Consider sarcoidosis in patients with nephrocalcinosis, even if the chest roentgenogram is normal

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Introduction

Sarcoidosis is considered to be a chronic pulmonary disease which occasionally involves other organ systems, including lymph nodes, the eye, the nervous system, the kidneys, the gastrointestinal tract, the heart, and the skin. A normal chest roentgenogram occurs in less than 5% of patients. Hypercalcaemia may occur in 10–20% of patients, but these patients almost invariably have pulmonary involvement, since activated pulmonary macrophages are responsible for the increased production of 1,25(OH)2D. We recently encountered a patient who exhibited almost all the rare manifestations of sarcoidosis, including nephrocalcinosis, in the face of a normal chest roentgenogram. Although sarcoidosis is responsible for about 0.2% of patients with hypercalcaemia and 2.5% of patients with hypercalciuria, the presence of renal tubular acidosis (RTA) is unusual.

Case report

The patient is a 23 year old man who was referred because of nephrocalcinosis. He had noted fatigue, vague abdominal discomfort, and episodes of headache with vomiting. He also reported a 12-kg weight loss in the past year. The patient denied fever, night sweats, or pulmonary symptoms. He had experienced nocturia approximately twice nightly but had not passed kidney stones. An internist performed an outpatient gastroscopy a year prior to admission and diagnosed gastritis and duodenitis; the histology showed epithelioid cell granulomas with giant cells. Because of a positive helicobacter test a course of antibiotics was prescribed which resulted in some, but not complete improvement in the gastrointestinal symptoms. His blood pressure, pulse, respiratory rate, and body temperature were normal. A 2-cm diameter movable lymph node was palpable at the right angle of the jaw; however, the parotid gland was neither tender nor enlarged. Shotty, smaller nodes were palpable in the axillae and both inguinal regions. Heart and lungs were unremarkable and the liver and spleen were not enlarged. Neurologically, he was slowed, his gait was broad based and he tended to be unstable with heel-toe walking. Funduscopic examination disclosed chororetinitis.

Laboratory evaluation revealed haemoglobin 9 mmol/l, haematocrit 0.37, white count 3.9 × 109/l. He had a marked lymphopenia of 0.09 × 109/l. His erythrocyte sedimentation rate was 60 mm/h, while the C-reactive protein was normal. A tuberculin and a tetanus toxoid skin test were negative despite immunizations for both. A urinalysis revealed trace protein with a normal urinary sediment. The urine pH was 6.5–7.0. The creatinine was 135 μmol/l; the electrolytes were Na 138, K 4.3, Cl 101, and HCO3 24 mmol/l respectively. The serum calcium concentration ranged between 2.5 and 2.8 mmol/L with phosphate values in the normal range. The parathyroid hormone (PTH) level was low at 5 pg/dl; the 1,25(OH)2D concentration was at the upper limits of normal at 56 ng/ml. Liver function tests, including alkaline phosphatase were normal. A serum angiotensin-converting enzyme (ACE) level was 1392 nkat/l, which is twice the level of normal for our laboratory.

The chest roentgenogram was normal (Figure 1), as was a lung computerized tomogram (CT). A roentgenogram of the abdomen demonstrated bilateral nephrocalcinosis (Figure 1). A magnetic resonance imaging (MRI) study disclosed communicating hydrocephalus with enhancement along the leptomeninges and subependyma (Figure 2). A lumbar puncture revealed an opening pressure of 27 cm H2O. The albumin content was elevated at 1.7 g/l and a pleocytosis (2.7 × 106 l) of 0.79 lymphocytes and 0.16 monocytes was found. An MRI scan of the abdomen

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showed bilateral para-aortic lymph node enlargement extending from the diaphragm to the aortic bifurcation. A 24-h urine collection revealed a calcium excretion 7.9 mmol/24 h. We tested for incomplete RTA by first administering ammonium chloride in sufficient amounts to lower the serum bicarbonate to 21 mmol/l. However, the patient’s urinary pH remained above 5.5. We next gave sodium bicarbonate to alkalinize the urine up to pH 7.7. Under these conditions, his urinary pCO$_2$ was 53 mmHg, while his blood pCO$_2$ was 41 mmHg.

A bone marrow aspirate showed no evidence of an infiltrative process. We then performed a fine-needle aspiration under CT guidance to obtain tissue from one of the enlarged para-aortic lymph nodes. The large node at the right jaw angle was also excised. Both nodes showed evidence of inflammation with confluent epithelioid cell granulomas and giant cells with Schaumann bodies, consistent with sarcoidosis (Figure 3). Cultures of cerebrospinal fluid, urine, and sputum after saline nebulization revealed no growth. A diagnosis of sarcoidosis was made and corticosteroids were begun. At 3 months, he had gained weight, was no longer hypercalcemic, and his symptoms of headache and listlessness had improved. His serum creatinine value also decreased to 101 µmol/l; the erythrocyte sedimentation rate, ACE activity, and parathyroid hormone level were in the normal range.
Fig. 2. T1-weighted magnetic resonance imaging (MRI) scan of the head. The cerebral ventricles are dilated. The leptomeninges (arrows) show granular contrast enhancement consistent with inflammation.
Fig. 3. a,b. a, H & E sections from a cervical lymph node; a, evidence of inflammation with confluent, non-caseating, epithelioid cell granulomas; b, multinucleated giant cells (left arrow) containing Schaumann bodies (right arrow). Size markers indicate 200 μM and 50 μM respectively.
Discussion

Our patient exhibited several unique abnormalities including nephrocalcinosis with incomplete distal renal tubular acidosis, chronic aseptic meningitis with communicating hydrocephalus, chorioretinitis, and granulomatous gastritis. In spite of this clinical constellation, his sarcoidosis featured a normal chest roentgenogram, which underscores the fact that alveolar macrophages are not the only source of increased 1,25(OH)₂D, and that macrophages in granulomas elsewhere in the body must also be responsible. We reported a hypercalcaemic, anephric, dialysis patient earlier who proved to have sarcoidosis in view of normal chest roentgenogram [1]. This patient, and our present case, had increased serum ACE levels. ACE is also produced by activated macrophages and has been suggested as a disease activity marker; however, ACE appears less reliable than a serum 1,25(OH)₂D level that fails to decrease with oral calcium loading. Basile et al. [2] showed that oral calcium loading in normal persons results in a prompt decrease in 1,25(OH)₂D, whereby no such decrease occurred in patients with sarcoidosis. Our patient had low PTH values in the face of hypercalcaemia. His 1,25(OH)₂D level was in the high normal range for our laboratory, but nevertheless, inappropriate for his calcium level and his PTH values.

We elected not to perform a renal biopsy on our patient, since we were able to make the diagnosis on the basis of lymph-node biopsy. Renal stones are present in 10%, nephrocalcinosis in 5%, and also tubular damages as nephrogenic diabetes insipidus have been described. We were able to show that our patient had distal RTA, since he was unable to acidify his urine with acid loading and was also unable to excrete sufficient hydrogen ions to raise his urinary pCO₂ to > 70 mmHg in the face of an alkaline urine. Our patient actually had a normal serum HCO₃⁻ on admission to the hospital, so that he must be viewed as having incomplete RTA. RTA is not common in sarcoidosis; however, both distal and proximal RTA have been described [4]. Whether or not the tubular dysfunction is related to granuloma activity, circulating immune globulins, or to hypercalcaemia and hypercalciuria is not clear. Hypercalciuria and vitamin D excess are both known causes of distal RTA and were probably responsible for the condition in our patient [5]. We have not retested our patient under steroid therapy, to see if his ability to maintain a hydrogen ion gradient has improved.

Neurologic manifestations are not common in sarcoidosis; however, when they occur they may be dramatic [6]. Such was the case in our patient, who presented with chronic aseptic meningitis, communicating hydrocephalus, and signs of increased intracranial pressure. Ocular involvement was also present in our patient. He did not present with classical uveoparotid fever, since his parotid gland was unremarkable. Sarcoidosis of the stomach, duodenum, and jejunum has been described, resulting in ulcer disease and gastrointestinal bleeding [7].

In summary, our patient presents a broad spectrum of rare manifestations attributed to sarcoidosis. Granulomatous gastritis, chronic meningitis with communicating hydrocephalus, chorioretinitis, nephrocalcinosis, and incomplete distal renal tubular acidosis, were all present in our patient even though his chest roentgenogram was normal. Sarcoidosis must be considered in the differential diagnosis of nephrocalcinosis with hypercalcaemia even if the chest roentgenogram is normal.

References


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