Unusual association of diseases/symptoms

Hypergammaglobulinemia, normal serum albumin and hypercalcaemia: a case of systemic sarcoidosis with initial diagnostic confusion

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Summary

A 53-year-old Afro-Caribbean woman presented to casualty with a constellation of symptoms pointing to a diagnosis of hypercalcaemia. This was confirmed on laboratory investigation. Findings of a raised serum protein (108 g/l) and normal albumin (35 g/l), lead to an initial working diagnosis of multiple myeloma. However, later serum protein electrophoresis found a polyclonal gammopathy and further investigation lead to a diagnosis of sarcoidosis. The patient responded well to conventional treatment with oral prednisolone. A number of learning points have been highlighted including the pitfalls of pattern recognition in diagnosis and the various manifestations of systemic sarcoidosis. A brief review of the history and various manifestations of sarcoidosis including the pathophysiology of hypercalcaemia in sarcoidosis are presented as well as of polyclonal gammopathy.

BACKGROUND

Hypercalcaemia is a common cause for presentation to the medical take with a wide differential diagnosis. Identifying the aetiology can be challenging and requires understanding of the complex conditions that present with this electrolyte abnormality. When relying on pattern recognition or 'non-analytic reasoning' this can lead to further challenge and even play a role in diagnostic error. We present here, the case of a patient with hypercalcaemia, raised serum protein and normal albumin, and highlight a number of learning points for the hospital physician.

CASE PRESENTATION

A 53-year-old Afro-Caribbean woman presented to casualty with vomiting and a 2-week history of constipation. Over the previous month she had developed an itchy rash

on her back. A history of lethargy, hair loss and episodes of itchy eyes over the past 6 months was also elicited. Loss of weight and low mood were noted, although the patient attributed this to the recent death of a relative. Medical history included hypertension, diabetes mellitus, cerebrovascular disease and Raynaud's disease.

Physical examination revealed cervical lymphadenopathy and hepatomegaly. The patient had a nodular rash with crops of lesions over the upper back without any alteration in pigmentation (figure 1). Per rectal examination did not reveal an obstructive cause for her constipation.

INVESTIGATIONS

Chest radiograph was normal, and abdominal radiograph revealed faecal loading. The most striking biochemical abnormality on admission was an elevated corrected

Figure 1 Photograph of the patient's upper back showing nodular lesions in crops.

calcium (4.00 mmol/l) along with elevated urea (14 mmol/l), creatinine (173 µmol/l), alkaline phosphatase (233 IU/l), γ-glutamyl transpeptidase (407 IU/l), erythrocyte sedimentation rate (102 mm/h), C reactive protein (14 mg/l) and serum protein (108 g/l). Serum albumin was normal (35 g/l). A 12-lead ECG demonstrated left axis deviation and left ventricular hypertrophy. Treatment of the hypercalcaemia was commenced with intravenous fluids followed by intravenous bisphosphonate infusion.

In the light of her clinical presentation, an initial diagnosis of myeloma was considered, with secondary hypercalcaemia accounting for her presenting symptoms. Serum immunoglobulin electrophoresis and urine analysis were undertaken. These however, showed polyclonal proliferation (IgA and IgG) and blood and protein (but not Bence Jones protein) in the urine, not in keeping with myeloma. Hypercalciuria was unfortunately not tested for in the acute stage.

Granulomatous disease was then considered. Serum ACE was found to be elevated at 255 IU/l. A high resolution CT scan of the chest demonstrated bilateral hilar, pretracheal and subcarinal lymphadenopathy and peribronchiolar nodularity throughout both lungs, more so in the upper lobes. A small pericardial effusion was also seen. Bronchoscopy and transbronchial biopsy showed well-formed granulomas with multi-nucleate giant cells with no necrosis, suggesting a likely diagnosis of systemic sarcoidosis. She was commenced on 40 mg prednisolone daily and advised on a reducing dose regime with good effect.

DISCUSSION

Sarcoidosis is a granulomatous disorder that can have a variety of presentations. It was first noted in 1877 by Sir Jonathan Hutchinson who described the case of a gentleman who presented with purple symmetrical skin plaques on his legs and hands.¹ He referred to the ailment as 'livid papillary psoriasis.' In 1899 the term 'sarkoid' was coined by Cesar Boeck who likened the lesion to sarcoma, hence the name.

Most often associated with pulmonary involvement, sarcoidosis can also affect many, if not all, other body systems. The array of presenting complaints can lead to diagnostic difficulty and prolonged investigation, as in our patient.² In addition to the systemic effects of hypercalcaemia our patient exhibited cutaneous, pulmonary, gastrointestinal, haematological and possibly cardiac manifestations of sarcoidosis.

Hypercalcaemia is a well-recognised complication of sarcoidosis.³⁻⁴ Clinical manifestations of hypercalcaemia include altered mental state, polyuria, constipation and vomiting. It arises in part, from the increased production of 1, 25(OH) 2D (calcitriol) by activated macrophages and sarcoid granulomas, that have increased intrinsic 1 α-hydroxylase activity.⁵ Calcitriol is the active form of vitamin D and acts to increase serum calcium by increasing intestinal absorption, renal reabsorption and bone resorption. Hypercalciuria is also known to occur in sarcoidosis and prolonged exposure may lead to nephrocalcinosis with resultant renal dysfunction.⁶

Management of hypercalcaemia in sarcoidosis involves intravenous fluid administration (to correct dehydration and provide renal protection) and intravenous bisphosphonate

(eg, pamidronate) in severe cases. The use of corticosteroids in this setting is thought to be beneficial through inhibition of 1 α-hydroxylase in activated macrophages.⁷ Loop diuretics (eg, frusemide) also promote renal excretion of calcium. Ketoconazole has also been shown to decrease calcitriol in sarcoidosis,⁸ but is rarely used.

Vomiting and constipation in our patient's case were most likely a result of hypercalcaemia than other gastrointestinal involvement. Sarcoidosis in this setting is often asymptomatic with derangement of liver function tests and hepatosplenomegaly, which were both noted in our patient's case.

Cutaneous sarcoidosis is reported to occur in up to 30% of patients.⁹ Crops of small papular lesions were present on our patient's upper back (figure 1). The lesions were not biopsied on this occasion. However, it should be noted that thorough examination of the skin and subsequent biopsy can aid in the early diagnosis of sarcoid, providing a visible clue to the often atypical and non-specific presentation of this disorder. It has been deemed a dermatologic masquerader due to its multitude of cutaneous manifestations.¹⁰ Other cutaneous manifestations include erythema nodosum (tender erythematous nodules most often on the tibia) and lupus pernio (violaceous plaques most often around the nose).

Our patient did not exhibit any respiratory symptoms. However, her CT scan highlighted the common bilateral hilar lymphadenopathy associated with sarcoidosis. Lung involvement is the most common manifestation of sarcoidosis, reported in up to 90% of patients. Lofgren syndrome is an acute variant of sarcoidosis comprising a triad of bilateral hilar lymphadenopathy, erythema nodosum and arthritis.

In our case, diagnostic confusion arose from the haematological manifestation of hypergammaglobulinemia. Unlike the afore mentioned presentations, which are commonly discussed with respect to sarcoidosis, the polyclonal gammopathy associated with sarcoidosis may lead clinicians, as it did in our case to consider a diagnosis of multiple myeloma. The constellation of raised serum protein, ESR and calcium with normal albumin pointed to diagnosis of multiple myeloma. However, myeloma is a monoclonal gammopathy. Yet this can only be shown following protein electrophoresis. This diagnostic confusion has been previously reported in the literature.¹¹ Hyperglobulinaemia was reported by Professor H A Salvesen in 1935 in three patients with sarcoidosis. IgG, IgM and IgA are the most common immunoglobulins. Kataria *et al* have conducted a number of studies looking at the presence of immunoglobulins in patients with sarcoidosis and found levels to be raised more often in African than Caucasian subjects.¹² The presence of elevated IgM and IgA has been stipulated to be associated with acute disease while IgG with chronic disease.¹³

Polyclonal gammopathy is seen in a number of clinical conditions. In a retrospective cohort study (n=148) from the Mayo clinic, liver disease was the most common pathology associated with polyclonal hypergammaglobulinemia. This was followed by connective tissue disorders, chronic infection, haematologic disorders and non-haematologic malignancies.¹¹ The cause of polyclonal hypergammaglobulinemia is yet to be elucidated but is thought to be the result of immune system dysregulation and chronic

stimulation. IL-6, IL-10, various cytokines and T cell dysfunction have been implicated. An interesting observation made in the literature is the increased susceptibility of blacks to harbouring a polyclonal gammopathy.¹¹ This supports the earlier finding by Kataria.

Finally, our patient exhibited possible cardiac involvement by sarcoidosis with the presence of pericardial effusion on CT. Cardiac manifestations of sarcoidosis are more often electrophysiological with conduction defects which can lead to heart failure and arrhythmia. Recurrent pericardial effusions have also been reported.

CONCLUSION

The case highlights the multi-systemic nature of sarcoidosis. Greater awareness of the variety of presenting features may lead to earlier diagnosis and treatment. The association of polyclonal gammopathy is also highlighted and awareness of its occurrence in a variety of disorders including sarcoidosis may avoid confusion with multiple myeloma or other haematological malignancies.

Learning points

- ▶ Polyclonal gammopathy is a less well-recognised feature of systemic sarcoidosis, highlighting the immune dysregulation that occurs in this disorder; its presence should make clinicians consider the diagnosis.
- ▶ Polyclonal gammopathy is most commonly associated with: chronic liver disease, connective tissue disorders, infection and haematological disorders.
- ▶ Sarcoidosis can affect any body system and as such, a thorough history including systems review is very important.
- ▶ Biopsy of skin lesions in atypical cases may be helpful in making the diagnosis.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Nageshwaran S, Majumdar K, Russell S. Hypergammaglobulinemia, normal serum albumin and hypercalcaemia: a case of systemic sarcoidosis with initial diagnostic confusion. *BMJ Case Reports* 2012;10.1136/bcr.01.2012.5478, Published XXX

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