An elderly man with confusion, hypercalcaemia and acute renal failure—an important diagnosis not to miss

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Keywords: acute renal failure; granulomatous interstitial nephritis; hypercalcaemia; sarcoidosis

Introduction

The commonest causes of hypercalcaemia in an elderly man include: multiple myeloma, hyperparathyroidism, bony metastases and humoral hypercalcaemia of malignancy. Other less common causes include hyperthyroidism, sarcoidosis, vitamin D excess, Addison’s disease and drugs (especially thiazide diuretics). Acute renal failure may be caused by several of the diseases listed or may be as a consequence of the hypercalcaemia itself.

Case report

A 71-year-old Caucasian man presented via his general practitioner to the general medical outpatients with a 6-month history of systemic symptoms. He complained of lethargy, nausea and 10 kg weight loss over the last 4 months. His wife had also noted that he was becoming increasingly confused and was suffering from short-term memory loss. He was also currently under the urologists for prostatic symptoms with a raised prostatic specific antigen (PSA) of 31.6 μg/l (normal range <4.0 μg/l) and a malignant feeling prostate gland on rectal examination although prostatic biopsies were entirely benign. Two months earlier his creatinine was 234 μmol/l (normal range 50–110 μmol/l). He had stopped smoking over 25 years ago and occasionally drank alcohol. Physical examination revealed an elderly gentleman. His pulse rate was 60/min and blood pressure 160/100 mmHg. There were no abnormal findings other than an irregular, enlarged prostate gland. A chest X-ray was normal. A full blood count revealed: haemoglobin 10.4 g/dl (normal range 12–16 g/dl); white cell count 5.7 × 10⁹ (normal range 4–11 × 10⁹/l); platelet count 309 × 10⁹/l (normal range 150–400 × 10⁹/l). Blood chemistry showed a normal sodium (142 mmol/l (normal range 135–145 mmol/l)) and potassium (4.5 mmol/l (normal range 3.5–5.0 mmol/l)) but a raised urea (35.6 mmol/l (normal range <8 mmol/l)) and serum creatinine (647 μmol/l). The only other abnormal result was a serum calcium concentration of 2.87 mmol/l (normal range 2.20–2.65 mmol/l).

A renal ultrasound was performed which showed both kidneys were of normal size, shape and echogenicity and that there was no dilatation of the pelvicalyceal system. Urinalysis revealed blood 2+, protein + and glucose + and urine microscopy revealed no red blood cells, a few white blood cells, no organisms and some granular casts. A renal biopsy was performed as shown in Figure 1, which showed foci of lymphocytic tubulitis and a mild mononuclear interstitial infiltrate.

Fig. 1. Renal biopsy showing foci of lymphocytic tubulitis and a mild mononuclear interstitial infiltrate.

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lymphocytic tubulitis and a mild mononuclear interstitial infiltrate. There were several discrete non-necrotizing epithelioid granulomata comprised of epithelioid macrophages and Langerhans-type giant cells. Ziehl–Neelsen staining for acid-alcohol fast bacilli was negative and there was some focal peri-tubular interstitial calcification. A histological diagnosis was made of acute on chronic granulomatous interstitial nephritis with nephrocalcinosis. The differential diagnosis included systemic infections such as tuberculosis, drug hypersensitivity and sarcoidosis. On further questioning the patient denied any drug use. The patient had a computed tomography (CT) scan of his chest, which showed some calcified mediastinal lymph nodes between the trachea and the aorta. There were also some intra-pulmonary nodules scattered throughout the upper and lower lobes diffusely without any apparent perivascular or peri-septal association. A CT scan of the head was also performed in view of his confusion and memory loss but this was normal. A negative Mantoux test was obtained on two occasions and a Gallium scan was performed, as shown in Figure 2. This demonstrated increased tracer uptake bilaterally in the hilar regions with further uptake in the parotids and also low level activity in the kidneys. The scan findings were consistent with sarcoidosis. A serum angiotensin-converting enzyme (ACE) level was 183 U/l (normal range 27–82 U/l). An autoantibody screen (anti-nuclear, smooth muscle, rheumatoid factor, Crithidia DNA, extractable nuclear antigen and anti-neutrophil cytoplasmic antibodies) was negative. Myeloma was excluded by way of a normal serum electrophoretic strip, a normal bone scan and no detectable urinary Bence–Jones proteins. A parathyroid hormone (PTH) level was appropriately suppressed at 10 ng/l (normal range 10–65 ng/l). A clinical diagnosis of sarcoidosis was made and the patient commenced 40 mg prednisolone/day orally.

Upon treatment, the patient’s condition rapidly improved. He began to gain weight and noted that his urine volumes were increasing. Both his mental state as well as his memory also improved. His serum calcium fell within 1 week of starting treatment. Subsequently, his serum ACE fell to 56 U/l and his calcium to 2.45 mmol/l within 6 weeks of commencing the steroid course. Within 3 months of starting the prednisolone his urea had gone from 33.0 to 13.3 mmol/l and serum creatinine had fallen from 736 to 198 μmol/l. At 6 months his serum creatinine is 164 μmol/l and he is maintained on 10 mg prednisolone/day.

Discussion

Sarcoidosis is a multi-system disorder of unknown aetiology. It can occur at any age but is uncommon under 15 or over 65 years. It is characterized by non-caseating granulomas [1]. Patients usually present with respiratory, skin or ocular involvement. However, virtually any organ system can be involved in sarcoidosis including the joints, kidney, liver, gastrointestinal tract, heart and nervous system.

A variety of functional and structural renal disorders may be associated with sarcoidosis. The incidence of renal involvement is unknown, as it is often silent though studies suggest that more than 50% of patients with sarcoidosis have a clinical abnormality [2]. Hypercalcaemia, nephrocalcinosis, granulomatous interstitial nephritis and glomerular disease may all occur with sarcoidosis.

Hypercalcaemia occurs in up to 10–15% of patients. This may cause abnormal glomerular or tubular function, nephrocalcinosis or nephrolithiasis (10% of cases) [1]. Macrophages within sarcoid granulomas contain the enzyme 1-alpha hydroxylase that is responsible for activating vitamin D to form excess levels of calcitriol, which subsequently cause hypercalcaemia [3]. This phenomenon is not unique to sarcoidosis as it occurs
in other granulomatous disorders associated with hypercalcaemia [4].

Granulomatous interstitial nephritis (GIN) is a rare condition. There are a number of causes including infection (mycobacterial, fungal and bacterial), drugs (including antibiotics, non-steroidal anti-inflammatory drugs, diuretics, etc.), sarcoidosis, berylliosis, Wegener’s granulomatosis and hyperoxalosis [5]. The actual prevalence of GIN in sarcoidosis is uncertain as it is often clinically silent and figures vary between 15 and 40%. This probably represents the differing opinions to the need for renal biopsy in patients with sarcoidosis. Granulomatous interstitial nephritis may occur as the only manifestation of sarcoidosis as in this case or it may appear simultaneously with multiorgan involvement [6].

The treatment of choice for both hypercalcaemia and GIN is glucocorticoids. They act by blocking the extrarenal calcitriol synthesis by inhibiting the macrophage 1-alpha hydroxylase activity [1]. However, the duration of treatment varies between the two conditions, as the hypercalcaemic nephropathy will respond to a much shorter course of glucocorticoid. If treatment of GIN is for less than 6 months duration, it is frequently followed by a relapse of the nephropathy. On reviewing the literature there is no clear consensus as to the daily dosage of glucocorticoid recommended for GIN. Doses vary between 0.5 and 1.5 mg/kg body weight [7,9,10]. Méry et al. suggest that the dose be progressively tapered after 2 months and then switched to an alternate day regimen and that treatment should be at least for 9 months to 1 year [1]. Therefore, this highlights the importance of renal biopsy in sarcoid patients with abnormal renal function to confirm the presence or absence of GIN so the correct duration of therapy can be determined. Our patient responded almost immediately to the glucocorticoids and therefore a significant proportion of his symptoms were likely to be due to his hypercalcaemia. The initial ACE level in our patient was contributory to the diagnosis of sarcoidosis and after treatment was commenced it fell. However, previous studies have shown that raised serum ACE levels are not reliable in establishing the diagnosis but are more useful in following the clinical course [8]. This was in both patients undergoing spontaneous remission and those being treated with prednisone.

**Teaching point**

Sarcoidosis should be considered as a potential diagnosis in any patient with hypercalcaemia and acute renal failure, and a biopsy performed if other obvious causes such as myeloma, carcinoma with secondary metastases and primary hyperparathyroidism have been excluded.

**References**