Sarcoidosis, Hypercalcemia and Calcium-sensing Receptor Mutation: A Case Report

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Sarcoidosis is a multisystem granulomatous disease of unknown aetiology. It predominantly affects the lungs; however, 25% of patients have skin involvement, ranging from non-specific maculopapular eruptions to erythema nodosum and lupus pernio (1).

Familial hypocalciuric hypercalcaemia (FHH) results from an autosomal dominantly inherited inactivating mutation of the calcium-sensing receptor (CaSR) gene and is typically asymptomatic (2). Sarcoidosis has not previously been reported in FHH. We had the opportunity to study a patient with sarcoidosis that has a CaSR mutation.

CASE REPORT

A 70-year-old woman was referred by her endocrinologist with suspected sarcoidosis on the background of FHH diagnosed in 2006. She was heterozygous for a TGC-CGC nucleotide change that predicts an alteration of cysteine to arginine at codon 765 (C765R).

On examination erythematous patches were seen on the right side of the patient's forehead and nose, small plaques on her knees, and multiple firm subcutaneous mobile nodules on the dorsum of both hands and elbows.

An excisional biopsy of a subcutaneous nodule showed a nodular lesion composed of dense fibrous tissue with clusters of epithelioid histiocytes in the subcutis. There was mild lymphocytic infiltratation, a few multinucleated giant cells, and a few clusters of histiocytes. No caseating necrosis, foreign body, calcification or atypia were observed. No fungal elements or acid-fast bacilli were demonstrated on Alcian Blue and Periodic acid-Schiff (ABPAS) stains. The features were those of chronic sarcoidal granulomatous reaction and moderate fibrosis.

Blood tests included full blood count, renal and liver function tests, lipid profile, vitamin D, calcium, phosphate, parathyroid hormone (PTH) and angiotensin-converting enzyme (ACE), all of which were normal, except for calcium, which was 2.78 mmol/l (normal range 2.15–2.55 mmol/l). A bone density scan revealed osteopaenia, and a chest X-ray showed increased hilar size and superior mediastinal lymphadenopathy.

The patient had a good response to high-dose prednisone, but failed methotrexate, plaquenil, minocycline and doxycyline. She is currently on 10 mg oral prednisone.

DISCUSSION

In FHH, hypercalcaemia is a result of an abnormality of the gene encoding the CaSR. The CaSR functions by sensing small changes in circulating calcium concentration, and coupling this information to intracellular signalling pathways that modify PTH secretion or renal cation handling in the kidney. Hypercalcaemia results as calcium is trapped in the kidney (2).

The incidence of hypercalcaemia in patients with sarcoidosis is approximately 10% (3). It has previously been found that these abnormalities of calcium metabolism are due to dysregulated production of calcitriol by activated macrophages trapped in pulmonary alveoli and granulomatous inflammation (4). Conversion of calcidiol to calcitriol is facilitated by 1 alpha-hydroxylase, a cytochrome P450 enzyme. The activity of 1 alpha-hydroxylase is tightly regulated through complex mechanisms that depend on the circulating levels of calcium, phosphorus, PTH, 1,25 (OH)2D3 (calcitriol) and calcitonin. The role of CaSR in the regulation of 1 alpha-hydroxylase has not been defined, although there are suggestions that CaSR activation can repress the enzyme (5).

The incidence of FHH in patients with sarcoidosis is unknown. Considering that FFH is an asymptomatic condition, it is likely that it is underdiagnosed in the population. It may also be easily missed in sarcoidosis patients who have hypercalcaemia. Although there is clearly a link between sarcoidosis and hypercalcaemia, the role of CaSR in sarcoidosis is unknown. Our patient raises the issue of a connection between CaSR mutations and sarcoidosis. A further study assessing the prevalence of CaSR mutations or polymorphisms in sarcoidosis would be useful in understanding the mechanism regulating 1 alpha-hydroxylase, and the processes involved in the aetiology of sarcoidosis.

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