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

Sandy Tun Min\textsuperscript{a}  Ina I.C. Nordman\textsuperscript{a, b}  Huy A. Tran\textsuperscript{b, c}

\textsuperscript{a}Department of Medical Oncology, Calvary Mater Newcastle, Newcastle, NSW, Australia; \textsuperscript{b}University of Newcastle, Newcastle, NSW, Australia; \textsuperscript{c}Department of Clinical Chemistry, John Hunter Hospital, Newcastle, NSW, Australia

Keywords
Immunotherapy · Merkel cell carcinoma · Avelumab · Hypercalcaemia · Sarcoidosis

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].

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/m². 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/m². 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 8.1 mmol/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 hypercalcaemia 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.

Funding Sources

This case report receives no specific funding.

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.

References

1. Kaae J, Hansen AV, Biggar RJ, Boyd HA, Moore PS, Wohlfahrt J, et al. Merkel cell carcinoma: incidence, mortality, and risk of other cancers. J Natl Cancer Inst. 2010 Jun;102(11):793–801.
2. Youlden DR, Soyer HP, Youl PH, Fritschi L, Baade PD. Incidence and survival for Merkel cell carcinoma in Queensland, Australia, 1993-2010. JAMA Dermatol. 2014 Aug;150(8):864–72.
3. Iyer JG, Blom A, Doumani R, Lewis C, Tarabashkar ES, Anderson A, et al. Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma. Cancer Med. 2016 Sep;5(9):2294–301.
4. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D’Angelo SP, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol. 2016 Oct;17(10):1374–85.
5. Kaufman HL, Russell JS, Hamid O, Bhatia S, Terheyden P, D’Angelo SP, et al. Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after ≥1 year of follow-up: JAVELIN Merkel 200, a phase 2 clinical trial. J Immunother Cancer. 2018 Jan;6(1):7.
6. Tissot C, Carsin A, Freymond N, Pacheco Y, Devouassoux-G. Sarcoidosis complicating anti-cytotoxic T-lymphocyte-associated antigen-n-4 monoclonal antibody biotherapy. Eur Respir J. 2013 Jan;41(1):246–7.
7. Cousin S, Toulmonde M, Kind M, Cazeau AL, Bechade D, Coindre JM, et al. Pulmonary sarcoidosis induced by the anti-PD1 monoclonal antibody pembrolizumab. Ann Oncol. 2016 Jun;27(6):1176–9.
8. Danlos FX, Pagès C, Baroudjian B, Vercellino L, Battistella M, Mimoun M, et al. Nivolumab-Induced Sarcoid-Like Granulomatous Reaction in a Patient With Advanced Melanoma. Chest. 2016 May;149(5):e133–6.
9. Firwana B, Raviola R, Raval M, Hutchins L, Mahmoud F. Sarcoidosis-like syndrome and lymphadenopathy due to checkpoint inhibitors. J Oncol Pharm Pract. 2017 Dec;23(8):620–4.
10. Montaudie H, Pradelli J, Passeron T, Lacour JP, Leroy S. Pulmonary sarcoid-like granulomatosis induced by nivolumab. Br J Dermatol. 2017 Apr;176(4):1060–3.
11. Reddy SB, Possick JD, Kluger HM, Galan A, Han D. Sarcoidosis Following Anti-PD-1 and Anti-CTLA-4 Therapy for Metastatic Melanoma. J Immunother. 2017 Oct;40(8):307–11.
12 Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007 Nov;357(21):2153–65.
13 Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. JAMA. 2011 Jan;305(4):391–9.
14 Patterson KC, Chen ES. The Pathogenesis of Pulmonary Sarcoidosis and Implications for Treatment. Chest. 2018 Jun;153(6):1432–42.
15 Braun NA, Celada LJ, Herazo-Mayo JD, Abraham S, Shaginurova G, Sevin CM, et al. Blockade of the programmed death-1 pathway restores sarcoidosis CD4(+) T-cell proliferative capacity. Am J Respir Crit Care Med. 2014 Sep;190(5):560–71.
16 Ungprasert P, Carmona EM, Crowson CS, Matteson EL. Diagnostic Utility of Angiotensin-Converting Enzyme in Sarcoidosis: A Population-Based Study. Lung. 2016 Feb;194(1):91–5.
17 Kruit A, Grutters JC, Gerritsen WB, Kos S, Wodzig WK, van den Bosch JM, et al. ACE I/D-corrected Z-scores to identify normal and elevated ACE activity in sarcoidosis. Respir Med. 2007 Mar;101(3):510–5.
18 Selroos O, Grönhagen-Riska C. Angiotensin converting enzyme. III. Changes in serum level as an indicator of disease activity in untreated sarcoidosis. Scand J Respir Dis. 1979 Dec;60(6):328–36.
19 Sandron D, Lecossier D, Grodet A, Basset G, Battesti JP. [Diagnostic, prognostic and developmental value of serum angiotensin converting enzyme in sarcoidosis]. Ann Med Interne (Paris). 1984;135(1):46–50.