SARCOIDOSIS AND HYPERPARATHYROIDISM: WHEN BOTH DIAGNOSIS COEXIST

SARCOÏDOSE ET HYPERPARATHYROÏDIE: QUAND LES DEUX DIAGNOSTICS COEXISTENT

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ABSTRACT

Introduction: The coexistence of primary hyperparathyroidism (PHPT) and sarcoidosis is rare and presents a diagnostic challenge, as both disorders can independently cause hypercalcemia.
Case report: We report the case of a 49-year-old woman with ocular and pulmonary sarcoidosis who developed progressive asthenia and persistent hypercalcemia despite corticosteroid therapy. Serum calcium was 2.8 mmol/L, with elevated parathyroid hormone (PTH) at 296 pg/mL. Cervical ultrasonography and 99mTc-sestamibi SPECT/CT localized a left inferior parathyroid adenoma. Surgical excision normalized serum calcium levels with sustained biochemical remission at 2-year follow-up.
Conclusion: Persistent hypercalcemia despite corticosteroid therapy in a patient with sarcoidosis should prompt investigation for concomitant PHPT to guide appropriate treatment.
Keywords: Sarcoidosis, Primary hyperparathyroidism, Hypercalcemia, Parathyroid neoplasms, Vitamin D

RESUME

Introduction: La coexistence de l'hyperparathyroïdie primaire (HPTP) et de la sarcoïdose est rare et constitue un défi diagnostique, car ces deux affections pouvant indépendamment entraîner une hypercalcémie.
Cas clinique: Nous rapportons le cas d'une patiente de 49 ans, suivie pour une sarcoïdose oculaire et pulmonaire, présentant une asthénie et une hypercalcémie persistante malgré une corticothérapie adéquate. La calcémie était à 2,8 mmol/L, avec une parathormone (PTH) à 296 pg/mL. L'échographie cervicale et la TEMP/TDM au 99mTc-sestamibi ont localisé un adénome parathyroïdien inférieur gauche. Son exérèse chirurgicale a permis une normalisation immédiate de la calcémie, maintenue après 2 ans de suivi.
Conclusion: La persistance d'une hypercalcémie malgré une corticothérapie chez un patient atteint de sarcoïdose doit conduire à rechercher une HPTP concomitante, afin d'adapter la prise en charge.
Mots-clés: Sarcoïdose, Hyperparathyroïdie primaire, Hypercalcémie, Tumeurs de la parathyroïde, Vitamine D

INTRODUCTION

Hypercalcemia is one of the most diagnostically challenging metabolic disorders, with primary hyperparathyroidism (PHPT) and granulomatous diseases such as sarcoidosis among its leading, and sometimes coexisting, causes. While each condition independently accounts for a significant proportion of hypercalcemia cases, their simultaneous occurrence is rare, affecting approximately 5% to 10% of patients with either disease, and remains diagnostically challenging [1,2]. The difficulty lies not only in recognizing the dual etiology, but in correctly attributing the hypercalcemia to its dominant driver and adopting the appropriate management strategy accordingly. Missing a concurrent PHPT in sarcoidosis carries real clinical consequences, as hypercalcemia is often attributed solely to the granulomatous disease. This diagnostic assumption typically results in prolonged or escalated corticosteroid therapy, while the unrecognized PHPT continues to cause renal, skeletal, and cardiovascular damage. We report the case of a 49-year-old woman followed for ocular and pulmonary sarcoidosis under corticosteroid therapy, who was referred for incidentally discovered elevated PTH levels, and in whom steroid-resistant hypercalcemia led to the diagnosis of a coexisting parathyroid adenoma.

CASE PRESENTATION

The patient's medical history was notable for sarcoidosis with ocular and pulmonary involvement, diagnosed following investigation of recurrent bilateral granulomatous panuveitis associated with dyspnea. Chest computed tomography revealed an interstitial syndrome. A bronchoscopy with bronchial biopsy was performed. Histopathological examination demonstrated granulomas with multinucleated giant cells without caseous necrosis, confirming the diagnosis of sarcoidosis with pulmonary involvement. Molecular testing for Mycobacterium tuberculosis (BK) by polymerase chain reaction (PCR) was negative, excluding tuberculous etiology. Azathioprine (Imurel ®) was initiated for the treatment of sarcoidosis.

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During follow-up, the patient reported progressively worsening asthenia and fatigability, associated with bone pain. Laboratory investigations revealed hypercalcemia at 2.8 mmol/L, with marked hypercalciuria confirmed on 24-hour urine collection. Serum phosphate levels were normal, while 25-hydroxyvitamin D levels were low, consistent with vitamin D deficiency.

Assessment of hypercalcemia-related target organ damage showed normal renal function; renal ultrasound demonstrated normal renal morphology with no evidence of nephrocalcinosis nor renal lithiasis. Standard radiographs showed no pathological fractures, whereas bone densitometry revealed osteopenia with a T-score of -2.

Corticosteroid therapy was initiated at a dose of 1mg/kg/day, with vitamin D supplementation subsequently introduced to correct the documented vitamin D deficiency. Despite adequate treatment, repeat biochemical evaluation demonstrated persistent hypercalcemia. The lack of response to corticosteroid therapy raised suspicion of a concurrent, independent underlying pathology.

This unexpected clinical evolution prompted further investigations. Parathyroid hormone (PTH) levels were measured and found to be significantly elevated at 296 pg/mL (reference range: 15–65 pg/mL). The combination of hypercalcemia, hypercalciuria, normal serum phosphate, and markedly elevated PTH levels was biochemically consistent with primary hyperparathyroidism (PHPT). This finding established a dual diagnosis, with PHPT occurring concurrently with the previously confirmed sarcoidosis. Cervical ultrasonography revealed a hypoechoic nodular lesion in the location of the left inferior parathyroid gland. Parathyroid scintigraphy using single-photon emission computed tomography/computed tomography (SPECT/CT) with 99mTc-sestamibi confirmed the presence of a hyperfunctioning lesion consistent with a left inferior parathyroid adenoma, in concordance with the ultrasonographic findings (Figure 1). No evidence of ectopic parathyroid tissue or multiglandular disease was identified.

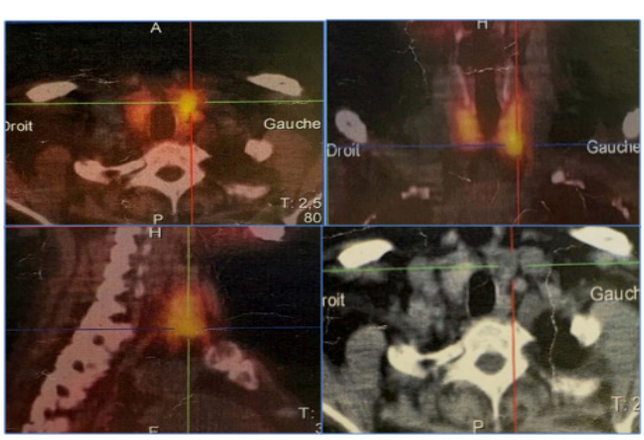


Figure 1: SPECT/CT with 99mTc-sestamibi confirming the presence of a hyperfunctioning lesion consistent with a left inferior parathyroid adenoma.

The patient underwent a cervicotomy with targeted excision of the left inferior parathyroid adenoma. Intraoperative PTH monitoring, showed a decrease in serum PTH from a preoperative level of 126 pg/mL to 73 pg/mL 10 minutes after adenoma excision. The resected specimen consisted of a well-encapsulated, ovoid nodule measuring 15 mm in maximum diameter. Histopathological examination revealed an encapsulated proliferation of chief cells arranged in trabeculae and cords within a rich capillary network, devoid of stromal fat, consistent with a parathyroid adenoma. Notably, no granulomatous tissue was identified within the parathyroid gland, proving no histological evidence of parathyroid involvement by sarcoidosis. (Figure 2)

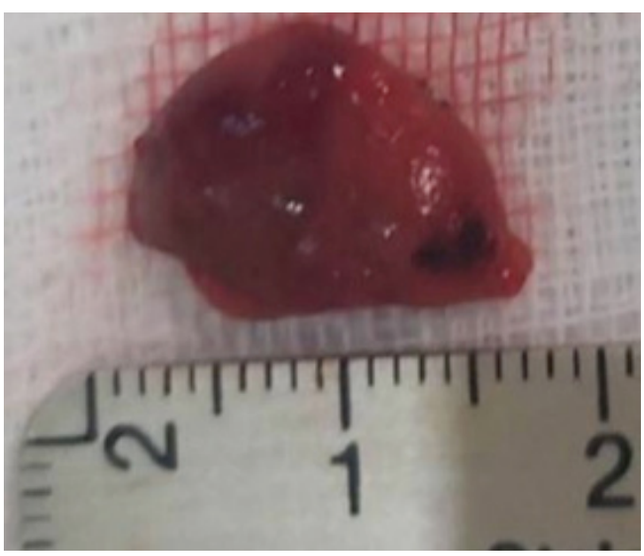


Figure 2: Surgical specimen of the excised left inferior parathyroid adenoma.

Serum calcium levels normalized promptly on the first postoperative day, reaching 2.1 mmol/L. At the one-month follow-up, serum calcium remained within the normal range, with a PTH level of 52 pg/mL. These biochemical findings remained stable at the six-month follow-up, consistent with sustained biochemical remission of PHPT. Corticosteroid therapy for sarcoidosis was continued. At the two-year follow-up, the patient remained free of biochemical evidence of recurrent hypercalcemia or PHPT.

DISCUSSION

Hypercalcemia is a common metabolic disturbance in clinical practice, with primary hyperparathyroidism (PHPT) and malignancy accounting for the large majority of cases [3]. Granulomatous disorders, especially sarcoidosis, represent a less frequent but well-characterized cause. Those disorders act through a separate, PTH-independent, mechanism [4,5]. We illustrate these diagnostic considerations through the case of a patient in whom both conditions coexisted. This case under review describes a 49-year-old woman diagnosed with sarcoidosis involving pulmonary and ocular sites, in whom follow-up revealed hypercalcemia

manifesting as asthenia and bone pain. Hypercalcemia in this context is reported in the literature with variable frequencies, reflecting the heterogeneity of the populations studied and of the diagnostic criteria used over time. Its prevalence varies from 10 to 30% of patients with sarcoidosis [6–9].

The biological profile observed in our patient, characterized by hypercalcemia and marked hypercalciuria, is consistent with this well-documented association. In sarcoidosis, hypercalcemia typically results from the extrarenal production of 1,25-dihydroxyvitamin D (calcitriol) by activated macrophages within granulomatous tissue [5,10,11]. This autonomous extrarenal production of calcitriol occurs independently of PTH regulation [12,13]. A hallmark of this mechanism is the frequent reduction in serum 25-hydroxyvitamin D levels due to its increased conversion into calcitriol [4]. This was indeed the case in our patient, who presented with a low serum 25-hydroxyvitamin D level. Vitamin D deficiency was corrected; however, hypercalcemia persisted. The persistence, or even worsening, of hypercalcemia following vitamin D supplementation may reflect ongoing, dysregulated extrarenal production of calcitriol by active granulomatous tissue [9,14]. Corticosteroid therapy was initiated as both a therapeutic and diagnostic intervention, as the glucocorticoid-mediated suppression of calcitriol production has historically been used as a diagnostic rest, referred to as the hydrocortisone suppression test [15–17]. Sarcoidosis-associated hypercalcemia is typically highly responsive to corticosteroid therapy, which suppresses the extrarenal production of calcitriol [18,19]. In our patient, the persistence of hypercalcemia despite adequate corticosteroid treatment raised the possibility of an additional, independent underlying etiology. This prompted measurement of serum PTH levels, which led to the diagnosis of concomitant PHPT. Accordingly, persistent or steroid-resistant hypercalcemia in patients with sarcoidosis should prompt evaluation for coexisting PHPT [1,2]. The subsequent normalization of serum calcium levels following parathyroidectomy further supported PHPT as the underlying cause of the persistent hypercalcemia [1,20]. The coexistence of sarcoidosis and PHPT in the same patient is rare but well documented and may pose significant diagnostic challenges, particularly in determining the etiology of hypercalcemia and guiding appropriate management [20,21]. To date, the largest published series is that reported by Vivian Lim and al., comprising 50 cases identified over a 31-year period, whereas the remainder of the literature consists predominantly of isolated case reports [1]. The apparent rarity of this association may, however, reflect underdiagnosis rather than a truly low prevalence. In a recent large-scale cohort study involving more than 117,000 patients with sarcoidosis, hypercalcemia was identified in nearly one-third of patients; however, fewer than one-third of those with hypercalcemia underwent PTH measurement. Among patients who underwent PTH testing, approximately one-third met the biochemical criteria for concomitant PHPT, and more than three-quarters of these cases had not been previously diagnosed. These findings suggest that coexisting PHPT in patients with sarcoidosis may be substantially underrecognized in routine clinical practice [8].

A normal 25-hydroxyvitamin D level is not, in isolation, specific for PHPT and does not establish a PTH-dependent mechanism of hypercalcemia. However, in the setting of sarcoidosis, as observed in our patient, a normal 25-hydroxyvitamin D concentration may prove indirect support of a PTH-mediated mechanism, particularly when considered alongside an inappropriately elevated PTH level [22].

The clinical course of our patient is consistent with previously reported outcomes. In the largest retrospective study of patients with coexisting sarcoidosis and PHPT, 86% of patients who underwent parathyroidectomy experienced resolution of hypercalcemia, supporting the role of parathyroid surgery in patients with confirmed concomitant PHPT [1]. Nevertheless, persistent or only partially corrected hypercalcemia following parathyroidectomy has also been reported, particularly in the presence of ongoing granulomatous disease activity, reflecting the potential contribution of sarcoidosis-related calcitriol production to calcium homeostasis [23,24].

CONCLUSION

The coexistence of sarcoidosis and PHPT is uncommon and may present significant diagnostic challenges in the evaluation of hypercalcemia. Persistence or corticosteroid-resistant hypercalcemia in a patient with sarcoidosis should prompt careful assessment of PTH-dependent causes, particularly PHPT. A thorough evaluation of the underlying mechanisms is essential to establish the correct diagnosis and guide appropriate treatment. Long-term follow-up is warranted to monitor both diseases, given the potential for persistent sarcoidosis-related hypercalcemia and the possibility, although rare, of recurrent PHPT.

Conflict of interest:

The are no conflict of interest.

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Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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