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Case Report

# A Case of Sjogren's Syndrome Associated with Sarcoidosis and Hypercalcemia Related to Secondary Hyperparathyroidism

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## Abstract

A 65-year-old woman suffering from primary Sjogren's syndrome was admitted to our department of internal medicine for uncontrolled diabetes. Investigations revealed clinical and biological cholestasis with steatotic hepatomegaly and granulomatous hepatitis with eosinophilic necrosis and cholestatic lesions. Taking into consideration, the diagnosis of sarcoidosis, special investigations were performed revealing a hypercalcemia, labial granulomatous lesions of minor salivary glands, a pulmonary restrictive syndrome and bilateral micronodules and lymph nodes of Barety's space. The diagnosis of sarcoidosis was then made and a prednisone therapy started. The course was favorable except for the persistence of hypercalcemia. Hyperparathyroidism with severe vitamin D deficiency were diagnosed. No parathyroid nodule was found. This patient received alfacalcidol. The outcome was satisfactory with normalization of the blood calcium level and of the parathyroid hormone but the vitamin D deficiency persisted. This case presents several special features. First, the association between sarcoidosis and Sjogren's syndrome has been rarely reported in the literature. Second, the association between each of these disorders and hyperparathyroidism that is secondary to vitamin D deficiency which involves several mechanisms.

**Keywords:** Sarcoidosis; Sjogren's syndrome; Hypercalcemia; Hyperparathyroidism; Vitamin D deficiency

## Introduction

Sarcoidosis is a systemic inflammatory disease characterized by the presence of noncaseating epithelioid granulomas in many organs. Coexistence of sarcoidosis and Sjogren's syndrome (SS) has been reported occasionally [1,2,3].

In this study, we report a case of sarcoidosis associated with SS and a persisting hypercalcemia after treatment of the sarcoidosis.

## Case Report

A 65-year-old woman was admitted to the department of internal medicine of Mongi Slim hospital for uncontrolled type 2 diabetes mellitus of 8 years' standing. The patient also had a history of diffuse rarefying osteopathy and primary SS for 10 years revealed by xerostomia, xerophthalmia (positive shirmer's test), arthralgia, and a presence of Chisholm grade 4nodular inflammatory lymphocyte infiltrates in a salivary gland biopsy. The patient had been on sulfonylurea, fenofibrate, colchicine, prednisone (5mg/day), calcium and vitamin D supplement since 2006.

On examination, the patient weighed 68 Kg (body mass index at 28 $Kg/m^2$). Skin and scleral icterus were noted. Urinary test strips didn't detects proteinuria, and showed a urine pH at 7. Her blood pressure was 120/70 mmHg and her pulse was 74. A hepatomegaly at 16 cm was noted. There was no peripheral lymphadenopathy, nor any splenic or parotid enlargement.

Serum levels of electrolytes, triglycerides, transaminases, prothrombine and total protein were within normal ranges, and so were the renal function tests and the complete count findings. The serum levels of glucose and of total cholesterol was elevated to 11.65 (normal, 4.4-6.1 mmol/l) and 5.84 mmol/l (normal, 3.1-5.16 mmol/l) respectively.

A biological cholestasis was found: elevated total bilirubin (44 µmol/l; NL < 17), gamma-glutamyltransferase (GGT) (100 UI/l; NL < 30) and alkaline phosphatase (ALP) (307 UI/l; NL: 100-219).

The Chest x-ray was normal. The abdominal ultrasound revealed an enlarged fatty liver at 16.9 cm. Upper gastrointestinal endoscopy showed a corrosive gastritis.

The patient was seronegative for anti-mitochondrial auto antibodies and for hepatitis B and C. A liver puncture biopsy was performed and histological examination revealed a granulomatous hepatitis with eosinophilic necrosis and cholestatic lesions.

Hypercalcemia was noticed and confirmed by several assessments: 2.8 mmol/l, 2.72 mmol/l, 2.78 mmol/l, and 2.75 mmol/l (reference range: 2.25-2.63 mmol/l). Urine tests were performed and showed a high level of calcium: 427 mmol/24H (100-300) and low levels of Na+: 93mmol/24H (120-260) and of K+: 45mmol/24H (550-200). The hypercalcemia persisted even after stopping the calcium and vitamin D supplements and with a symptomatic treatment.

Microscopic examination of the biopsy sample of minor salivary glands revealed epithelioid Granulomas containing giant cells that can be consistent with sarcoidosis, in addition to chronic sialadenitis (Chisholm and Mason grade 4)

The patient then underwent a chest CT scan that revealed diffuse bilateral micronodules, with blurred margins, that predominates in the two upper lobes and centimetric lymph nodes of Barety's space (Figures 1 and 2). Pulmonary function tests showed a restrictive syndrome. A bronchoscopy was performed without any abnormalities. Bronchoalveolar lavage showed no hypercellularity and a CD4/CD8 ratio of 2.3. The blood level of angiotensin-converting enzyme was elevated: 110 U/l (reference range: 12-68).

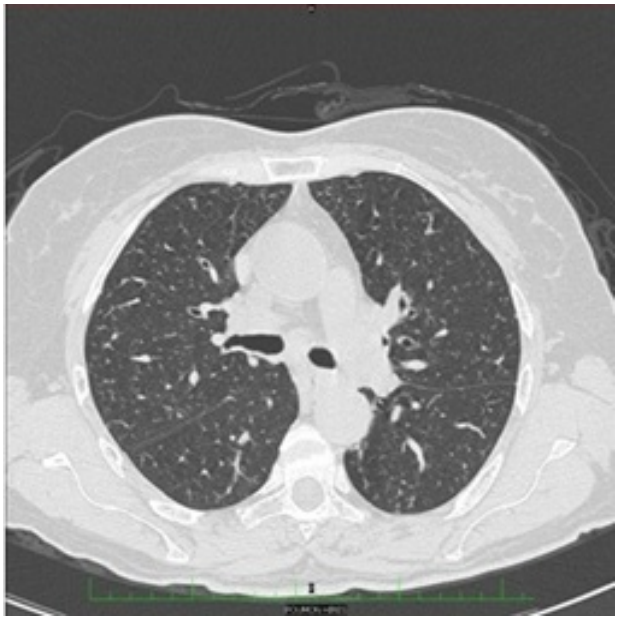

Figure 1: Chest CT scan shows bilateral micronodules, with blurred margins, that predominate in the two upper lobes.

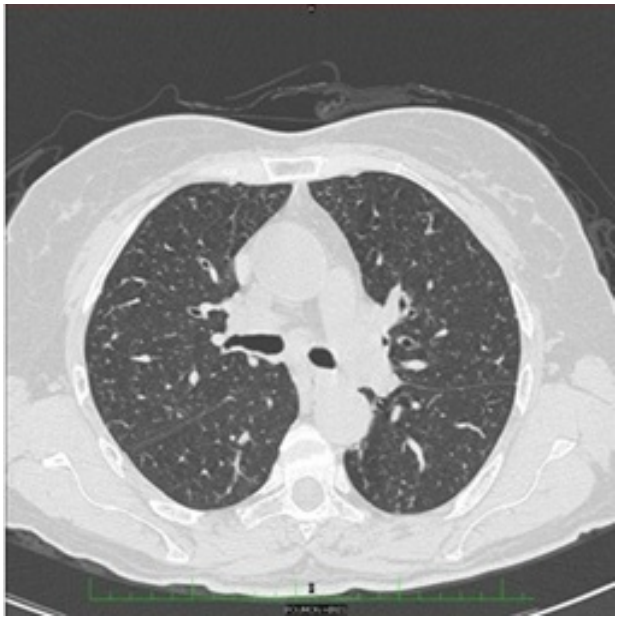

Figure 2: Centimetric lymph nodes of Barety's space.

In view of the lung micronodules, the restrictive syndrome, the elevated angio-tensin converting enzyme blood level, the persistent hypercalcemia and the liver and labial granulomatous lesions, the diagnosis of sarcoidosis was made and prednisone therapy (1mg/kg/d) started.

The clinical and hematological course was favorable marked by weight gain, lysis of asthenia and a decline in the biological signs of cholestasis.

Two monitoring chest CT-scans performed 10 and 20 months later didn't reveal any peritoneal, mediastinal or retroperitoneal adenomegaly or any parenchymal signs of sarcoidosis but showed nevertheless a persistent moderate homogeneous hepatomegaly.

On the other hand, the hypercalcemia persisted. Faced with a persistent hypercalcemia in a patient suffering from sarcoidosis and treated with corticoids, we preceded with a parathyroid hormone (PTH) assessment which revealed an elevated level of 197pmol/l (reference range: 12-72pmol/l).

In order to investigate the hyperparathyroidism,a series of investigations were performed: serum phosphorus level which was normal, hands and pelvis x-ray which didn't reveal any abnormality, bone mineral density that diagnosed an osteoporosis with a T-score for the lumbar spine and femoral neck respectively of -3.6 SD and -1.2 SD, cervical ultrasound which revealed a multinodular thyroid (thyroid hormone concentration was normal) and no parathyroid nodule, cervical and thoracic MRI without abnormality and a parathyroid scintigraphy to Tc99m MIBI that showed no evidence of a cervical parathyroid or ectopic mediastinal adenoma.

Vitamin D (25-OH D) was then assessed and a severe vitamin D deficiency was revealed: 5ng/ml (reference range: 30-80ng/ml).

This patient received alfacalcidol (2µg/day). The course was favorable with normalization of the serum calcium level (2.55mmol/l, controlled by several assessments) and of PTH (49.9pg/ml), but the level of 25OHD was still low at 7ng/ml (30-80).

Administration of intra-muscular ergocalciferol was considered given the persistence of the vitamin D deficiency.

Discussion

The study is about the case of a Tunisian woman with Sjogren's syndrome associated with sarcoidosis and a hypercalcemia related to secondary hyperparathyroidism caused by severe vitamin D deficiency.

Sarcoidosis is a multisystem granulomatous dis¬ease of unknown etiology. Lung and lymph nodes are the most com¬monly affected tissues. Skin, eye, heart, nervous system, bone marrow, liver, and spleen may also be involved [4].

Sarcoidosis is associated with hypercalcemia in 10 to 20% of cases [5]. Elevation of serum calcium level is due to dysregulated production of 1,25-(OH2)D3 (calcitriol) by activated macrophages trapped in pulmonary alveoli and granulomatous inflammation. These macrophages contain the activated enzyme 1α-hydroxylase, which converts 25-hydroxyvitamin D from the liver to active vitamin D 1,25(OH)2D3 [4,5].

In the present case, the persistence of hypercalcemia along with prednisone therapy was an unusual outcome of sarcoidosis. It was related to elevation of PTH which can be due to primary or to secondary hyperparathyroidism, whose causes are listed in Table 1 [6,7,8]. Investigations revealed that the hyperparathyroidism was secondary to vitamin D deficiency.

| | | |
|---|---|---|
| Hypocalcemia | Defect in phosphorus removal | Disturbance of vitamin D metabolism |

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|---|---|---|
| Vitamin D inadequacy or vitamin D resistance | Aluminium intoxication | Disturbance of vitamin D metabolism |
| HPT following surgery | Certain types of cancers | Breast feeding |
| HPT owing to autoimmune disease or genetic causes | Malabsorption | Decreased production of vitamin D in the skin |
| Renal disease or ESLD causing vitamin D inadequacy | Malnutrition | Obesity |
| PHPT or PPHPT | Nephropathy | Malabsorption |
| Metastatic or heavy metal (copper, iron) infiltration of the PTG | | Hyper-catabolism |
| Hypomagnesemia or hypermagnesemia | | Decreased synthesis of 25-OH D |
| Sclerotic metastases | | Increased urinary loss of 25-OH D |
| Hungry bone syndrome | | Decreased synthesis of 1,25(OH)2-D3 |
| Postparathyroidectomy | | Inherited vitamin D metabolism abnormalities |
| Infusion of phosphate or citrated blood transfusions | | Acquired vitamin D metabolism abnormalities |
| Critical illness | | |
| Drugs (eg, high-dose intravenous bisphosphonates) | | |
| Fanconi syndrome | | |
| Past radiation of PTG | | |

Table 1: Causes of secondary hyperparathyroidism HPT: hypoparathyroidism, ESLD: end-stage liver disease, PHPT: Pseudohypoparathyroidism, PPHPT: pseudopseudohypoparathyroidism, PTG: parathyroid gland

Causes of vitamin D deficiency are listed in Table 1 [7]. In the case of our patient, this abnormality could be due to decreased vitamin D production in the skin (related to her advanced age, to the low sun exposure, to her dark skin and to the headscarf she was continuously wearing), to hyper-catabolism induced by corticosteroids and to hepatic sarcoidosis and steatosis that can affect 25-OH D synthesis.

But in sarcoidosis, PTH should be inhibited by the high levels of 1,25-dihydroxyvitamin D3 (1,25(OH)2-D3) and of calcium [9]. Carveval and al indicated that PTH concentration depended on that of ionized calcium only in subjects with 25-OH D levels greater than 16.35ng/mL, while for 25OHD less than 16.35ng/mL it depended on 25-OH D values by a negative correlation [10].

The severe deficiency of 25-OH D diagnosed in our patient could be related to multiple causes: Decreased production of vitamin D in the skin, hyper-catabolism induced by corticosteroids, hepatic sarcoidosis and steatosis that can affect 25-OH D synthesis. It is also possible that this vitamin D deficiency might be related to Sjogren's tubulopathy, considering the alkaline pH urine (pH=7), and which was not confirmed in our patient.

An association between sarcoidosis and hyperparathyroidism is uncommon; only 50 cases were reported in the literature in the past 40 years [9].

The association between SS and sarcoidosis has been reported in only 1% of patients with SS. Gal et al reported 5 patients with sarcoidosis among 464 patients with SS [3]. Fuke et al reviewed 28 cases of histologically diagnosed sarcoidosis complicated by primary SS [2]. Tokuyasu has described a case of a primary SS complicated by sarcoidosis [1]

## Conclusion

In summary, we describe a case of SS associated with sarcoidosis and hypercalcemia related to secondary hyperparathyroidism caused by severe vitamin D deficiency. The decrease in 25-OH D is not unusual in sarcoidosis but the level remains often greater than 16.35 ng/ml. What is typical feature of this patient is that this level remained very low by a multi factorial mechanism.

## References

1. Tokuyasu H, Harada T, Touge H, et al. (2008) Primary Sjogren'syndrome Complicated by Sarcoidosis. Inter Med 47: 2049-2052.
2. Fuke S, Yamaguchi E, Makita H, et al. (2002) A Case of sarcoidosis complicated by primary Sjogren's syndrome. Nihon Kokyuki Gakkai Zasshi 40: 686-691.
3. Gal I, Kovacs J, Zeher M (2000) Case series: coexistence of Sjogren's syndrome and sarcoidosis. J Rheumatol 27: 2507-2510.
4. Krikorian A, Shah S, Wasman J (2011) Parathyroid hormone-related protein: an unusual mechanism for hypercalcemia in sarcoidosis. EndocrPract 17: 84-86.
5. Sharma OP (2000) Hypercalcemia in granulomatous disorders: a clinical review. CurrOpinPulm Med 6: 442-447.
6. Slatopolsky E (1998) The role of calcium, phosphorus and vitamin D metabolism in the development of secondary hyperparathyroidism. Nephrol Dial Transplant 13: 3-8.
7. Tsiaras WG, Weinstoc MA (2011) Factors Influencing Vitamin D Status.ActaDermVenereol 91: 115–124.
8. Fong J, Khan A (2012) Hypocalcemia: updates in diagnosis and management for primary care. Can Fam Physician 58: 158-162.
9. Porter N, Beynobn HL, Randev HS (2003) Endocrine and reproductive manifestations of sarcoidosis. Q J Med 96: 553–561.
10. Carnevale V, Nieddu L, Romagnoli E, et al. (2010) Regulation of PTH secretion by 25-hydroxyvitamin D and ionized calcium depends on vitamin D status: a study in a large cohort of healthy subjects. Bone 47: 626-630.