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Case Report

Hypercalcaemia due to Sarcoidosis during Treatment with Avelumab for Metastatic Merkel Cell Carcinoma

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Abstract
Merkel cell carcinoma is a rare but aggressive skin cancer. Response to chemotherapy is not durable but avelumab, an anti-PD-L1 inhibitor, showed promising ongoing response in a phase II trial. Checkpoint inhibitors including avelumab are known to cause overactivation of the immune system, leading to immune-related adverse events (irAE). We describe the first reported case of hypercalcaemia secondary to reactivation of sarcoidosis in a patient with metastatic Merkel cell carcinoma on avelumab. Hypercalcaemia was managed with corticosteroids to full resolution and avelumab therapy was safely continued.

Introduction

Merkel cell carcinoma is an uncommon but aggressive skin cancer with incidence varying from 0.2 to 1.6 per 100,000 persons per year based on geographical locations [1, 2]. Although response rates to first line chemotherapy can be as high as 55%, this is not durable with median progression free survival of only 94 days [3].

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Responses are even poorer for further lines of therapy until the promising results of recent phase II JAVELIN Merkel 200 trial [4]. This phase II study assessed the efficacy of avelumab (fully human IgG1 monoclonal antibody against PD-L1). Response rate was 33% and it was durable with 74% of the responders showing ongoing responses at 1-year follow-up [5]. The safety profile of avelumab was as expected for a checkpoint inhibitor and immune-mediated side events included endocrinopathies, pneumonitis, hepatitis, and nephritis [4].

To the best of our knowledge, re-activation of sarcoidosis as an adverse event of avelumab in metastatic Merkel cell carcinoma has not been previously encountered. Although there are few reports of sarcoidosis in patients treated with other immunotherapy agents [6–11], we report here the first case of reactivated sarcoidosis associated with the use of avelumab for Merkel cell carcinoma.

Case Report

A 77-year-old man presented with metastatic Merkel cell carcinoma including iliac, inguinal nodal and bone metastases. He underwent 6 cycles of chemotherapy with carboplatin and etoposide which was completed after approximately 6 months.

His other medical history was notable for sarcoidosis diagnosed 10 years prior when he presented with hypercalcaemia and later confirmed on mediastinal biopsy. Remission was achieved after 12 months of glucocorticoid therapy although calcified mediastinal and hilar lymphadenopathy persisted.

After completion of chemotherapy, staging investigations showed partial response with resolution of most inguinal lymphadenopathy and no new sites of disease. Pulmonary, hilar and calcified mediastinal lymph nodes remained unchanged from 10 years ago. Avelumab was initiated as second line therapy. After 3 doses of avelumab, hypercalcaemia was evident at 2.81 mmol/L with chronically impaired but stable creatinine clearance (CrCl) of 0.70 mL/s/m^2. This was initially presumed to be hypercalcaemia of malignancy and was managed with intravenous (IV) zoledronic acid and fluids. Avelumab was continued and calcium status was monitored closely.

Unfortunately, hypercalcaemia indeed deteriorated to 3.07 mmol/L after 2 weeks and with reduction of CrCl to 0.52 mL/s/m^2. Although asymptomatic, in view of worsening renal function and hypercalcemia, the patient was admitted for further management including additional IV fluids and a second dose of zoledronic acid.

Further investigations included serum parathyroid hormone level which returned suppressed at 5 ng/L, (Reference Range [RR], 15–68). Serum 25-hydroxy-vitamin D was replete at 66 nmol/L (RR, 50–140) but 1,25-dihydroxy-vitamin D was elevated at 280 pmol/L (RR, 60–210) with hypercalciuria at 8.1mmol/day (RR, 2.5–7.2). Serum Angiotensin Converting Enzyme (ACE) level was 2,200 nkat/L, (RR, 483–1,866). Restaging investigations did not demonstrate any progression of disease when compared to studies prior to initiation of avelumab.

In view of stable radiological appearance of his cancer combined with PTH independent hypercalcaemic parameters and elevated serum ACE level, the hypercalcemia was felt to be due to reactivation of dormant sarcoidosis, a rare adverse event of immune therapy. Although there were no other symptoms, lack of response to bisphosphonate therapy prompted initiation of prednisone 40mg daily. Calcium level normalised within a week and prednisone was weaned off over a month. Avelumab was continued as the reactivated sarcoidosis and associated hypercalcaemia came rapidly under control.

Twelve months after commencement of immunotherapy, his Merkel cell carcinoma continued to respond to avelumab. His sarcoidosis was still in remission, with normocalcaemia and an improved serum ACE level of 1,300 nkat/L. No other adverse events related to avelumab were detected.

Discussion

Sarcoidosis is a multisystem immune-mediated granulomatous disease which affects predominantly lungs but can have involvement of the skin, liver, eyes, cardiac tissue and the nervous system [12, 13]. Non caseating granuloma formation is the hallmark pathological feature of sarcoidosis. It is proposed that in response to an unknown antigen, T lymphocytes are activated by antigen presenting cells in cell-mediated immune response. Activated T cells release cytokines including interleukin 2 (IL-2), IL-12, interferon-γ and tumour necrosis factor α (TNF-α), recruiting more inflammatory cells including macrophages and facilitating granuloma formations downstream [12–14]. In addition, sarcoidosis tissue specimens have been found to have higher expression of PD-L1 compared to healthy controls [15]. Hence, it is likely that avelumab, which has anti-PD-L1 activity, triggers cell-mediated immune response in susceptible individuals or increased sarcoidosis activity in patients with previous diagnosis.

In the diagnosis of sarcoidosis, serum ACE lacks sensitivity and specificity [12, 16]. In addition, insertion or deletion genetic polymorphism in the ACE gene may impact on the accuracy of measurement and interpretation of its activity [17]. Nonetheless, in patients with elevated activity, it can be reflective of disease activity [18, 19] which has been a useful marker for sarcoidosis activity in this case. A combination of normal calcium level and decreasing serum ACE activity was indicative that the diagnosis was correct and the appropriate treatment was effective.

A search of the literature revealed a few case reports of sarcoidosis associated with other checkpoint blockers [6–11]. It has been reported with anti-PD1 therapy given as single agent or as combination therapy with anti-CTLA4, mostly in the treatment of melanoma but also in a case of uterine leiomyosarcoma. Patients in those cases presented with pulmonary or cutaneous sarcoidosis, which is the classical presentation in up to 90% of patients [12, 13]. It is interesting that our patient presented with sarcoidosis related hypercalcaemia since it is only seen in 11% of patients [12]. In this situation, the diseased macrophages alter calcium homeostasis by converting 25-hydroxy-vitamin D to the active 1,25-dihydroxy-vitamin D and as a consequence, increase serum calcium levels [12]. Our patient did not develop pulmonary or other end organ involvement and was able to continue avelumab with only a short course of corticosteroid similar to most of the other cases.

This case report recognizes that sarcoidosis is an uncommon but potentially serious adverse event of immune checkpoint therapy. It appears safe to continue or to re-challenge with immunotherapy if the sarcoidosis responds to glucocorticoid therapy. It also highlights the fact that although hypercalcaemia of malignancy is the most common cause of elevated calcium in cancer patients, alternative and potentially more favourable differential diagnoses should be considered if the hypercalcaemia does not respond to conventional standard treatment.

Statement of Ethics

Ethical approval was not applicable to this case report but full written informed consent was obtained from patient to publish this manuscript.

Disclosure Statement

The authors declare that there are no conflicts of interest.

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Author Contributions

Sandy Tun Min: Design and conception of the manuscript; data collection and drafting the manuscript; approval for it to be published and agreeable to be accountable for all aspects of the manuscript.

Ina IC Nordman: Conception of the manuscript; Revising it critically; approval for it to be published and agreeable to be accountable for all aspects of the manuscript.

Huy A Tran: Conception of the manuscript; Revising it critically; approval for it to be published and agreeable to be accountable for all aspects of the manuscript.

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