Sarcoidosis and primary hyperparathyroidism

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THE ETIOPATHOGENICAL RELATIONSHIP BETWEEN SARCOIDOSIS AND PRIMARY HYPERPARATHYROIDISM IS NOT YET FULLY DEFINED. THIS COEXISTENCE REMAINS RARE IN MEDICAL LITERATURE DESPITE THEIR RELATIVELY HIGH PREVALENCE. THEREFORE, THIS POTENTIAL ASSOCIATION SHOULD BE CONSIDERED IN THE DIFFERENTIAL DIAGNOSIS OF A PATIENT WITH SARCOIDOSIS PRESENTING SYMPTOMS OF HYPERPARATHYROIDISM.

IN THIS PAPER WE DESCRIBE THE CASE OF A PATIENT DIAGNOSED WITH SARCOIDOSIS WHO PRESENTED AN INITIAL EPISODE OF SYMPTOMATIC HYPERCALCEMIA SUCCESSFULLY TREATED WITH CORTICOIDS. AFTER REMAINING ASYMPTOMATIC FOR YEARS, HYPERCALCEMIA REAPPEARS IN SEVERAL TESTS. THE COMPLETE STUDY ON CALCIUM METABOLISM LEADS THE DIAGNOSIS TOWARD PRIMARY HYPERPARATHYROIDISM.

THIS CASE IS RELEVANT AS IT EMPHASIZES THE NEED TO AVOID ATTRIBUTING TO HYPERCALCEMIA A REACTION PROPER TO SARCOIDOSIS. THUS, IT IS INTENDED TO HIGHLIGHT THE NEED TO APPROACH DIFFERENTIAL DIAGNOSIS OF HYPERCALCEMIA INSTEAD OF ADMINISTERING A TREATMENT WITH CORTICOIDS.

SARCOIDOSIS, HYPERPARATHYROIDISM, HYPERCALCEMIA.

Introduction

Sarcoidosis is an inflammatory disease of unknown etiology. It causes non-caseating epithelioid granulomas, accumulation of T lymphocytes and macrophages, frequent lung disease, hilar lymph nodes and skin, eye and renal manifestations (4).

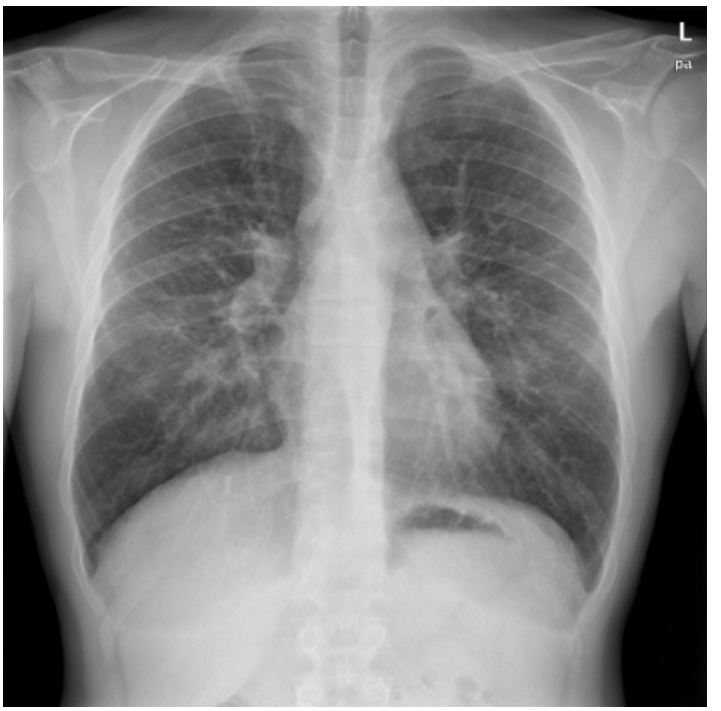
It has a worldwide distribution of unknown actual incidence, since it usually presents few symptoms in incidental scans. The estimated prevalence is 40 cases / 100,000 population in developed countries, being higher in young women.

The clinical course is variable and may resolve spontaneously. Manifestations may include increased absorption of calcium, as occurs in the present case, where symptomatic hypercalcemia is normalized after treatment with corticoids (3). Years later hypercalcemia is detected again, suspecting reactivation of the disease. A complete metabolic study reveals concomitant primary hyperparathyroidism, leading to radically changing the treatment.

The interest of this case lies in showing the importance of avoiding the tendency to initially diagnose hypercalcemia, approaching a differential diagnosis instead.

Presentation of case

42 year old male who complains of asthenia, polydipsia and polyuria. He refers only heat intolerance. No fever, dysthermia or any other relevant data. Several recent tests carried out by his general practitioner (GP) show persistent hypercalcemia. He is admitted to the Rio Hortega University Hospital (Valladolid) to be studied.



▲ **Figure 1**. *Radiography showing lung involvement and sarcoidosis granulomas.*

Physical examination only shows discrete data referring skin and mucus dehydration.

The blood test run after the admission shows biochemical alterations (normal range in brackets): serum creatinine of 3.2 mg/dL (0.9-1.3), calcium of 13.9 mg/dL (8.6-10), urea of 75.8 mg/dL (12.8-42.8). The urine analysis presents urea levels of 1448 mg/dL. On the 24-hour urine test hypercalciuria is detected. Thyroid hormones' levels are normal and parathormone intact molecule is practically undetectable (<5 pg/mL). Haemoglobin is 11.3 d/dL (13.2-16.8). Tumour markers are normal.

In further explorations, hilar and mediastinal adenopathies are visible using X-ray and are confirmed by CT scan.

The fibrobronchoscopy shows a lymphoid cellularity of 46%, 97% of which are CD3, 78% CD4 and 15% CD8, with CD4/CD8 of 5.2.

Transbronchial biopsy reveals non-caseating granulomas.

The abdominal echography demonstrates splenomegaly (maximum diameter of 14 cm) and nodular hypoecogenic diffuse echogenicity, consistent with secondary infiltration. Enhanced cortical echogenicity in both kidneys, consistent with nephropathy, is observed.

According to these results, the patient is diagnosed of state-II, active sarcoidosis, with hypercalcemia and secondary renal failure. Treatment with physiological saline, furosemide and corticoids is applied.

During the stay at the hospital, the patient shows clinical and analytical improvement, presenting the following levels before discharge: calcaemia 10.4 mg/dL, urea 60 mg/dL, creatinine 1.8 mg/dL and PTH 20.7 pg/mL (12-72).

The follow-up is carried on an out-patient basis. He keeps a treatment based on prednisone (70 mg a day) with a descending pattern for 3 months, omeprazole and enalapril (20 mg a day).

For years, the patient evolves well, without progression in his illness on neither radiology checks (X-ray and CT scan) nor functional tests (spirometry, CO diffusing capacity). Calcaemia levels stay at a normal range.

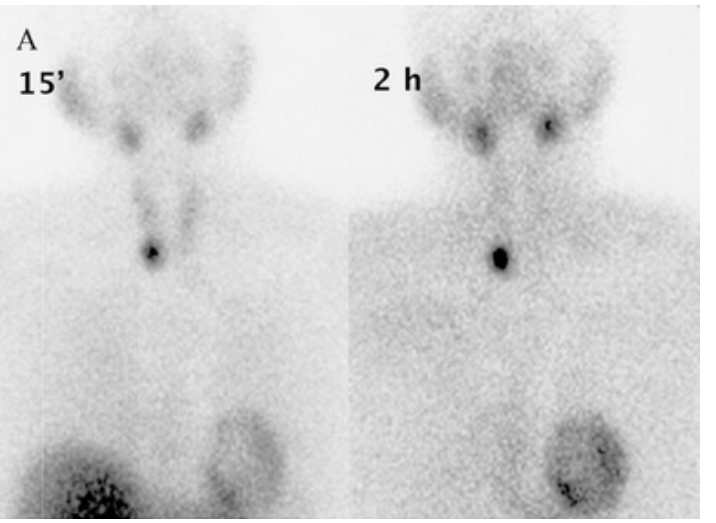
After 7 years asymptomatic, hypercalcaemia is found during a medical check, without accompanying symptoms.

The blood test shows high levels of calcaemia (10.18 mg/dL), ionic calcium (5.33 mg/dL) and calcium/creatinine index in 24-hour urine (249.8 mg/g), creatinine (12.244); it's preeminent the lack of suppression of parathyroid hormone (iPTH 128 pg/mL) (12-72); we find relatively normal levels of 25-OH-Vitamin D3: 26 mcg/L (30-80) and normal ones of serum angiotensin-converting enzyme.

Because of this, the diagnosis of primary hyperparathyroidism is considered.

A cervical and mediastinal study with 99mTc-MIBI and SPECT/CT is performed, finding a small round area, with mildly increased uptake, posterior to the inferior pole of the right thyroid lobe, giving the impression of a parathyroid adenoma. The study is completed with neck MRI (Magnetic Resonance Imaging) without contrast, that discloses an increase in the size of the right inferior parathyroid gland, as well as cervical and mediastinal adenopathies.

In a subsequent check, months later, calcaemia and serum ionic calcium remain elevated, with iPTH still very high. The treatment of choice is parathyroidectomy, extracting the parathyroid gland that contains the adenoma.



▲ **Figure 2**. *Scintigraphy with prolonged radiopharmaceuticals retention by right inferior parathyroid gland adenoma.*

Discussion

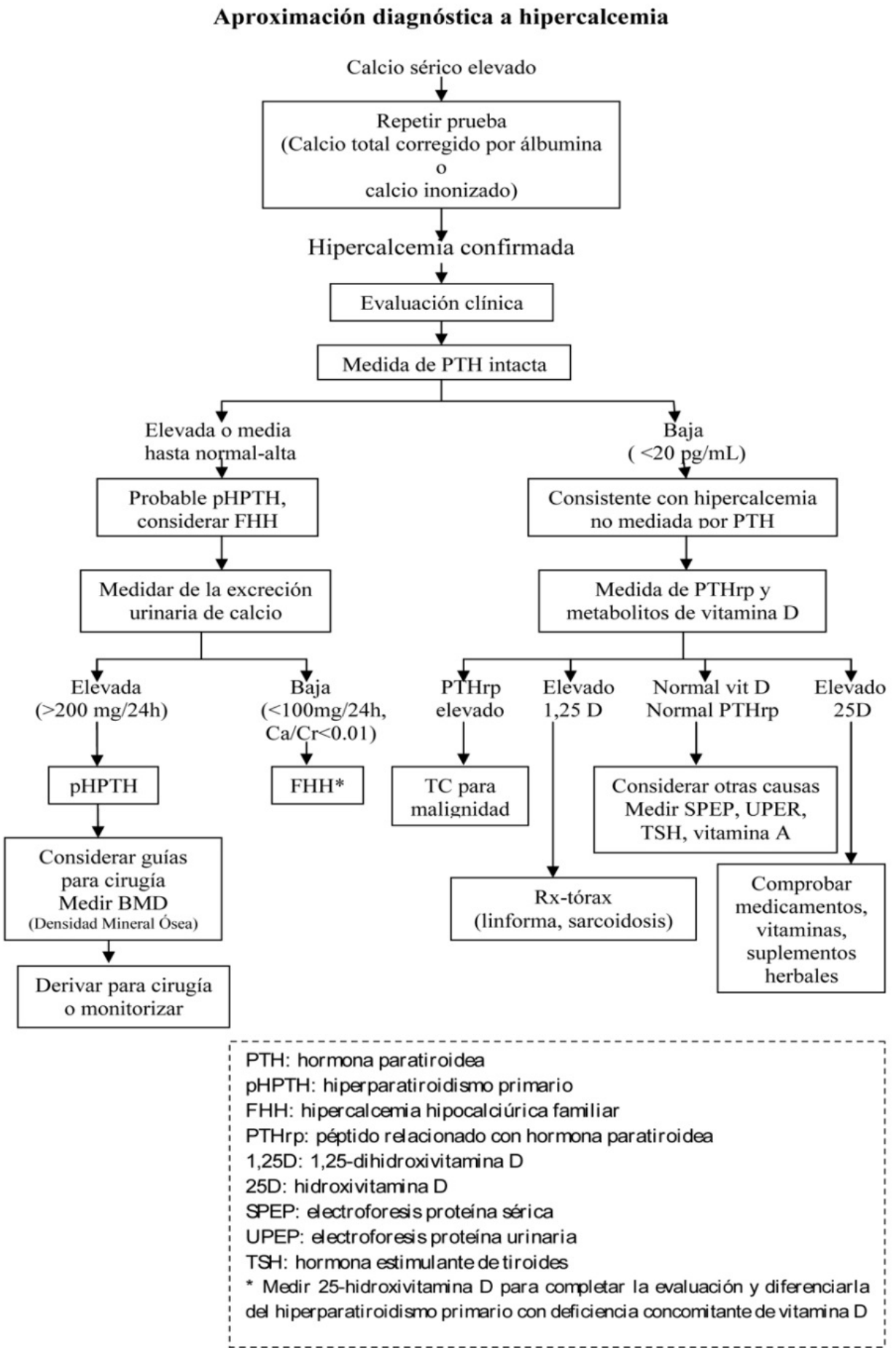
In this patient, the reactivation of sarcoidosis would explain hypercalcemia, but not the increased PTH secretion, being suppression of PTH the normal physiological response. Thus, further investigation is considered in order to provide an alternative diagnosis to the persistent hypercalcemia.

Hypercalcemia is a frequent clinical finding, with primary hyperparathyroidism and malignancy as the most frequent etiologies. In malignancy, calcium levels are superior and clearly symptomatic. On the contrary, primary hyperparathyroidism is usually diagnosed in healthy ambulatory patients, with mild or borderline hypercalcemia.

After detecting the hypercalcemia and carrying out a complete anamnesis one should determine serum value for PTHi.

In the differential diagnosis, it should be taken into account that high levels of PTHi are usually due to primary hyperparathyroidism. In contrast, familial hypocalciuric hypercalcemia shows no significance increase of PTHi levels.

Granulomatous diseases, such as sarcoidosis, can show hypercalcemia and hypercalciuria. Calcium absorption is increased due to production of 1, 25-(OH) VitamineD3 and ACE. This translates into a serum increase of their levels. Parathyroid hormone (PTHi) would be diminished due to negative feedback (given elevated levels of 1, 25-(OH) 2D3) on parathyroid cells). This is synergic with the inhibitory effect that calcium synthesis has on these cells surface receptors (3, 6).



▲ **Figure 3**. *Differential diagnosis of hypercalcemia (8).*

Primary hyperparathyroidism (PHPT) is caused by an augmented secretion of PTH on the parathyroid glands that manifests as hypercalcemia. It shows occasionally produced by an often solitary adenoma, localized in the lower glands, as is the case.

Diagnosis is mainly biochemical: rise of total calcium and ionic serum levels with increased PTH levels. Imaging techniques (CAT, MR and 99mTc-MIBI gammagraphy) are only used to locate the abnormal gland prior to the intervention. Parathyroidectomy is the basic treatment, after which normal calcium levels and analytical parameters are restored.

Coexistence between sarcoidosis and primary hyperparathyroidism are a rare clinical entity, with least than 100 cases published since 1958, when first described (1, 3, 5). Even so, only individual or small series of cases with both diseases have been described. Hence, a definite relationship between both diseases has not been established, since both modify calcium metabolism through different mechanisms.

However, it seems unlikely that this association is casual. Some authors consider both diseases have incidence high enough for concomitant emergence to occur. Other authors point out that sarcoidosis causes hypercalcemia, hypercalciuria and alterations of vitamin D dependent on calcium metabolism. This would induce hyperplasia of the parathyroid glands, favoring the subsequent development of adenoma (4). There have been publications of cases in which sarcoidosis is diagnosed after the primary hyperparathyroidism (2, 3), sometimes without hypercalcemia at the time of diagnosis.

Conclusions

The association between primary hyperparathyroidism and sarcoidosis has relevant theoretical interest, since no etiopathogenical relationship has been established.

Moreover, hypercalcemia can show more than one etiology and sarcoidosis is one of the diseases that hinder the differential diagnosis of primary hyperparathyroidism.

Diagnosis of both entities could be considered when evaluating hyperparathyroidism in the context of a patient suffering from sarcoidosis with hypercalcemia, changing the upcoming diagnosis and treatment radically (1, 2, 5).

When distinguishing both clinical entities one should bear in mind several aspects.

Sarcoidosis-based hypercalcemia shows fluctuant levels, diminished PTHi, normal or lower borderline phosphate levels, increased 1,25-(OH)2D3, increased serum immunoglobulins and increased red cell sedimentation serum ratio. When active, it shows even lower PTH and phosphatemia levels with increased ACE levels (1, 2, 3, 7).

Primary hyperparathyroidism shows hypercalcemia and increased PTHi serum levels. It can also be combined with hypercalciuria, hypophospatemia, increased 1, 25-(OH) vitamin D3, hypercloremia with metabolic acidosis and increased bone turnover markers (alkaline phosphatase) and tubular calcium reabsorption. It also shows osteitis fibrosa by subperiostic reabsorption.

If primary hyperparathyroidism and clinically active sarcoidosis coexist, ACE levels will be increased, with diminished PTH and phosphate levels when compared to inactive sarcoidosis.

Corticoids, alone or associated with other immunosupressants, are the base of the treatment for sarcoidosis. Hypercalcemia in these patients should not be attributed to a reactivation of sarcoidosis, especially when there is no response to treatment, as in the case presented.

References

1. Yoshida T, Iwasaki Y, Kagawa T, Sasaoka A, Horino T, *el al.* Coexisting Primary Hyperparathyroidism and Sarcoidosis in a Patient with Severe Hypercalcemia. Endocrine Journal. 2008;55(2):391–395.

2. Lim V1, Clarke BL. Coexisting primary hyperparathyroidism and sarcoidosis cause increased angiotensin-converting enzyme and decreased parathyroid hormone and phosphate levels. The Journal of Clinical Endocrinology and Metabolism. 2013;98(5):1939-45.

3. Schweitzer VG, Thompson NW, Clark KA, Nishiyama RH, Bigos ST. Sarcoidosis, hypercalcemia and primary hyperparathyroidism. The vicissitudes of diagnosis. The American Journal of Surgery. 1981;142(4):499-503.

4. Pino V, Pardo G, Marcos M, Pereda JM, Marques L, *et al.* Primary Hyperparathyroidism associated with Pulmonary Sarcoidosis. Otorrinolaringologia e Cirurgia Cérvico-Facial .Revista Portuguesa. 2009;41(1):53-55.

5. Dent CE, Watson L. Hyperparathyroidism and sarcoidosis. British Medical Journal. 1966;1(5488):646-9.

6. Kinoshita Y1, Taguchi M, Takeshita A, Miura D, Tomikawa S, Takeuchi Y. 1,25-dihydroxyvitamin D suppresses circulating levels of parathyroid hormone in a patient with primary hyperparathyroidism and coexistent sarcoidosis. J Clin Endocrinol Metab. 2005;90(12):6727-31.

7. Lief PD, Bogartz LJ, Koerner SK, Buchberg AS. Sarcoidosis and primary hyperparathyroidism: An unusual association. The American Journal of Medicine. 1969; 47(5):825–830.