Pathologic features of sarcoidosis and a case report of unusual gastrointestinal location

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Sarcoidosis is a systemic granulomatous disease of unknown etiology and is more common in young/middle-aged patients and in females [1]. Pulmonary involvement, with classic bilateral hilar adenopathy and parenchymal lung disease, in association with eye or skin lesions, represents the most common finding in sarcoidosis patients; however, virtually any organ in the body may be involved.

Sarcoidosis is an immune-mediated multisystem disease: it is hypothesized a single or various environmental factors may drive an immune inflammatory response in a genetically susceptible host [2].

A genetic predisposition to sarcoidosis is supposed when considering the familial aggregation and differences between racial groups [3,4,5]. Recent genetic studies [6] have identified specific class I and Class II Human Leukocyte Antigen (HLA) genes (specifically HLA-B7, HLA-B8, DRB1*03, DRB1*11, DRB1*12, DRB1*14 and DRB1*15) as risk factors in sarcoidosis. Also two non-HLA genes have been discovered: the butyrophilin-like 2 (BTNL2) gene, as risk factor, and the annexin A11 (ANXA11) gene, which could function as protective gene.

Various non-infective agents, as well as some environmental and occupational exposures, have been proposed as potential antigens for sarcoidosis, without any definitive conclusion [7].

Similarly, among potential etiologic agents of sarcoidosis, many infective organisms have also been taken into consideration. Of these, Mycobacterium has been the most investigated: a meta-analyses of studies concerning the
presence of mycobacterial DNA or RNA in sarcoidosis tissue revealed that in 26% of sarcoidosis tissues mycobacterial nucleic acid is present, thus suggesting a connection between sarcoidosis and the bacterial infection [8]. It’s noteworthy to underline that the only detection of mycobacterial agents doesn’t represent a proof of sarcoidosis etiology; otherwise it should be hypothesized that Mycobacteria agents could assume a complementary function in the pathogenesis of sarcoidosis.

The characteristic lesion of sarcoidosis is a well-defined granuloma composed of a “core” of epithelioid and Langhans giant cells with a rim of lymphocytes at the periphery; it does not contain caseous necrosis.

It has been widely demonstrated that the sarcoid granuloma originates from a stimulation of cell-mediated immunity. T helper cell activation is a necessary step for granuloma formation: in favour of this, it has been found that the center of the granuloma is composed of T4-helper lymphocytes, with a few number of CD8+ T cells at the periphery [9]. Besides, increased percentage of T-cells are found in bronchoalveolar lavage (BAL) fluid of patients with pulmonary sarcoidosis, resulting in 20-60% of the total cell count, with a CD4+:CD8+ T-cell ratio typically >3:5:1 (vs 2:1 in normal subjects).

Several studies reveal that the T cell response is directed toward a T helper 1 (Th1) cytokine profile. When unknown antigen is presented by macrophages T cells have the task of recognize the antigen and amplify the local immune response. Activated macrophages and T-lymphocytes within the granuloma release a number of key inflammatory cytokines, including interleukin-2, monocyte chemotactic factor, and immune interferon, which in turn call up other immune cells. IFN-\(\gamma\) plays a central role in the immune response, inducing macrophages to phagocytosis and oxidant production; IL-2 and IL-15 induce T cell proliferation [2,10]. Furthermore, dendritic cells (DCs) are now known to be critical in the pathogenesis of sarcoidosis. Berge et al. [11] have found increased number of mature, functionally competent DCs in BAL, but not in blood, from sarcoidosis patients, in respect to healthy subjects; DCs intrinsically induce T cell proliferation and differentiation as well as increased levels of TNF\(\alpha\).

However, in contrast to the “hyper-immune” state present locally in the affected granulomatous tissue, a paradoxical state of anergy has been found in the blood of patients with sarcoidosis, as demonstrated by decreased lymphocyte cells \([12]\). T regulatory cells may play an important role in causing this peripheral anergy \([13]\).

Considering pathogenesis of sarcoidosis, it should be kept in mind that this systemic disease may have also a partial autoimmune origin, as demonstrated by elevated serum IgG, IgM and IgA values respectively in 50%, 25%, and 10% of patients \([14]\). Sarcoidosis shows some similarities with many of the collagen vascular diseases, especially progressive systemic sclerosis and systemic lupus erythematosus (SLE), sharing such entities some clinical manifestations. As a further argument in favour of its immune origin is the finding that most patients with specific autoimmune disorders (Graves’ disease, Sjögren’s syndrome, ie) have hyperglobulinemia, which occasionally may be present in sarcoidosis \([15]\). Besides, both such patients and sarcoidosis patients are responsive to corticosteroid therapy.

An association between sarcoidosis and coeliac disease has been identified \([16]\). Mc Cormick et al. \([17]\) demonstrated that intraepithelial lymphocytes (IEL) are increased in patients with sarcoidosis and that 41% of these patients have also elevated values of circulating antibodies to alpha-gliadin (AGA), both the values being elevated in coeliac disease; so an altered gastrointestinal mucosal may occur in sarcoidosis patients.

In our recent case report entitled “Colonic sarcoidosis: unusual onset of a systemic disease” \([18]\) we presented the unusual case of colonic sarcoidosis in a 57-year-old male patient in apparent good health who presented with abdominal pain and costipation; he had no previous diagnosis of sarcoidosis or familiar predisposition to autoimmune disease. A colonoscopy showed an obstructing lesion at the caecum-ascending colon transition, which could not be definitely characterized on endoscopic biopsy, and was interpreted at radiologic examination as malignant colonic lesion. An exploratory laparotomy revealed a stenotic lesion in the caecum-ascending colon with peritoneal micronodules and locoregional lymphadenopathies, thus leading the surgeon to perform a right hemicolecotomy. Examination of the resected specimen showed multiple noncaseous granulomas in the ulcerated lesion, where no acid-fast bacilli at Ziehl-Nelsen staining were identified; so the diagnosis of sarcoidosis was made. Additionally, a chest CT showed lung involvement with atypical radiologic findings, which were confirmed as manifestation of pulmonary sarcoidosis after histologic examination of parenchymal lung from CT-guided biopsy.

Gastrointestinal involvement in sarcoidosis is rare, representing less than 1% of cases. Only ten cases of colonic sarcoidosis from 1966 to 2003 have been reported in a systematic review by Beniwal et al. \([19]\).
Despite most of the cases reported in literature [20,21], this is the first case in which sarcoidosis appears with symptomatic gastrointestinal location, and is associated with atypical radiologic pulmonary findings.

Imaging and endoscopic findings are not specific for sarcoidosis and overlap with many other diseases, such as chronic inflammatory bowel disease, infectious disease, and neoplastic lesion [22]; so histologic examination is necessary to make diagnosis of sarcoidosis.

In case of a previous diagnosis of sarcoidosis and/or a definitive diagnosis on endoscopic biopsy, patients can benefit from corticosteroid therapy; otherwise surgery will be necessary.

Conflicting interest

The authors declare that they have no conflicting interests.

References