

**Case Report**

## Sarcoidosis presenting with hypercalcaemia following withdrawal of long-term immunosuppression in renal transplantation

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Long-term immunosuppression, including corticosteroids, is a hallmark of renal transplantation. We describe a patient who had a failed transplant after 15 years, subsequent graft nephrectomy and withdrawal of his immunosuppression therapy including prednisolone. Within months of complete cessation of prednisolone, he developed hypercalcaemia and subsequent systemic symptoms including ocular, respiratory and dermatological. A skin biopsy demonstrated non-caseating granulomatous lesion and a diagnosis of sarcoidosis was confirmed. Re-commencement with prednisolone resulted in complete resolution of clinical and biochemical features of sarcoidosis. Sarcoidosis is unlikely to present in the immunosuppressed patient. This case highlights that unexplained hypercalcaemia at the time of withdrawal of immunosuppression, including corticosteroids, may be a feature of sarcoidosis.

### INTRODUCTION

A hallmark of renal transplantation is the requirement for long-term immunosuppression. Over time, this requirement wanes, and in certain situations such as graft loss, immunosuppression, including oral steroids, may be stopped by the clinician. We describe a case of sarcoidosis presenting with hypercalcaemia following withdrawal of immunosuppression.

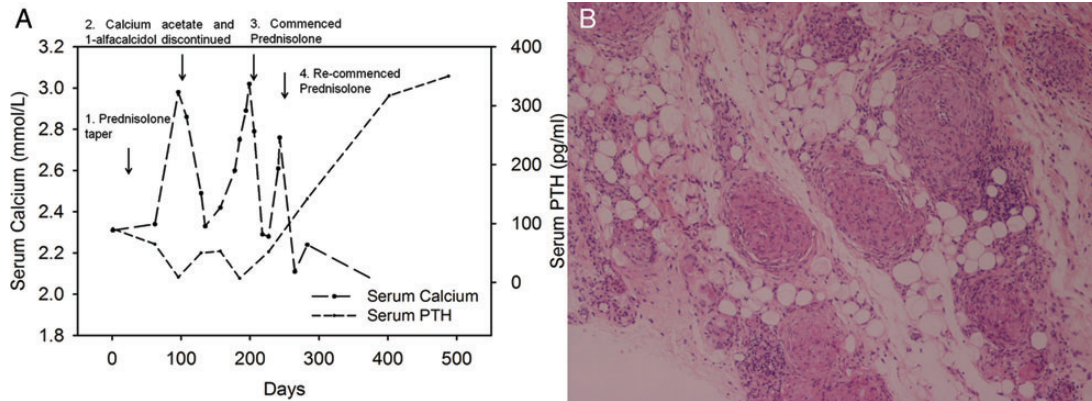
### CASE REPORT

A 45-year-old man had established renal failure (ERF) secondary to reflux nephropathy. He was treated with renal transplantation, which after 15 years failed and he was re-established on haemodialysis. Owing to recurrent sepsis, he underwent a transplant nephrectomy and following this his long-term immunosuppression including prednisolone was weaned and eventually withdrawn.

Interestingly, prior to complete cessation of prednisolone, routine bone mineral chemistry revealed a hypercalcaemic episode that resolved following discontinuation of calcium acetate 1 g t.d.s and 1-alfacalcidol 0.25 µg daily (treatment for secondary hyperparathyroidism) (Fig. 1A).

One month after discontinuing prednisolone, he started feeling generally unwell. A random cortisol level excluded hypoadrenalism. Three months after discontinuing prednisolone, he presented with a fever and cough, and was given antibiotics for a presumed chest infection. Despite this therapy, his symptoms worsened and 2 days later he was admitted to hospital. He complained of sore red eyes and his cough had worsened. He was dyspnoeic with an exercise tolerance of only 10 m. He had 4 kg of unintended weight loss and appeared cyanosed. Clinical examination demonstrated red, hard, firm nodules on the dorsum of his hands. Ophthalmological examination revealed bilateral pterygia with inflamed conjunctiva. Chest examination revealed fine basal crepitations. A CXR was normal.

Serum biochemistry again revealed hypercalcaemia (3.02 mmol/l) (Fig. 1A) and a serum ACE was 132 units/l (reference range 8–52 units/l). Other causes of hypercalcaemia such as multiple myeloma and prostate cancer were considered and excluded. There was no evidence of concurrent mycobacterial infection on CT thorax and no previous documented infection or exposure to tuberculosis. Given the clinical and biochemical findings, we suspected systemic sarcoidosis and a course of oral prednisolone 20 mg daily was



**Figure 1:** Biochemical course and histological analysis. (A) Biochemical changes since prednisolone dose tapered (1) Initial rise in serum calcium and fall in parathyroid hormone levels leading to cessation of calcium-containing phosphate binders and 1-alfacalcidol (2) Further subsequent rise leading to the diagnosis of sarcoidosis and treatment with prednisolone (3) leading to rapid control of hypercalcaemia and return of parathyroid hormone levels to those typical of a patient with established renal failure with secondary hyperparathyroidism. Abrupt discontinuation of prednisolone leading to return of symptoms and hypercalcaemia—there was rapid resolution upon restarting prednisolone (4) (B) Skin Biopsy. High power view magnification Haematoxylin and Eosin stain, ×100. Several non-caseating granulomas composed of epithelioid cells are seen in fat.

commenced. A skin biopsy of the nodular lesions confirmed non-caseating granulomas within the subcutaneous tissue (Fig. 1B).

Following steroid treatment, there was rapid improvement in all symptoms including shortness of breath. Following discharge, the course of prednisolone was inadvertently stopped after only 2 weeks. The symptoms rapidly returned prompting a further admission. Prednisolone was recommenced and the symptoms resolved.

One year later, his symptoms have not returned. His prednisolone dose has been reduced to a maintenance dose of 2 mg daily. His serum ACE levels have normalized and his serum calcium remains within the low-normal range (Fig. 1A) with a serum PTH level consistent with secondary hyperparathyroidism due to ERF.

## DISCUSSION

Sarcoidosis is a multisystem disorder of uncertain aetiology. It typically presents with one or more of the following abnormalities: bilateral hilar lymphadenopathy, pulmonary infiltrates, skin lesions and ocular involvement. It is characterized pathologically by non-caseating granulomas. There is an association with hypercalcaemia in 10–20% of cases [1, 2], but clinically important renal disease is less common [2]. Treatment of sarcoidosis is usually with corticosteroids. For this reason, it would be unusual that sarcoidosis should present in the context of corticosteroid use during solid organ transplantation.

In our case, hypercalcaemia was detected before complete cessation of prednisolone therapy following renal transplant nephrectomy. The coincidental use of 1-alfacalcidol and calcium-containing phosphate binders initially confounded the aetiology of the hypercalcaemia. Subsequent symptoms of sore eyes, myalgia, cough, mild fever following complete cessation of prednisolone are all consistent with sarcoidosis. There had been no previous evidence of sarcoidosis in the patient's past

medical history, and no evidence of non-caseating granulomas was found on histological examination of the graft following nephrectomy. A further rise in serum calcium levels coincided with the development of skin nodules and shortness of breath. The persistence of hypercalcaemia following the withdrawal of calcium supplementation should have prompted investigation. The suppressed PTH level would have initially led to the possibility of a malignant condition, which is usually clinically apparent in the presence of hypercalcaemia.

In our case, the development of sarcoidosis appears to have occurred while the patient was still on low-dose corticosteroids. Initial non-specific symptoms developed after corticosteroids were stopped. Our first consideration was hypoadrenalism, while other considerations may have included disease recurrence or immune-mediated rejection in the context of steroid withdrawal. In the setting of long-term immunosuppression, the onset of systemic symptoms should also lead to a suspicion of tuberculosis. Consideration of a granulomatous cause of hypercalcaemia would have ensued once the additional symptoms developed. The development of *de novo* sarcoidosis in this context is rare but has been previously described [3, 4].

Reactivation of known sarcoidosis has also been described in the setting of renal transplantation. The most detailed examples of this were reviewed in a case series of 18 patients who underwent renal transplantation with a previous diagnosis of sarcoidosis [5]. In five patients who had recurrence, two developed renal sarcoidosis and three had extra-renal manifestations, a mean period of 13 months following transplantation. All patients were receiving immunosuppression (including low-dose prednisolone) at the time. Kukura *et al.* [6] report the finding of non-caseating granuloma in a pregnant woman with a renal transplant. Herrero *et al.* [7] describe the onset of systemic symptoms following withdrawal of immunosuppression in a patient with a failed renal transplant. Brown *et al.* [4] describe renal failure following withdrawal of prednisolone post-renal transplant. Sarcoidosis was confirmed on renal

biopsy as the cause of this. Sarcoidosis as a cause of the initial renal failure was made retrospectively.

The most similar case to ours is described by Quack *et al.* [8]. In this case, the suspicion of 'de novo' sarcoidosis was raised in a case with hypercalcaemia presenting 12 weeks after cessation of corticosteroids. There had been associated weight loss and arthralgia. In this case, thoracic imaging demonstrated hilar and mediastinal lymphadenopathy. A diagnosis of sarcoidosis was supported by a raised serum ACE, soluble interleukin-2 receptor and bronchoalveolar lavage demonstrated a lymphocytic alveolitis where a raised CD4/CD8 ratio was found—a ratio >3.5 being consistent with sarcoidosis.

To conclude, sarcoidosis, which may normally be controlled with immunosuppression including corticosteroids, is unlikely to manifest in the immunosuppressed patient. However, hypercalcaemia and symptoms suggestive of a systemic disease, even in the immunosuppressed and especially when immunosuppression has been withdrawn should be investigated without bias. In our case, the systemic features including pulmonary symptoms, hypercalcaemia, raised serum ACE, histological findings on skin biopsy and the response to corticosteroids support the diagnosis of sarcoidosis. Delays in recognizing such pathology may lead to increased morbidity and distress for the patient.

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## REFERENCES

1. Sharma OP. Vitamin D, calcium, and sarcoidosis. *Chest* 1996;**109**:535–539.
2. GÖbel U, Kettritz R, Schneider W, Luft FC. The protean face of renal sarcoidosis. *J Am Soc Nephrol* 2001;**12**:616–623.
3. Schmidt RJ, Bender FH, Chang WWL, Teba L. Sarcoidosis after renal transplantation. *Transplantation* 1999;**68**:4.
4. Brown J, Jos V, Newstead C, Lawler W. Sarcoid-like granulomata in a renal transplant. *Nephrol Dial Transplant* 1992;**7**:1.
5. Aouizerate J, Matignon M, Kamar N, Thervet E, Randoux C, Moulin B, *et al.* Renal transplantation in patients with sarcoidosis: a French multicenter study. *Clin J Am Soc Nephrol* 2010;**5**:2101–2108.
6. Kukura Š, Viklický O, Lácha J, Voska L, Honsová E, Teplan V. Recurrence of sarcoidosis in renal allograft during pregnancy. *Nephrol Dialysis Transplant* 2004;**19**:1640–1642.
7. Herrero JC, Morales E, Dominguez-Gil B, Carreño A, Usera G, Aguado JM, *et al.* Reactivation of multisystemic sarcoidosis after immunosuppression withdrawal in a transplanted patient returning to chronic dialysis. *Nephrol Dial Transplant* 1998;**13**:3280–3281.
8. Quack I, Woznowski M, Schieren G, Weiner S, Winnekendonk G, Tokmak F, *et al.* Hypercalcemia after transplant nephrectomy in a hemodialysis patient: a case report. *J Med Case Rep* 2007;**1**:164.