ASSOCIATION BETWEEN SARCOÏDOSIS AND CROHN'S COLITIS : A CHANCE OR A REAL LINK?

ASSOCIATION ENTRE UNE SARCOÏDOSE ET UNE MALADIE DE CROHN : LIEN FORTUIT OU ETIOPATHOGENIQUE

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Abstract

Sarcoïdosis and Crohn's disease are granulomatous, auto-immune diseases of unknown etiology. Although they share many similarities, their association is rare. We report here a case of a 42-year-old woman, with a history of pulmonary sarcoïdosis, who developed a Crohn's colitis three years later. We try to demonstrate that the association between crohn's colitis and sarcoïdosis is more than a coincidence.

Key words : Sarcoïdosis; Crohn's disease

Résumé

La sarcoïdose et la maladie de Crohn sont deux maladies granulomateuses, auto-immunes d'étiologie indéterminée. Bien qu'ayant plusieurs points de similitudes, leur association est rare. Nous rapportons le cas d'une patiente âgée de 42 ans, suivie pour sarcoïdose pulmonaire et qui a développé 3 ans plus tard une maladie de Crohn de localisation colique. A travers cette observation nous allons essayer de démontrer que cette association n'est pas fortuite

Mots clés : Sarcoïdose ; Maladie de Crohn

ملخص

الساركويد و مرض كرون هما اثنان من الأمراض الحبيبية من نوع المناعة الذاتية و المرتبطة بمسببات غير محددة.
بالرغم من وجود عدة نقاط من التشابه، فإن تصاحبهم لدى مريض واحد يبدو شكلا نادرا.
قمنا بدراسة حالة مريضة تبلغ من العمر 42 عاما، وقع تتبعها سريريا لمرض الساركويد الرئوي و الذي تطور بحصول مرض كرون متموقع بمستوى المعي الغليظ أو القولون بعد 3 سنوات.
من خلال هذه الملاحظة سوف نحاول أن نثبت أن هذا الرابط المرضي ليس مفاجئ أو اعتباطي.

الكلمات المفاتيح: الساركويد ; مرض كرون

INTRODUCTION

Sarcoïdosis and Crohn's disease (CD) are both granulomatous diseases of unknown etiology, but they rarely occur together in the same patient. We report here the case of a 42-yeay-old female patient with a well-documented sarcoïdosis and Crohn's colitis.

CASE REPORT

We report the case of a forty two-year old woman followed since February 2006 for systemic sarcoïdosis. The diagnosis of sarcoïdosis was suspected on the presence of cervical lymphadenopathy. The cervical nodes biopsies have found non-caseating granulomas. The angiotensin-converting enzyme (ACE) level was twice as high as the normal value. A chest computed tomography scan found bilateral hilar lymphadenopathy with some under pleural micronodules of the left lower lobe. Lung function testing was normal, but showed a diffusion capacity reduced to 60% of the normal value. Bronchoscopy showed a normal macroscopic aspect. Transbronchial needle biopsy showed non-necrotizing granulomas. The bronchoalveolar lavage contained 53,7 % lymphocytes with a CD4/CD8 ratio of 75. The patient was given steroids. She recovered rapidly and lymph nodes disappeared. The steroids were stopped in January 2009. In June 2009, the patient was admitted in our hospital because of the development of a bloody diarrhea with 10 to 15 stools per day and a diffuse abdominal pain. The physical examination found a diffused abdominal tenderness and a perineal fissure at 6 hours in a genu-pectoral position. In November 2008, the patient suffered from bloody diarrhea occurring 10 times a day and which stopped spontaneously within 2 months. Biological exams found mild microcytic hypochromic anaemia with iron deficiency. Colonoscopy revealed highly inflamed mucosa with aphthous lesions and ulcerations involving the whole colon mainly the ascending colon and the coecum. The ileum had a normal macroscopic aspect. The anatomopathologic study of the ulcerated areas biopsies revealed non-specific inflammatory tissue with no granulomas. A diagnosis of CD was made on the basis of endoscopic and histologic findings. No other localization of CD was found by upper endoscopy and by barium enema of the small intestine. No extra-intestinal manifestations of CD were found. The patient was treated with sulphasalazine (6 g daily). Her symptoms resolved after the treatment. There has been no symptomatic organ involvement during the ensuing 64 months of follow-up.

DISCUSSION

Sarcoïdosis and CD are both granulomatous diseases of unknown etiology. Although considered to be distinct disease entities, over 30 reported cases show an "overlap" between inflammatory bowel disease (IBD) and sarcoïdosis [1]. Because of the rarity of this association, it is not established whether it occurs by chance or it is due to a common underlying immunologic disorder leading to different clinical pictures in response to common exogenous stimuli. Interestingly, family association is reported only for CD and sarcoïdosis [2,3], suggesting the possible involvement of transmissible agents, like mycobacteria, detected in tissue specimens in both conditions [4]. In fact, a polymerase chain reaction has been used to detect *mycobacterium* from the intestine tissue of patients with CD and from the lung of patients with sarcoïdosis, which suggests a common bacteriologic etiology. On the other hand, since both diseases have been described in siblings and in families, interest has been directed to the search for a genetic susceptibility [2,3,5]. Recent research has revealed that several mutations of the caspase-activating recruitment domain 15 (CARD15) gene on chromosome 16 are associated with CD, of which the most prevalent mutations are SNP8, SNP12 and SNP13 [6]. Due to the histological similarity between CD and sarcoïdosis, studies from Germany [7], the USA [8] and in ethnic Danish patients [9] have searched for an association between sarcoïdosis and CARD15 mutations with negative results and heterozygosity for such mutations apparently has no influence on the course of the disease. However, one study reported this abnormality in early onset but not in classical sarcoïdosis [10]. However, other genetic markers in sarcoïdosis and IBD have been reported. Although HLA B8 and DR3 are not genetic markers for CD, Gronhagen and al, reported a family association of sarcoïdosis and CD in which all members had a haplotype that includes B8 and DR3 [2]. Neither chronological sequence of appearance nor preferential anatomic location of CD in association with sarcoïdosis was apparent. In our patient, CD developed 3 years after the

diagnosis of sarcoïdosis.

The similarities of CD and sarcoïdosis are striking. In fact, they share many clinical and immunological features which suggest that they may be more closely related. In fact, in both of them, we can find erythema nodosum, uveitis and arthritis and the Kveim test may be positive in CD. On the other hand, it has been demonstrated that an expansion of T-cell subsets, similar to the one observed in LBA in case of sarcoïdosis, exists in the lung of patients with CD [3]. CD4 lymphocytes are also activated in the intestinal mucosa of patients with CD, suggesting a cell-mediated disease mechanism in the gut similar to that displayed by pulmonary sarcoïdosis. Moreover, there is an evidence of an increased mucosal permeability of the gastrointestinal and respiratory tracts in active and inactive CD [11]. Inversely, increased gut permeability in active pulmonary sarcoïdosis has also been described [12]. Nevertheless, some alterations have been observed supporting the hypothesis of immunoregulatory defects as a common initiating factor in both disorders: a) heightened activity of circulatory killer and natural killer lymphocytes b) excess of T helper lymphocytes in sites of disease activity in the intestinal mucosa and alveolar wall c) the presence of circulating immune complexes and autoantibodies [13]. Thus, distinguishing sarcoïdosis from CD can be difficult when sarcoïdosis is limited to the gastrointestinal tract. 0n the other hand, pulmonary manifestations in CD are well-known, and usually accompany or follow the intestinal symptomatology. These manifestations include lymphocytic alveolitis found in up to 54%, interstitial disease, pulmonary function abnormalities, granulomatous inflammation and if found, they are often linked to sulfalazine and mésalamine [14,15]. However, the diagnosis of sarcoïdosis can be established once the extra-intestinal features become evident. Hence, increased CD4/CD8 ratios on bronchiolar lavage have been shown to be very specific for sarcoïdosis, often preceding granuloma formation [16]. Nevertheless, the specificity of serum ACE levels for sarcoïdosis is approximately 90%. In contrast, serum ACE levels in CD patients were normal or very low, especially during periods of active disease [17]. Findings of lymphocytic alveolitis with a CD4/CD8 ratio of 75 and ACE level to twice the upper normal value would have supported the diagnosis of sarcoïdosis in our patient. Moreover, the bilateral hilar lymph node enlargement with some under pleural micronodules of the left lower lobe found in our patient are not typical of CD.

On the other hand, the involvement of the gastrointestinal tract by sarcoïdosis has also been reported and usually occurred in patients with disseminated sarcoïdosis. The stomach is most commonly involved. The localization of the disease in the colon is rarer [18]. In our patient, a diagnosis of Crohn's colitis was made on the basis of endoscopic and histologic findings and on the presence of a perineal fissure.

In summary, CD and sarcoïdosis occur together very rarely. They may share a common pathogenesis and even a genetic basis. The identification of the precise genetic predisposition and/or environmental factors that target the sequence of their involvement, awaits further studies.

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