

Granulomatous thyroiditis: an unexpected finding leading to the diagnosis of sarcoidosis

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Abstract. A 59-year old male presented with dyspnoea, dull pain at the base of the neck, fever, and a history of severe recurrent coronary disease. In the past he had undergone two angioplasties, multiple stenting, and a triple aorto-coronary bypass. The patient also experienced a painful enlargement of the thyroid gland with bilateral multiple lymphadenopathies and thyrotoxicosis. Thyroid histology revealed interstitial non-caseating granulomas that are typical of thyroid sarcoidosis. The finding of granulomas in the thyroid allowed us to interpret the clinical manifestations of our patient leading to the diagnosis of sarcoidosis. The patient was ultimately treated for sarcoidosis and after one year of specific therapy has completely recovered without recurrence of cardiac or respiratory symptoms up to date.

Key words: Granulomatous thyroiditis, systemic sarcoidosis, coronary heart disease, thyrotoxicosis

Introduction

In systemic sarcoidosis, the thyroid gland is involved in 4.2-4.6% of cases (1), and the only mention of any endocrine association related to the disease is to either the overproduction of 1,25-dihydroxycholecalciferol by the granulomas or to diabetes insipidus due to pituitary or hypothalamic involvement (2, 3). Hyper- and hypothyroidism are considered very rare events not worthy of any mention.

In this report, we present a clinical case in which the diagnostic clue was achieved from the evidence of granulomas upon histological examination of the thyroid. This finding allowed us to comprehensively interpret the clinical manifestations of our patient. Systemic sarcoidosis provided a good explanation for the patient's thyrotoxicosis, repeated bronchitis and coronary heart disease.

Case report

A 59-year old man was admitted to our hospital for continuous-remittent fever (max. 39.0°C) with productive coughing and dyspnoea in the last two weeks. For such reason, he had within this time frame, previously been admitted to another hospital and treated with a round of ceftazidime 1g tid iv. He partially responded to the treatment but shortly thereafter experienced a recurrence of symptoms.

Approximately one year before his admission to our hospital, the patient suffered from severe anginal-like symptoms. A coronarography revealed extensive coronary disease affecting the anterior descendant artery, the circumflex artery, and the right coronary; thus, the patient was treated for revascularization of the anterior descendant artery with coronary angioplasty and multiple stenting. One month later he nee-

ded more treatment: angioplasty of an intra-stent segmental restenosis in the proximal tract of the anterior descendant artery. Finally, approximately three months before admission to our hospital, the patient had to undergo a triple aorto-coronary bypass. All of these severe events of ischemic cardiomyopathy peculiarly were not supported by any of the known risk factors (hypercholesterolemia, smoking, familiarity, hypertension, diabetes).

At admission the patient was suffering, dyspnoic (respiratory rate 18 breaths per minute), arterial pressure was 130/80 mmHg, cardiac rate was 90 bpm, and body temperature was 38.6°C. Upon chest examination, bilateral basal hypophonesis was discovered. The patient also suffered from a dull pain at the base of the neck, and palpation of the jugular region revealed a painful enlargement of the thyroid gland, chiefly at the level of the right lobe, with bilateral multiple lymphadenopathies (max 2 cm). The biochemical and hematological data are reported chronologically in Table 1.

The chest X-ray revealed bilaterally accentuated lung markings with greater evidence at the bases. A subsequent CT-scan showed micronodular thickening of the left posterior basal parenchyma and, to a lesser extent, of the right posterior basal parenchyma with two hilar lymphadenopathies (max diameter 1.5 cm). The bronchoalveolar lavage culture resulted in the isolation of three different germs (*Candida albicans*, *Acy-*

netobacter Lwoffii and *Xenotrophomonas maltophilia*); histology was undefined, and the cytology revealed presence of chronic inflammatory cells with a prevalence of lymphocytes, an uncommon finding for acute lower tract pulmonary infections. Based on the antibiogram a specific therapy was begun but only a partial response was obtained. In fact, two subsequent sputum cultures permitted the isolation of the following germs, respectively: in the first one, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Enterococcus faecalis* and negative-coagulase *Staphylococcus*, and in the second one, *Pseudomonas fluorescens* and coagulase-negative *Staphylococcus*. The evolution with recurrent saprophytic colonization of the lower respiratory tract, the radiographic pattern, and the results of cytology revealing a chronic inflammatory infiltration – notwithstanding the acute bronchopneumonia – suggested the hypothesis of any systemic disease inducing an immunodepressive state.

According to this hypothesis, diagnostic exams were performed: the Mantoux test was negative and the serum ACE levels were at the upper normal limits (54 U/L; N£55 U/L) as were tumor markers (CEA, CA 19.9). An endoscopy was also performed which did not reveal any specific condition. Finally, a transesophageal echocardiography – to exclude endocarditis – showed only an anterior mitral flap thickening with spotty echodensities, but no vegetation.

As a result of these tests, we decided to more dee-

Table 1. Biochemical and haematological evolution from 15 months before to 12 months after therapy conclusion. It is remarkable the progressive decrease of cholesterol with the instauration of thyrotoxicosis, the decrease of haemoglobin and finally the complete recovery of all parameters lasting til 12 months after discontinuation of therapy

| Date (d/m/y) | 3/6/98 | 6/10/98 | 7/11/98 | 8/9/99 | 14/9/99 | 5/10/99 | 14/10/99 | 7/12/01 |
|--------------------------------|---------|---------|---------|--------|---------|---------|----------|---------|
| Hgb ¹ | 14.7 | 12.3 | | 10.6 | | | 8.8 | 13.9 |
| WBC | 7.600 | 5.600 | | 13.400 | | | 8.200 | 5.600 |
| Plts (x10 ³) | 172 | 186 | | 435 | | | 366 | 173 |
| AST/ALT (<46/<56) ² | 21/16 | 21/14 | | 30/43 | | | 20/25 | 28/18 |
| ALP (<126) | | | | 131 | | | 168 | 73 |
| GGT (<78) | | | | 134 | 202 | 296 | 312 | 64 |
| ESR | | | | 96 | 110 | 115 | 100 | 2 |
| CRP(<9) | | | | 180.7 | | 120 | | |
| Tot. Chol/HDL | 223/48 | 212 | 205 | 127 | | | | |
| TG/LDL | 113/152 | | | 60 | | | | |
| Ca ⁺⁺ | | | | 9.56 | | | 9.40 | 8.8 |

¹ ALP= Alkaline Phosphatase; CRP= C reactive Protein; ESR= Eritrosedimentation rate; GGT= g-Glutamyl Transferase; Hgb= Hemoglobin; Plts= Platelets; TG= Triglycerides; Tot. Chol = Total Cholesterol; WBC= white blood cells

² Upper normal limits

ply evaluate the painful goiter. The CT pictures of the thyroid gland revealed significant enlargement with a nonhomogeneous nodule with microcalcifications occupying the whole right lobe and extension toward the upper anterior mediastinic region, trachea dislocation to the left, and also bilateral cervical lymphadenopathies (max diameter 1.7 cm). Moreover, the biochemical tests showed a thyrotoxic state (TSH <0.1 μ U/ml, FT3 9.4 pg/mL and FT4 5.5 ng/dL); however, results for anti-microsomal and anti-thyreoglobulin auto-antibodies were negative. Calcitonine was in the normal range, and human thyreoglobulin slightly above the upper limits of normal range. A total thyroidectomy was performed due to trachea dislocation and to the strong clinical feeling of neoplasia notwithstanding negative thyroid tumor markers. The thyroid histology revealed interstitial non-caseating granulomas (Figure 1). A Ziehl-Neelsen stain was negative for acid-fast bacilli.

These histological findings were the final complement for the diagnosis of systemic sarcoidosis. In fact, the pattern of distribution of thyroid granulomas was typical of sarcoidosis: interstitial granulomas without any link with the colloid, is the decisive criterion for diagnosing of sarcoidosis as an alternative to De Quervain thyroiditis (4, 5).

Heart complications from sarcoidosis were suggested by the presence of left anterior hemiblock at

ECG and by mitral valve anterior flap thickening with spotty echodensities revealed by the trans-esophageal echocardiography. An endomyocardial biopsy was not performed considering the poor specificity of the test (6), but regardless, the clinical history of a significant and recurring ischemic cardiopathy in the absence of evident risk factors strongly suggested a cardiac complication induced by sarcoidosis.

Discussion

The involvement of thyroid from sarcoidosis is considered a rare occurrence and thyrometabolic alterations a really exceptional event (1). Also in recent review articles on sarcoidosis, endocrinological manifestations are limited to either calcium metabolic disorders – due to 1,25-dihydrocholecalciferol overproduction from granulomas – or to diabetes insipidus (2, 3). Although a remarkably high incidence of thyroid autoantibodies and a higher prevalence of Hashimoto's thyroiditis in patients of middle to advanced age with sarcoidosis was previously reported (7), direct thyroid involvement by sarcoidosis was rarely described.

On the contrary, thyroid sarcoidosis may entirely explain our patient's thyrotoxicosis and that is the reason for presenting this case.

The possibility that thyroid sarcoidosis mimics malignancy is sporadically reported (8, 9), as we observed with our case, and moreover as a primary presentation of the disease (8). In fact, our patient presented a very hard asymmetric goiter and at echography a single nodule was evidenced occupying the entire right lobe of the thyroid with a nonhomogeneous appearance, multiple microcalcifications within, and various latero-cervical lymphadenopathies, which all taken together resulted in a very suggestive picture for malignancy. The concomitant trachea dislocation and the thyrotoxic state prompted us to perform a thyroidectomy without previous demonstration of malignancy by fine needle cytology, as correct approach should have been.

That thyroid involvement from sarcoidosis could be associated with hyperthyroidism was recognized since Taillander suggested that granulomas could trigger an immune reaction causing hyperthyroidism th-

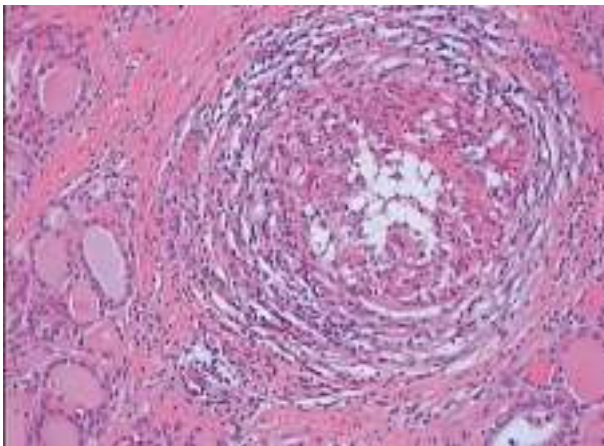


Figure 1. Histology of the thyroid showing an interstitial non-caseating granuloma. Typically granuloma epithelioid cells are not surrounding colloid in sarcoidosis as would be the case in De Quervain thyroiditis. Original magnification 200X, H. E.

rough follicles disruption (10). However, this hypothesis still has yet to be proven.

In our patient anti-thyroid auto-antibodies tested negative including anti-thyrotropin-receptor antibodies, but we cannot exclude the role of T cell mediated damage, as in sarcoidosis an increased *in situ* production of T helper-1 cytokines is described during granuloma formation (2, 3).

The histological picture was the hallmark for sarcoidosis. A more frequent form of granulomatous thyroiditis is De Quervain thyroiditis in which granulomas are set off by a foreign-body-like reaction toward the follicles, so that "granulomas surround the follicles and giant cells surround a core of colloid" (4), on the opposite in sarcoidosis typically we can observe "interstitial (that is not surrounding the follicles) non-caseating granulomas" (5). *Mycobacteria* could also produce a granulomatous reaction; in this case the golden standard for diagnosis is colture or isolation of acid-fast bacilli: this possibility was ruled out by a negative Zeehl-Neelsen stain, a negative Mantoux reaction and finally *ex adjuvantibus* by the clinical evolution after steroid therapy.

Thyrototoxicosis and the evidence of granulomas at the histological level represented the key for diagnosis and treatment of our patient.

The history of severe coronary artery disease of our patient could not be easily explained in the absence of the known risk factors (hypercholesterolemia, diabetes, cigarette smoking, hypertension, familiarity). We therefore, conceived the hypothesis of some kind of relationship with cardiac sarcoidosis. Approximately 27% of sarcoidosis-suffering patients have a cardiac involvement, even if it is diagnosed only in 5% of the cases (11). As it is well known, myocardial sarcoidosis can cause several dysfunctions including arrhythmia, misconduction and even sudden death (12, 13).

The cardiac involvement does not usually cause alterations of the main coronary arteries; instead, the Thallium scan defects are assumed to be caused by alterations of microcirculation functionally mimicking the abnormalities produced by severe lesions of the coronary arteries (14, 15).

Microcirculation abnormalities consist of microvascular spasms possibly resulting from local release of

vasoactive mediators (serotonin, histamine, etc.) due to activated macrophages or mast-cells surrounding sarcoid granulomas (16), but also a main coronary artery spasm cannot be ruled out (17, 18).

In our patient there were no coronary artery disease risk factors. His severe coronary lesions could be explained only on the basis of cardiac involvement by sarcoidosis that in very rare occasions can cause main coronary artery angiitis (19-20).

In addition to explaining his cardiac complications, sarcoidosis is also a likely explanation for the lung ailments of the patient. The recurring infections of the lower respiratory tract mostly sustained by opportunistic germs, as well as the low response to both empiric and specific antibiotic therapy (3, 21) could all be complications from sarcoidosis.

Currently, the diagnosis of sarcoidosis is based on the exclusion of other known causes of granulomatous pathology and often is derived from a puzzle of data without any specific serological or histological test (2, 3). After 12 months of steroid therapy our patient is doing well with a complete recovery from respiratory or cardiologic symptoms and normal blood testing (Table 1), evidence in itself of a skilled diagnosis.

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