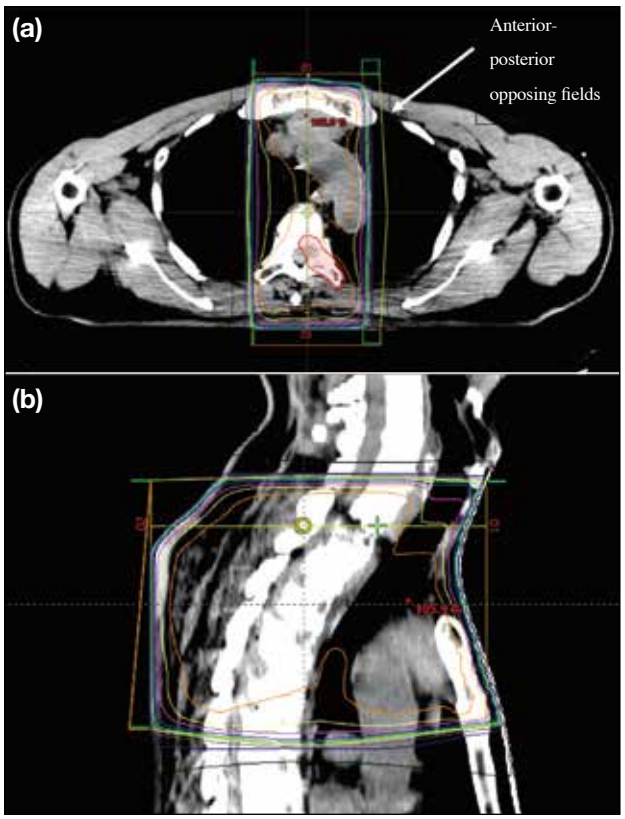

Figure 3. Radiation portal covering the thymic tumour and bone metastases at the cervical (a) and thoracic spine (b).

to the treatment. The plan was to consider second-line chemotherapy if there was progressive disease. A CT performed 2 months after the presentation of hyperglycaemia showed stable disease.

The patient's diabetic control was brittle and he required three admissions within 2 months for insulin titration. The first admission was due to hyperglycaemia, whereas the latter two were for hypoglycaemia. In the third admission, he had persistent hypotension requiring escalation of hydrocortisone replacement for stabilisation. He ran a progressive downhill course with deconditioning and was readmitted for *Klebsiella pneumoniae* chest infection. He succumbed in May 2022, 4 months after the presentation of DKA and 17 months after the diagnosis of thymic carcinoma. Details about the patient's timeline of events are illustrated in online supplementary Figure 1.

DISCUSSION

This patient developed life-threatening DKA following pembrolizumab treatment. Since the patient's baseline fasting glucose level was normal and type 1 diabetes mellitus (T1DM) was considered unlikely for the patient's age, his condition was most probably related to pembrolizumab.

In the past decade, immune checkpoint inhibitors (ICIs) have revolutionised the field of oncology. Pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, has been studied in thymic carcinoma and shown promising efficacy in this entity with a poor prognosis.[1,2] Despite important clinical benefits, ICIs are known for their immune-related adverse events (irAEs). These can target virtually any organ system and their severity can range from mild to life threatening. ICI-associated autoimmune diabetes mellitus (CIADM) is a rare complication of therapy, with an incidence of 0.2% to 1.4%.[3] With increasing clinician awareness of CIADM, its incidence is likely to increase.

The pathophysiology of CIADM involves the development of autoreactive T cells to pancreatic beta cells in response to a previous environmental trigger in genetically predisposed individuals. These T cells are generally controlled by immune checkpoints but pathology may result when activated by anti–PD-1/programmed death-ligand 1 (PD-L1) therapy.[2,3]

The presentation of CIADM is variable, ranging from asymptomatic hyperglycaemia to severe diabetic complications. This patient's presentation with DKA is the most common presentation of CIADM. In a pooled analysis of 200 case reports, 67.5% of CIADM patients presented with DKA.[4] The onset of CIADM varies with a median of 6 to 9 weeks but can occur as early as 1 week and as late as after the end of ICI treatment.[5]

The diagnosis of CIADM is characterised by two hallmark features of hyperglycaemia and low C-peptide level. When C-peptide level is normal, alternative causes of hyperglycaemia during ICI therapy should be considered, including exacerbation of type 2 diabetes mellitus, steroid-induced hyperglycaemia, autoimmune pancreatitis, and lipodystrophy.[3] Compared with T1DM where autoantibodies are present in >90% of cases, autoantibody positivity is lower in CIADM, ranging from 0% to 71%.[3] Therefore, negative values for this patient did not exclude CIADM.

Due to the rarity of CIADM, evaluating its risk factors based on clinical characteristics and biomarkers is

challenging. A recent systematic review identified that close to 60% of CIADM patients had susceptibility haplotypes for T1DM, and patients with positive T1DM antibodies had an earlier onset of CIADM.[4] Although this provides important information about the disease nature and clinical course of CIADM, it does not help clinicians assess which patients need enhanced surveillance. Suazo-Zepeda et al[6] demonstrated that high PD-L1 expression is associated with the development of immune-related adverse reactions in patients with non–small cell lung cancer. Whether this correlation is also observed for CIADM and patients with thymic carcinoma is uncertain. Unfortunately, our patient had passed away at the time of writing this case report, and it was not possible to retrieve his archival specimen for PD-L1 testing.

The mainstay of treatment for CIADM is insulin. In contrast to other irAEs, treatment with glucocorticoids or immunosuppressants is not effective in these patients due to the almost complete destruction of beta cells.[3,5] Steroids will likely negatively influence diabetes control in these patients and are not advised. In view of the irreversible damage to beta cells, similar to that in T1DM, a multi-dose basal-bolus regimen or continuous insulin pump is recommended to achieve glycaemic targets.[3] Our patient was prescribed long-acting insulin glargine only and discharged before C-peptide result was available, possibly one of the reasons for his labile glycaemic control.

Close surveillance for irAEs is essential while using ICIs. The 2021 American Society of Clinical Oncology guideline suggests testing of baseline fasting glucose level and monitoring of random glucose level before each dose of ICI.[7] Although CIADM is rare, regular monitoring to facilitate early endocrine team referral and insulin treatment to prevent life-threatening diabetic complications should be advocated. This patient had an elevated glycated haemoglobin level at presentation with DKA, suggesting he may have been hyperglycaemic during the preceding months. If regular surveillance of glucose level was performed, CIADM could have been diagnosed at an earlier stage. The suggested workflow for monitoring and treatment of the condition is depicted in online supplementary Figure 2.

In general, treatment of severe irAEs requires permanent discontinuation of the checkpoint inhibitor. Nonetheless similar to other immune-related endocrinopathies where the damage is irreversible, restarting treatment may be considered with close monitoring of diabetic control once glucose levels stabilise.[7]

In the two prospective phase II studies of the role of pembrolizumab in patients with thymic carcinoma, around 15% of patients developed grade >3 irAEs,[1,2] much higher than the pooled incidence of <2% in a systematic review and meta-analysis of clinical trials evaluating anti-PD1 and anti–PD-L1 checkpoint inhibitors.[8] Notably, the types of high-grade irAEs in these patients were rarely seen in other tumour histologies. Of the 66 thymic carcinoma patients in the two studies, three developed myasthenia gravis (4.5%), two developed myocarditis (3.0%), one developed myositis (1.5%), and one developed myoclonus (1.5%).[1,2] CIADM was observed in one patient (1.5%).[1,2] The higher incidence and unusual clinical presentations of irAEs in patients with thymic carcinoma warrant further study and validation in larger patient cohorts.

Another reason this patient developed CIADM is that he may have had an underlying autoimmune condition. This patient had a low baseline cortisol level before treatment with pembrolizumab. It is possible that he had undiagnosed autoimmune adrenalitis since thymic carcinomas are associated with autoimmune paraneoplastic syndromes, albeit at lower rates compared with thymomas.[9] In retrospect, further workup with blood tests for adrenocorticotropic hormone level and antiadrenal antibodies should have been performed. Patients with preexisting autoimmune conditions are known to have higher risks for irAEs and have flare-ups during immunotherapy.[10] This may also explain the need to escalate our patient's hydrocortisone dose after commencing pembrolizumab.

This case highlights the need for a heightened degree of suspicion amongst physicians for CIADM when treating patients with immunotherapy, especially those with thymic carcinoma, malignancies prone to paraneoplastic syndromes, or a past history of autoimmune diseases. Blood testing for C-peptide in patients who present with hyperglycaemia following immunotherapy aids the diagnosis of CIADM.

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