SARCOIDOSIS: HOW ITS DIAGNOSIS MIGHT REVEAL TROUBLED

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ABSTRACT

Introduction*: Sarcoidosis is a systemic inflammatory disease characterized by the presence of non-necrotic granulomas. Affected sites commonly include lungs, skin, liver, heart and lymph nodes. Sarcoidosis association with monoclonal gammopathy of undetermined significance (MGUS) is a rare finding with only 11 cases reported.*

Case presentation*: We report the case of a 70 yo female who, in the last two years, was repeatedly admitted at several Internal Medicine Units with generalized weakness, fever, anemia, stage 4 chronic renal failure, hypertension, type 2 diabetes, ischemic heart disease. At the last admission in our Unit the patient was anemic, with Chronic Renal Failure, hypercalcemic, with a monoclonal component IgG mounting lambda chains, heavy proteinuria. Hypercalcemia presented for the first time. Biopsy of a supraclavear node showed not necrotic granuloma-gigantic cellular inflammation, mimicking sarcoid. These latter together with chest computed tomography (CT) picture allowed the diagnosis of sarcoidosis.*

Conclusion*: Hypercalcemia was the most important clue to led to diagnosis, while the higher level of 1,25 Vitamin D that is part of sarcoidosis picture, was lacking and there was the presence of a plasma cell disorder, making the clinical picture more difficult to interpret. However, the presence of subtle abnormalities in repeated chest X rays performed at the accesses to Internal Medicine Units, in addition to the clinical symptoms and even in the absence of hypercalcemia, could have raised the suspect and driven the performing of a more accurate imaging analysis (chest CT), which could have allowed the diagnosis earlier.*

Keywords: *Sarcoidosis, Chest CT, hypercalcemia, Vitamin D, renal failure.*

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Introduction

Sarcoidosis is a systemic inflammatory disease characterized by the presence of nonnecrotizing granulomas. Affected sites commonly include lungs, skin, liver, heart and lymph nodes. Patients may be asymptomatic or with wide variety of clinical manifestations depending on the organs involved. Persistent cough, generalized weakness, fever, night sweats, peripheral lymphadenopathy, erythema nodosum, fatigue, and incidental chest radiograph abnormalities are the most common manifestations[(1)].

A sarcoidosis and malignant neoplasms association has been reported in the literature[(2)].

Sarcoidosis-lymphoma syndrome is characterized, in addition to sarcoidosis, by the development of lymphoproliferative disorders, with Hodgkin's lymphoma being the most common type[(3)]. Sarcoidosis association with monoclonal gammopathy of undetermined significance (MGUS) is a rare finding with only 11 cases reported[(4)].

The nonspecific clinical picture of sarcoidosis often leads to late diagnosis.

Case presentation

A 70 years old female in the last two years repeatedly presented at the A&E of Padova University Hospital with generalized weakness, fever, chronic renal failure stage 4 with secondary anemia, hypertension, type 2 diabetes on insulin, ischemic heart disease, was referred to our Nephrology Unit.

The patient, of Moroccan nationality one month before was referred to an Internal Medicine Unit and discharged with the same symptoms. At the admission in our Nephrology Unit she presented normal White Blood Count, anemic, with Chronic Renal Failure, hypercalcemic, with a monoclonal component at the serum protein electrophoresis: IgG mounting lambda chain, heavy proteinuria, negative Bence Jones proteinuria (Table 1). Hypercalcemia was noted for the first time.

Haemoglobin	8.7 g/dl
Serum Creatinine	317 umol
Serum Calcium	3.02 mmol
PTH	5.8 ng/L (n.r. 6.5-36.8)
25 Vitamin D	14 nmol (n.r.75-250)
1.25 Vitamin D	166 pmol (n.r.36-216)
Serum ACE	106 U/L (n.r.<52)
Hepatitis B and C, HIV serologies	negative
Syphilis serology	negative
Quanti-Feron TB Gold	negative

Table 1: Patient's laboratory picture.

The patient was frail and anorexic. The chest X-ray showed more evident pulmonary interstitium and enlarged mediastinum. The EKG showed 70 ppm, sinus rhythm and impaired repolarization. Neoplasia markers negative.

In consideration of hypercalcemia and suspecting occult neoplasia, a Positron Emission Tomography-Computed tomography with Fluoro Dexoxy Glucose was performed that showed diffuse limphoadenomegaly and disomogenous pulmonary infiltrates.

Enlarged supraclavear node was excised and described as sclerotic areas with minimal necrosis, huge not necrotic granuloma-gigantic cellular inflammation, mimicking sarcoid (Figure 1).

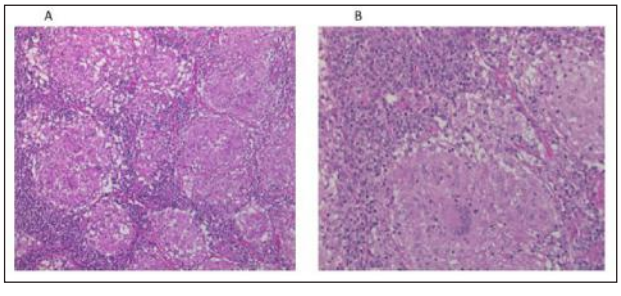

Figure 1: Hematoxylin and eosin staining of lymphnode shows (**A**) noncaseating epithelioid granulomas (original magnification x100) with (**B**) many epithelioid cells, Langhans giant cells and lymphocytes (original magnification x200).

Chest TC showed thickening of the lung interstitium with small nodules along the bronchial tree, enlarged nodes, some of them calcific (Figure 2).

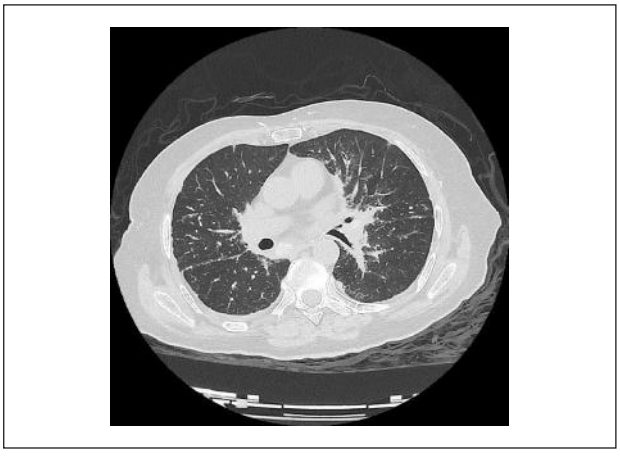

Figure 2:Chest TC showing thickening of the lung interstitium with small nodules along the bronchial tree, enlarged nodes, some of them calcific.

The case was reviewed by the Pneumologist and Sarcoidosis was diagnosed. The patient started prednisolone 40 mg in the morning and 20 in the evening; rapidly improving symptoms and normalizing calcium.

Discussion

Hypercalcemia was the most important clue for the diagnosis. It, in fact, addressed to PET-TC, which showed the multiple enlarged nodes. Vitamin D was not high as expected, contributing to the unclear clinical picture. However, the chest X-ray picture was present years before, and documented in all the repeated admissions in several Internal Medicine Units although not properly considered to include a chest TC, which would probably have clarified earlier the clinical picture.

Hypercalcemia in sarcoidosis is explained by the high concentration of 1,25 vitamin D, which is likely produced some place different from kidney such as granulomas. It has been shown, in fact, that serum 1,25 vitamin D was elevated in an anephric sarcoid patient and in patients with end-stage renal disease and sarcoidosis, therefore establishing that in these patients (5,6) the kidney was not the source of the higher 1,25 Vitamin D, indicating extrarenal and autonomous production most likely from activated mononuclear cells in the lung and/or lymph nodes. Macrophages, in fact, in sarcoid granulomas contain 1α hydroxylase, which converts vitamin D to its active form.

However, contrary to PTH that was appropriately suppressed, our patient's 1,25 vitamin D was not increased, as expected in sarcoidosis, making the picture more complex.

Corticosteroids are effective in all forms of hypercalcemia as they reduce gastrointestinal calcium absorption and inhibit osteoclast function, but are particularly effective in sarcoidosis due to their effects on Vitamin D metabolism. In fact, although corticosteroids have no effect on 1α hydroxylase in renal tubular cells, strongly inhibit it in the macrophages[7]. This effect was clear in our patient, whose hypercalcemia normalized in few days.

To our knowledge, our patient is the third reported in literature with sarcoidosis-induced hypercalcemia in the setting of (inappropriately) normal serum concentrations of 1,25 vitamin D and renal insufficiency[8]. In addition, this is another case of MGUS and sarcoidosis association. The simultaneous occurrence of sarcoidosis and plasma cell disorders is, however, rare. Only 11 cases have been reported thus far, which show a median latency period of four years between the diagnosis of sarcoidosis and MGUS[1].

In 30% of cases, sarcoidosis was the initial diagnosis, and in 30% was MGUS, as in our case. It has been suggested that the dysregulation of the immune system may induce development of autonomous plasma cell clones and result in the uncontrolled production of monoclonal immunoglobulins. Activation of CD4 positive T helper cells, suppression of CD8 positive T regulatory/suppressor cells, and increased cytokine production may contribute to the continuous stimulation of B cells, causing monoclonal or polyclonal hypergammaglobulinemia[9], although in our patient MGUS preceded sarcoidosis.

This case confirms that the diagnosis of sarcoidosis may be difficult. Hypercalcemia is obviously the main clue, which points to the suspect and compels to further proceed with more accurate imaging such as PET-TC. This was what drove our clinical path, which led us to the diagnosis. Furthermore, the higher level of 1,25 Vitamin D that is part of sarcoidosis picture, was lacking in our patient while there was the intriguing presence of a plasma cell disorder that can play a role in the pathophysiology of the disease, making the interpretation of clinical picture even more difficult.

Finally, we have to note that the presence of subtle abnormalities in repeated chest X rays performed in the several accesses to A&E, in addition to the clinical symptoms and even in the absence of hypercalcemia, could have raised the suspect and driven the decision to perform a more accurate imaging analysis such as a chest TC, which could have addressed the diagnosis earlier in time.

References

1) Vourlekis JS, Sawyer RT, Newman LS. Sarcoidosis: developments in etiology, immunology and therapeutics. Adv Intern Med 2000; 45: 209-57.
2) Bonifazi M, Bravi F, Gasparini S, La Vecchia C, Gabrielli A, Wells AU, et al. Sarcoidosis and cancer risk; systematic review and meta-analysis of observational studies. Chest 2015; 147:778-91.
3) Brincker H. The sarcoidosis-lymphoma syndrome. Br J Cancer 1986; 54: 467-73.
4) Sen F, Mann KP and Medeiros LJ. Multiple myeloma in association with sarcoidosis-a case report and review of the literature. Arch Pathol Lab Med 2002; 126:365-8.
5) Barbour GL, Coburn JW, Slatopolsky E, Norman AW, Horst RL. Hypercalcemia in an anephric patient with sarcoidosis: evidence for extrarenal generation of 1,25-dihydroxyvitamin D. N Engl J Med 1981; 305: 440-3.
6) Maesaka JK, Batuman V, Pablo NC, Shakamuri S. Elevated 1,25-dihydroxyvitamin D levels: occurrence with sarcoidosis with end-stage renal disease. Arch Intern Med. 1982; 142: 1206-7.
7) Adams JS, Gacad MA. Characterization of 1 α-hydroxylation of vitamin D3 sterols by cultured alveolar macrophages from patients with sarcoidosis. J Exp Med. 1985; 161: 755-65.
8) Falk S, Kratzsch J, Paschke P, Koch CA. Hypercalcemia as a result of sarcoidosis with normal serum concentrations of vitamin D. Med Sci Monit 2007; 13: CS133-6.
9) Hassanein M, Karapetyan L, Khan A, Rayamajhi S. Sarcoidosis and Monoclonal Gammopathy of Undetermined Significance (MGUS): A True Association or Just a Coincidence? Case Rep Hematol. 2018; 2018: 3790760

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