

‘Tiger woman sign’ hypercalcaemia: a diagnostic challenge

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ABSTRACT

Hypercalcaemia is a common electrolyte abnormality with 90% of cases due to either primary hyperparathyroidism or malignancy. Other causes of hypercalcaemia often require careful consideration. We describe an approach to the assessment of hypercalcaemia, particularly where preliminary tests are inconclusive.

This approach is illustrated by a case which posed a diagnostic challenge: a patient with significant hypercalcaemia due to acute atypical isolated sarcoid myositis. This case highlights an under-recognised clinical syndrome with distinct biochemical and radiological findings.

KEYWORDS: hypercalcaemia, sarcoidosis, PET

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Case presentation

A 57-year-old woman presented with a 4-week history of thirst and lethargy. She also reported multifocal aches and pains in areas including the neck, shoulders, ribs and hips which were worse with movement. Systemic enquiry was unremarkable.

The patient had no pre-existing medical issues. She was a smoker with an approximate 30 pack-year history and drank minimal alcohol. The patient took paracetamol for pain only and had no allergies. There was no significant family history.

Examination was unremarkable. Specifically, there was no lymphadenopathy or hepatosplenomegaly. No rashes, obvious synovitis, muscle tenderness or weakness were identified. There were no signs of recent weight loss or cachexia. Blood pressure was slightly elevated at 153/97 mm/Hg but all other observations were within normal range, including blood glucose.

Initial investigations revealed elevated calcium (2.92 mmol/L) with an acute kidney injury (creatinine 134 µmol/L from baseline 75 µmol/L). The calcium had not been checked previously. Parathyroid hormone (PTH) was suppressed (0.7 pmol/L). Thyroid function was normal. Myeloma screen was negative. Chest X-ray

(CXR) was normal with no hilar lymphadenopathy, infiltrates or masses. Electrocardiography showed a normal sinus rhythm with no acute changes.

Diagnosis

The investigation of hypercalcaemia starts with a thorough history and examination. Classic symptoms of hypercalcaemia include lethargy, constipation, polydipsia, polyuria and bony aches. A history suggestive of an underlying malignancy should be explored. Family history is important as genetic causes include familial hypocalcaemic hypercalcaemia and a comprehensive drug history should be sought for drugs including lithium and thiazide diuretics. Clinical signs of hypercalcaemia are uncommon but a general examination to look for signs of an underlying malignancy and an assessment of fluid balance is important.

Initial investigation should include calcium (adjusted for albumin), biochemical profile (renal, phosphate and liver function), thyroid stimulating hormone (TSH), full blood count and PTH. An elevated (or inappropriately normal) PTH is suggestive of primary hyperparathyroidism. Tertiary hyperparathyroidism should be considered in patients with chronically low estimated glomerular filtration rate.

If the PTH is suppressed, then screening for myeloma, with plasma and urine electrophoresis, should be considered. If this is negative then imaging to identify a malignancy is required, often starting with a computed tomography (CT) of the thorax, abdomen and pelvis. Blood samples for 1,25(OH)₂D should be considered if sarcoidosis is suspected.

A proposed approach to the initial investigation of hypercalcaemia is set out in Fig 1.

Case progression and outcome

In this case, calcium levels increased further despite rehydration, peaking at 3.24 mmol/L. A CT of the thorax, abdomen and pelvis was undertaken but no abnormal findings were identified.

Further imaging with positron emission tomography (PET) was therefore performed to exclude an occult malignancy. No focal mass was noted but there was diffuse uptake in a number of muscle groups. Creatinine kinase (CK) levels were, however, normal.

Despite the normal CXR and CT results, a serum angiotensin-converting enzyme (ACE) and 1,25(OH)₂D levels were requested. These both returned as elevated. A muscle biopsy was performed showing non-caseating granulomas confirming a diagnosis of systemic sarcoidosis with primary muscle involvement.

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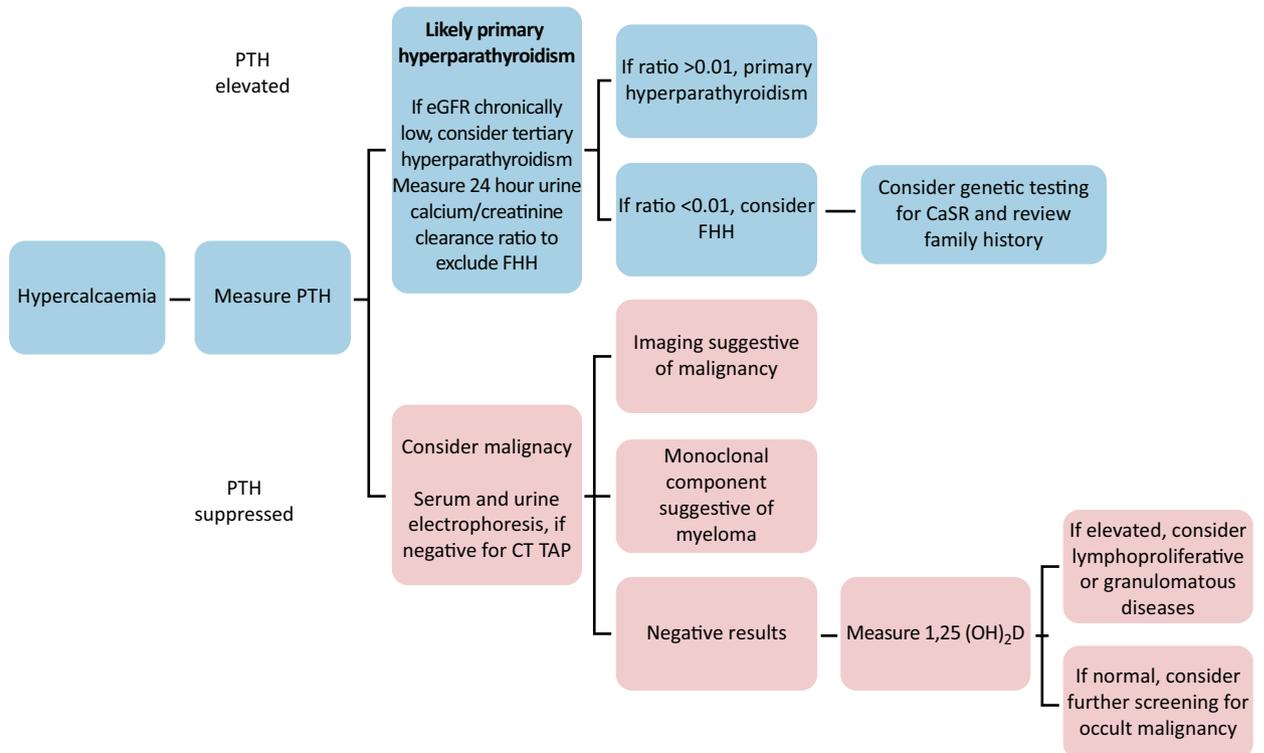


Fig 1. A proposed approach to the initial investigation of hypercalcaemia. CT = computed tomography; FHH = familial hypocalcaemic hypercalcaemia; CaSR = calcium sensing receptor; eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone; TAP = thorax, abdomen and pelvis.

Once a diagnosis of sarcoidosis was confirmed, the patient was initiated on 40 mg once per day of prednisolone and subsequently 20 mg weekly of methotrexate was added.

The patient's serum calcium level quickly normalised following treatment and symptoms began to resolve.

Discussion

Sarcoidosis is a multisystem granulomatous disease of unclear aetiology. Muscle involvement is described in around 80% of patients with sarcoidosis.¹ However, clinically significant myositis is

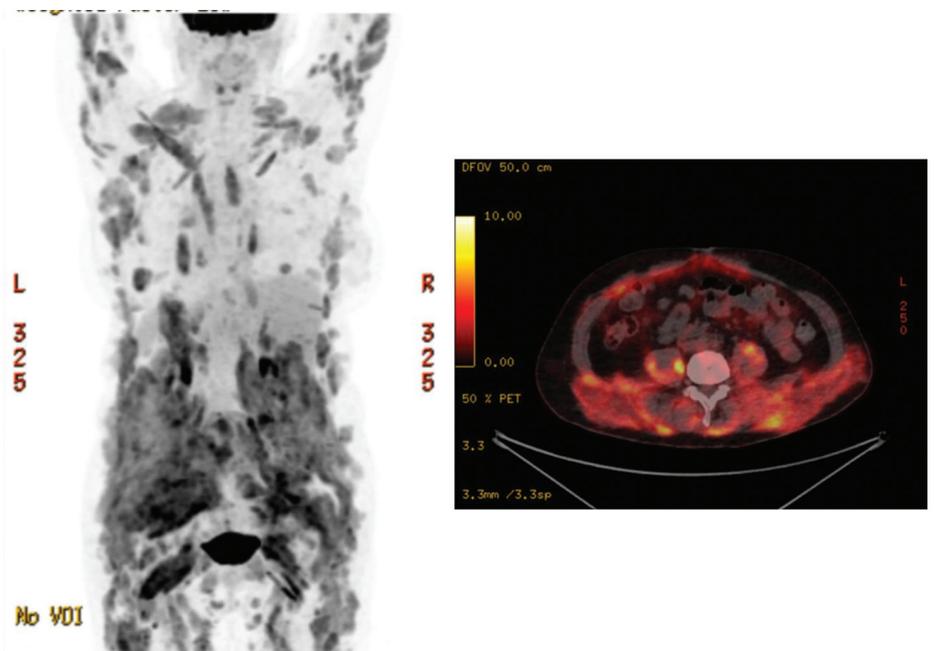


Fig 2. Positron emission tomography showing diffuse fluorodeoxyglucose uptake isolated to muscles. This pattern of uptake is characteristic of sarcoid myositis and coined as 'tiger man sign'.

uncommon, accounting for around 0.5% of cases and is seldom a presenting symptom.¹

Sarcoid myositis is typically classified as one of three types: chronic, nodular and acute. Chronic sarcoid myositis is slow and progressive in nature leading to a bilateral proximal myopathy and typically has a poor response to steroids. Nodular sarcoid myositis is characterised by palpable nodules, often associated with pain but rarely weakness. The rarest manifestation, acute sarcoid myositis, is typified by acute onset muscle pain and weakness, mimicking the presentation of acute polymyositis. Acute sarcoid myositis is classically associated with raised CK levels and often responds dramatically to steroid therapy.²

Calcitriol-mediated hypercalcaemia is a well-known complication of sarcoidosis.³ Moderate to severe hypercalcaemia, however, is detected in less than 5% of patients. Furthermore, isolated sarcoid myositis is not thought to be typically associated with hypercalcaemia.³ Hypercalcaemia associated with sarcoidosis is mostly the result of increased absorption of intestinal calcium due to increased 1,25(OH)₂D production by granuloma macrophages. Glucocorticoids are the mainstay of treatment for hypercalcaemia associated with sarcoidosis, working by inhibition of 1- α -hydroxylase activity in macrophages.³

In this case, our patient presented with significant hypercalcaemia secondary to isolated muscular sarcoidosis which is very uncommon. Interestingly, although the patient had generalised aches, she did not present with the classical descriptions of sarcoid myositis (acute onset muscle pain and weakness) and had a normal CK.

A recent literature review revealed only eight published cases of hypercalcaemia associated with acute isolated sarcoid myositis.⁴ In these cases, like ours, myositis was not initially suspected due to the non-specific symptoms and normal CK. All of the patients in this case series had PET performed for malignancy screening incidentally revealing intense, diffuse fluorodeoxyglucose (FDG) uptake isolated to muscles highlighting the utility of PET in this scenario. The PET in our case showed characteristic uptake in various muscles which has previously been described as characteristic for sarcoid myositis and coined 'tiger man sign'.⁵ All of the patients reported were treated with steroids, with all but one achieving rapid, complete and sustained remission.⁴

This case highlights the unusual presentation of hypercalcaemia associated with an isolated sarcoid myositis. This case, and others highlighted previously, seem to suggest a distinct clinical

syndrome from those that are classically described. PET seems to be of particular utility in the recognition of this condition and may be useful in monitoring treatment response.⁴ Hypercalcaemia associated with acute isolated sarcoid myositis appears to be highly responsive to steroids.⁴

Key points

- > Hypercalcaemia has a variety of causes, the most common being primary hyperparathyroidism which is diagnosed with a raised calcium in the context of a raised (or inappropriately normal) PTH.
- > In the context of a suppressed PTH, malignancy is the most common cause of the hypercalcaemia.
- > PET may be useful where initial investigations are inconclusive. The tiger man sign on PET is suggestive of sarcoid muscle involvement.
- > Acute isolated atypical sarcoid myositis associated with hypercalcaemia is a rare and under-recognised clinical entity.
- > Glucocorticoids are the mainstay of treatment in hypercalcaemia associated with sarcoidosis, including acute isolated atypical sarcoid myositis associated with hypercalcaemia. ■

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