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Association of sarcoidosis and ulcerative colitis: a review of 20 cases

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Abstract. Sarcoidosis and ulcerative colitis is a rare association. We report a case of this association and describe its clinical, radiological and functional characteristics based on a review of the literature. This association must be recognized by the physician and must be clearly distinguished from a systemic site of ulcerative colitis or drug-related pneumonitis. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 212-216)*

Key words: ulcerative colitis, sarcoidosis, HR-CT scan

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that can involve organs other than the gastrointestinal tract, mainly the respiratory tract (1-2). The association of sarcoidosis and UC (3-4) is rare and the link between the two disorders has not been clearly established. We report a personal case of UC-associated sarcoidosis and discuss the clinical features of this association based on a review of the literature.

Case report

A fifty-year-old man, ex-smoker, was referred for subacute breathlessness. He had been diagnosed, eight years previously, with UC based on clinical, endoscopic and histological criteria. He was successfully treated with salazopyrine and corticosteroid enema, and treatment was subsequently stopped following stabilization of the IBD. On admission, he presented features of UC relapse including abdominal pain, bloody diarrhea and 12 kg weight loss, associated with subacute respiratory failure characterized by NYHA class IV dyspnea and bilateral lung crackles. No signs of clinical pulmonary arterial hypertension or heart failure were demonstrated. Temperature was 37°C. Chest X-ray and chest HRCT scan showed enlargement of hilar and mediastinal lymph nodes associated with diffuse and bilateral micronodules in the upper lobes, and ground glass densities in the lower lobes. Arterial blood gases at 21% FiO_2 showed PaO_2 66 mmHg, $PaCO_2$ 33 mmHg, pH 7.44, SaO_2 94%, HCO_3^- 23 mmol/l. Complete blood count, serum electrolytes, protein, albumin globulin, renal and liver function tests were normal, as well as immunological and serological tests for *Mycoplasma*, *Chlamydia* and *Coxiella psittaci*. Angiotensin-converting enzyme was 124 IU/L. Bronchoalveolar lavage (BAL) fluid contained 10^6 cells per milliliter, with 78% lymphocytes (CD4+/CD8+ ratio: 5.2), 13% macrophages, and 4% neutrophils. Testing for

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Pneumocystis jiroveci, *Mycobacterium tuberculosis*, and yeasts remained negative. Transbronchial biopsies (TBB) revealed an epithelioid and giant cell granuloma pattern, consistent with stage II mediastinopulmonary sarcoidosis. Oral prednisone was started at 0.5 mg/kg/day. Lung function testing was performed after one month of treatment, showing FEV_1 at 79% predicted, FVC 74% predicted, FEV_1/FVC 84%, TLC 83% predicted, DLCO/VA 84% predicted. Prednisone dosing was tapered over an 18-month period, resulting in complete remission.

Methods

A PubMed database search identified 20 English-language articles documenting an association between sarcoidosis and ulcerative colitis, published between January 1985 and December 2012. Demographic, clinical, laboratory, and imaging data and comorbidities were analyzed.

Results

Demographic data

The sex ratio of patients with UC associated with sarcoidosis was 7 M/3 F.

Ulcerative colitis features (5-13)

The mean age at onset of UC was 38 ± 15.13 years. Gastrointestinal manifestations were the same as those usually reported, including bloody diarrhea (75%), abdominal pain (42%), rectal bleeding (17%). Intestinal involvement was diffuse (60%), localized to the rectosigmoid (35%). Extra-gastrointestinal (thoracic or extrathoracic) sites were not reported. UC histology was obtained in all cases. Medical treatment was initiated in 87% of cases, consisting of sulfadiazine alone (8.3%) or in combination with systemic steroids (75%). Surgical treatment was performed in 33% of patients, consisting of proctocolectomy (60%), or subtotal colectomy (20%). Remission was achieved in 64% of patients, but a chronic course with exacerbations was reported in 21.5% of cases. UC remained active despite treatment in 14.5% of cases (Table 1).

Table 1. Clinical and radiological characteristics of 20 cases of UC/sarcoidosis association; *n indicates the number of patients for which data are available in the literature

	n*	Number of Patients (%)
UC characteristics		
Gastrointestinal symptoms	12	
Bloody diarrhea		9 (75)
Abdominal pain		5 (42)
Rectal bleeding		2 (17)
Medical treatment	12	
Sulfasalazine		1 (8.3)
Sulfasalazine + SS		9 (75)
Bowel surgery	15	5 (33)
Follow-up	14	
Remission		9 (64)
Stability with relapses		3 (21.5)
Persistent activity		2 (14.5)
Sarcoidosis characteristics		
Pulmonary symptoms	14	8 (57)
Dyspnea		6 (75)
Cough		6 (75)
Dyspnea + cough		5 (62.5)
Chest pain		2 (25)
Extrathoracic manifestations	16	14 (87)
Cutaneous		3 (21.5)
Ocular		4 (29%)
Liver/spleen enlargement		3 (21.5)
Myalgia		3 (21.5)
Weight loss		3 (21.5)
Fever		2 (14)
Chest X-ray	19	
Stage 0		3 (16)
Stage I		4 (21)
Stage II		5 (26)
Stage III		7 (37)
Stage IV		0 (0)
HRCT		
Lymph nodes	6	5 (83)
Micronodules		3 (50)
Ground glass hyperdensity		1 (16.5)
Alveolar condensation		1 (16.5)
Pulmonary function tests	5	
Airways obstructive pattern		1 (20)
Restrictive pattern		3 (60)

Sarcoidosis features (5-13)

The mean age at onset of sarcoidosis was 42 ± 13.2 years. UC was the first disease in 62.5% of cases and sarcoidosis occurred up to 11 ± 5.4 years after onset of UC. In 25% of cases, the onset of UC was delayed with respect to sarcoidosis and in 12.5%

of cases, the two disorders occurred simultaneously. The first signs of sarcoidosis were associated with relapse of UC in 33% of cases. Pulmonary involvement was present in 57% of cases, including dyspnea (75%), cough (75%), both symptoms (62.5%) and pleural pain (25%). Extrathoracic manifestations were observed in 87% of cases, including skin (21.5%), ocular (29%), liver/spleen enlargement (21.5%) myalgia (14%), weigh loss (21%) and fever (14%) (Table 1). Radiographic patterns corresponded to stage 0 (16%), I (21%), II (26%), III (37%) sarcoidosis, but no type IV was reported. Data from chest HR-CT scan were available for 6 patients, consisting of interbronchial and mediastinal lymph node enlargement (83%), upper lobe micronodules (50%), alveolar condensation (16.5%), and ground glass hyperdensity (16.5%). Pulmonary function tests, available in only 25% of cases, revealed airway obstruction in 20%, and restriction in 60%. In 2 of the 3 reported cases, BAL showed an increased alveolar lymphocyte count with a mean value of 77%. The diagnosis of sarcoidosis was confirmed by biopsy in 80% of cases: bronchial/transbronchial (25%), liver (6%), scalene node (18%), skin (6%), and mediastinal node (6%). A comorbid condition was present in 31% of patients: pancreatic or bowel neoplasia (n=2), diabetes mellitus (n=2). An association with primary sclerosing cholangitis, Sjögren's syndrome, and cirrhosis was reported in one case each.

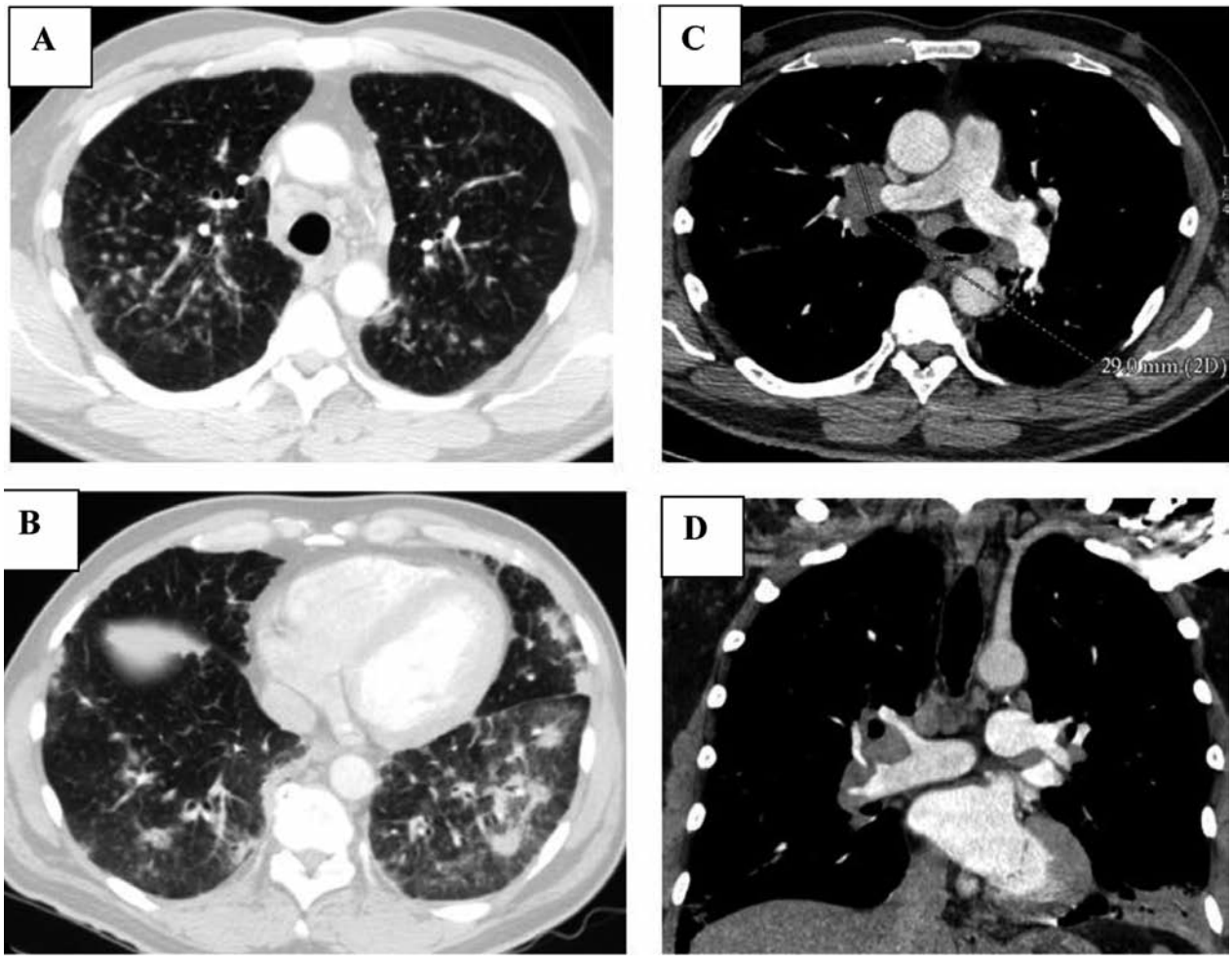

Fig. 1. Chest CT showing (A) micronodules in upper lobes (B) ground glass pattern, condensations and thickening of peribronchovascular bundles (C-D) interbronchial and mediastinal lymph node enlargement

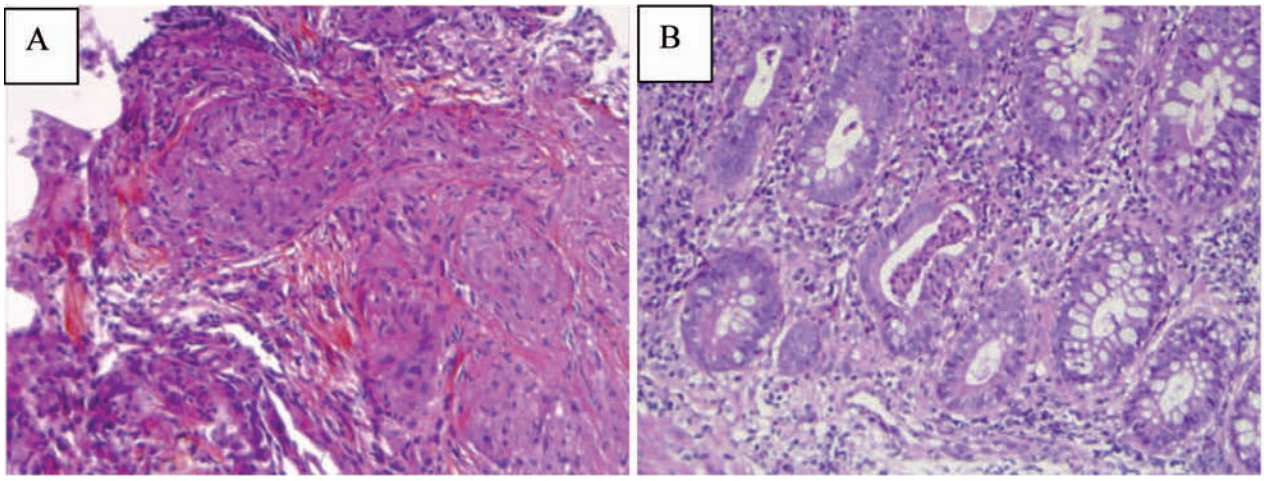

Fig. 2. (A) Bronchial biopsy showing noncaseating granulomas consisting of nodular clusters of epithelioid and giant cells (HPS x 20). (B) Rectal biopsy showing mucosal infiltration by mononuclear and polymorphonuclear cells. Proctitis activity is demonstrated by the presence of neutrophils infiltrating the wall of some crypts (HPS x 20)

Discussion

IBD are associated with various types of respiratory manifestations (1-2). A review of the literature comprising 155 cases of IBD associated with respiratory disorders showed that upper airway, large airway, lung parenchyma involvement, serositis and vasculitis are more often associated with UC than CD (1). Conversely, small airways disease is observed with a similar frequency in both types of IBD. Upper airway involvement is characterized by glottic/subglottic stenosis, tracheal inflammation with or without stenosis, and bronchial suppuration, possibly associated with bronchiectasis. Organizing pneumonitis (OP) is the most common interstitial lung disease associated with UC, a histological pattern that can also be attributed to aminosalicylate (ASA) or sulfasalazine exposures (1-4). Other lung inflammatory/fibrotic changes including Usual Interstitial Pneumonia, Non-Specific Interstitial Pneumonia, Desquamative Interstitial Pneumonia, and necrobiotic nodules have been reported. Respiratory involvement usually develops after clinical onset of UC, even after colectomy, but in some cases, it can predate the bowel disease (4). The development of respiratory involvement does not appear to be correlated with UC disease activity or severity, except for serositis (1).

Sarcoidosis is a systemic granulomatous disorder (14) that, in some cases, affects gastrointestinal tract (15-16). Conversely, CD shares the same epithelioid and giant cell granulomatous hallmark as sarcoidosis and can involve the respiratory tract. Furthermore, several cases of overlap syndrome have been reported (17), therefore making the distinction between the two disorders somewhat difficult. In contrast, the pathological feature of UC is a nongranulomatous inflammation of the intestinal mucosa (18).The presence of epithelioid and giant cell granulomas in the bronchial mucosa therefore suggests lung sarcoidosis rather than UC lung involvement. To our knowledge, 20 cases of this association have been published over the last 30 years (5-13). Several clinical features of UC-associated sarcoidosis differ from the classical form (Table 2) (19-20). Males are over-represented with a sex ratio of 7 males/3 females, contrasting with a female predominance in isolated sarcoidosis (14). In most cases, sarcoidosis occurs several years after onset of UC and the two diseases appear to have an independent clinical course (1-2, 4). In other cases, sarcoidosis appears before or at the same time as UC. UC-associated sarcoidosis is usually symptomatic at presentation, as 70% of patients complain of cough and dyspnea in the review of the literature. Radiographic patterns are similar between UC-associated sarcoidosis and isolated sarcoidosis, but radiographic stages II and III are more frequent that stage I, in contrast to isolated sarcoidosis (19). HR-CT scan data were available in only 6 cases, revealing similar patterns to those observed in the isolated form of sarcoidosis. Interbronchial and/or mediastinal lymph

Table 2. Comparison of clinical and radiographic features between classical and UC associated sarcoidosis. *from (14); ** from (19)

	Classical sarcoidosis	Ulcerative colitis-associated sarcoidosis
Median age at onset (yrs)*		
Male	38	44
Female	45	40
Male to female ratio	1.0	2.3
Respiratory symptoms (%)	30-50	57
Extrathoracic manifestations(%)*		
Skin	25-35	21
Ocular	25-80	29
Liver-spleen	5-15	21
Chest-X ray presentation (%)**		
Type 0	5-10	16
Type 1	50	21
Type 2	25-30	26
Type 3	10-12	37
Type 4	5	0

nodes were observed in all cases with the same characteristics as those reported in typical sarcoidosis (14, 19-20). Lung infiltration was associated with lymph nodes in 50% of cases, presenting as micronodules in the upper lobes, alveolar condensations or ground glass pattern in the lower lobes. Interestingly, two patterns of lung infiltration coexist, combining a well delineated distribution of micronodules in the upper lobes and a ground glass pattern in the lower lobes. Of note, crackles were present in the lung bases, a rare feature in typical sarcoidosis. This type of clinical presentation therefore suggests either a pulmonary site of UC or a drug-related pulmonary disease (21). As the patient reported here was not treated with 5ASA or other pneumotoxic drugs, a drug-induced lung disease was ruled out and the presence of epithelioid and giant cell granuloma in the bronchi was strongly in favor of the diagnosis of sarcoidosis.

In conclusion, UC and sarcoidosis is a rare association, as only 20 cases have been reported to date. Both disorders are chronic inflammatory diseases, but each of corresponds to different pathways. In sarcoidosis, the T-cell response is biased toward a Th-1 phenotype with increased production of IFN-γ and IL-12 contrasting with a Th-2 like condition in UC (14, 18, 22). There is therefore no evidence at the present time that the two disorders are due to the same immune activation process, suggesting a purely incidental association between these two disorders. Nevertheless, this association must be recognized by the physician and must be clearly be differentiated from a systemic site of UC or drug-related pneumonitis.

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