Journal of Crohn's and Colitis (2007) 1, 116–121

available at www.sciencedirect.com

SHORT REPORT

An unusual case of Crohn's disease with unresponsive pleural exudates. Is Crohn's disease finally a systemic immunological disorder?

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Received 7 August 2007; accepted 16 August 2007

KEYWORDS
Crohn's disease;
Pleural effusion;
Autoimmunity;
Systemic lupus erythematosus

Abstract

Crohn's disease has been infrequently associated with various respiratory manifestations. Reports of pleural effusions in Crohn's disease are even sparser, but differential diagnosis is rich, with causes either associated with the disease or being independent. Processes directly or indirectly related to therapy, entities overlapping with Crohn's disease in pathogenesis and common causes of effusions should all be considered, under the guidance of laboratory testing and imaging. We report here an unusual case of bilateral pleural effusions unresponsive so far to medical therapy, in a patient with long-standing Crohn's disease and several features of autoimmunity. A short review of the literature is presented, the differential diagnosis is outlined and the systemic immunological profile of Crohn's disease is discussed.

1. Introduction

Respiratory involvement in Crohn's disease (CD), although a rare extraintestinal manifestation,[1] covers a wide spectrum of clinical presentations, reviewed in detail by other authors[2,3] : Subclinical pulmonary function abnormalities, drug-induced disease, anatomic (fistulous) disease, overlap granulomatous disease, autoimmune vasculitis, upper respiratory tract inflammation, chronic bronchitis & bronchiectasis, interstitial lung diseases and pleural effusions. Drug-induced pulmonary disease due to sulphasalazine, mesalazine and methotrexate, although rare as a complication must always be ruled out in cases with pulmonary involvement.

Pleural effusions and/or pleuritis have been infrequently reported in CD in association with various entities: colobronchial fistula,[4] esophagopleural fistula,[5] ileobronchial fistula,[6] sulphasalazine/mesalazine therapy,[7–9] mesalazine-induced lupus,[10] pulmonary embolism,[11] infliximab-associated tuberculosis,[12] azathoprine-associated tuberculosis,[13] infliximab-associated lymphoma[14] and sarcoidosis.[15,16] Several case reports have focused on CD coexistence with

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doi:10.1016/j.crohns.2007.08.007

autoimmune disorders, namely Systemic Lupus Erythematosus.[17–23] Of course one should always consider and try to exclude the universal neoplastic, infectious, inflammatory and metabolic causes of any pleural exudate, which can equally be responsible for the occurrence of a pleural effusion in a patient with CD.

2. Case report

A 43-year-old woman with Crohn's disease for 21 years presented in October 2003 due to progressive dyspnea on exertion of 10 days duration. The patient did not report any fever, cough or pleuritic chest pain and no symptoms of bowel origin. She had discontinued oral methylprednisolone treatment 12 days ago following a slow dose tapering, after 3 months of therapy because of a presumed relapse with extraintestinal manifestations (myalgias, arthritis of the knees and ankles).

In 1981 our patient was first diagnosed with Crohn's colitis and severe perianal fistulizing disease. For 6 years the disease followed a fluctuating course, during which she was treated with a combination of medical treatment (steroid courses, anti-biotics, sulfasalazine) and surgery for the perianal disease. She was on remission from 1987 to 1992 when she relapsed with bloody diarrhea. Following institution of azathioprine therapy (never discontinued until now) she entered a long remission period, with no symptoms of gastrointestinal CD to date. Subsequently she had two exacerbations of extraintestinal musculoskeletal manifestations (myalgias of the lower extremities and mild ankle and knee arthritis), one on May 2002 and another in July 2003. Both responded to combination of methylprednisolone, azathioprine plus mesalazine (32 mg, 150 mg and 1.5 gr/day respectively), but 12 days after steroid withdrawal on the later occasion she presented with bilateral pleural effusions. The patient had never smoked tobacco, had never had occupational or accidental exposure to asbestos and had never suffered thromboembolic disease or fetal loss. She had been taking for 10 years Lamptrigine 200 mg daily for absence seizures and Clobazam 15 mg daily for psychoaffective disorders attributed to CD.

At presentation the patient, in otherwise good general condition and afebrile, had signs of bilateral free pleural fluid. Physical examination was otherwise unremarkable. The chest X-Ray showed bilateral pleural effusions (Fig. 1). ECG showed a mild sinus tachycardia and arterial blood gases were within the normal range. Full blood count showed mild leucopenia with normal eosinophil count, erythrocyte sedimentation rate was 12 mm and C-reactive protein was normal. A tuberculin skin test was negative (0 mm). Coagulation studies, serum calcium, creatinine and the usual biochemical panel were normal, as was urinalysis. Diagnostic thoracentesis revealed an exudate of clear appearance and normal glucose, amylase and lipid concentrations, with a white blood cell count of 645/μl and a predominantly lymphocytic differential count. Smears and cultures were negative for common pathogens, fungi and Mycobacteria. A PCR examination of the pleural fluid for M. Tuberculosis was also negative. Cytology showed signs of chronic lymphocytic inflammation with secondary hyperplastic mesothelial reaction but no signs of malignant disease, while flow cytometry of the pleural fluid was unremarkable.

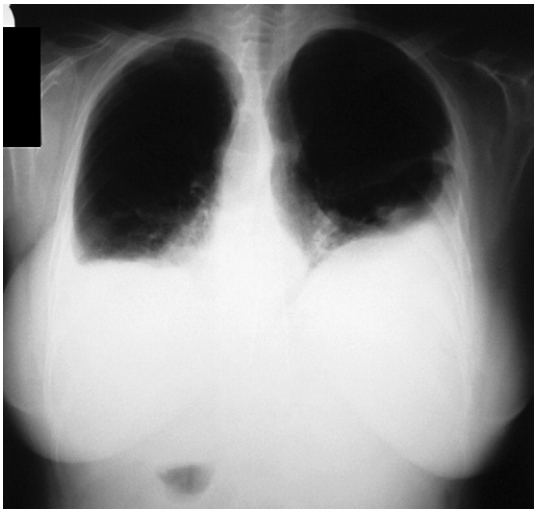

Figure 1 Chest X-Ray before thoracentesis.

There were no indications of monoclonal proliferation of β-lymphocytes or T-lymphocytes during gene rearrangement studies of heavy chain variable domain and TCR variable domain, respectively. Serum B_2-microglobulin, tumor markers, angiotensin converting enzyme, 24-hour calcium urinary excretion and thyroid function tests were all normal. Serological testing was negative for viral hepatitis, systematic bacterial and viral infection (with the exception of CMV IgG positivity). There was a mild increase in a_2-globulin fraction and in IgA concentration. C_4 was on the low-normal range on repeated tests. Rheumatoid factor, anti-cardiolipin anti-bodies, anti-dsDNA anti-bodies, anti-histone anti-bodies and ANCA were undetectable, while anti-nuclear anti-bodies (ANA) were present in a speckled pattern at a titer of 1/640 and anti-SSA (Ro52 & Ro60) were positive (Table 1). Immunological testing of the pleural fluid revealed low complement concentrations and ANA positivity in a speckled pattern at a titer of 1/320 with undetectable anti-dsDNA antibodies. A chest CT did not detect any enlarged mediastinal lymph nodes and revealed focal right middle lobe and lingual atelectasis, while an abdominal CT diagnosed left nephrolithiasis with otherwise normal findings. Methylprednisolone (32 mg daily) plus Ethambutol, Isoniazide, Rifampicin and Pyrazinamide (1200, 300, 600 and 2000 mg daily, respectively) were immediately started and Mesalazine was discontinued. Anti-tuberculous therapy was withdrawn after 10 days because of hepatotoxicity and paresthesias. Isoniazid monotherapy 300 mg daily was reinstituted on December 12th and was adequately tolerated.

The patient was readmitted on January 23rd 2004 due to left-sided pleuritic chest pain and dyspnea. There was a sinus tachycardia, mild hypoxemia and an enlargement of the left-side effusion on chest X-Ray. Pleural fluid was again a lymhocytic exudate, and a combined CT of the thorax/pulmonary angiography excluded pulmonary embolism and revealed a round lingual infiltrate (2.5 cm diameter). The patient responded to ceftriaxone i.v. plus analgesics.

On February 14th following therapeutic thoracentesis a failed attempt for needle biopsy of the pleura resulted in right-sided pneumothorax. After chest tube decompression

Table 1 Synopsis of laboratory findings in serum, urine, pleural fluid and bronchoscopy specimens

Blood tests		
Full Blood Count		Mild leukopenia, normal eosinophil count
ESR, CRP		Normal
Serum biochemistry		Ca, BUN, Cre, T3, T4, TSH normal
ACE		24 i.u./ml
CEA, Ca 19-9, AFP, Ca 15-3, b_2-microglobulin		Negative
Immunological testing		C4 16 mg/dl, ANA 1/320-1/640 speckled pattern, anti-SSA positive
Serology for Brucella Mellitensis, Leishmania Donovani, Leptospira Interrogans, Coxiella Burnneti and Mycoplasma pneumoniae		Negative
Serum electrophoresis & immunoglobulin concentration		Normal
Urine testing		
Urinalysis		Inactive sediment
24-hour calcium urinary excretion		178 mg/24h
Pleural fluid tests		
Microscopy	Cells	170–2980/μl
	Differential	Lymphocytes 50–95%, polymorphonuclear 4–50%, monocytes 1–40%
Biochemistry		Exudate (LDH ratio 0.49–0.9, protein ratio 0.69–0.74), Glucose 87–153 mg/dl
Cytology		Lymphocytic invasion, mesothelial reaction
Flow cytometry	1st	CD3 41%, CD19 6%, CD16+56 9%, CD38+46%, CD4 37%, CD8 16%
	2nd	CD4 95%, CD8 2%,
Gram stain, Ziehl–Nielsen, culture (& acid-fast), PCR M.Tb		Negative
CEA		0.5
Ca19-9		8
Ca15-3		25 i.u./ml
Ca125		45
β2-microglobulin		2037
Immunological testing		C3 22.1, C4 2.03 mg/dl, ANA 1/320 speckled pattern, anti-dsDNA negative
FOB		
Endoscopic findings		Normal
Sputum culture		Negative

CT of the thorax revealed encapsulated effusion on the left side with bilateral pleural thickening, focal bilateral atelectasis plus focal right basilar infiltrate. No evidence of endobronchial lesion was found on fiberoptic bronchoscopy and bronchoalveolar lavage findings were normal. Smears and cultures of bronchial washings and post-bronchoscopy sputum were again negative for Mycobacteria, mantoux was again negative and pleural fluid characteristics remained constant during multiple examinations, all of the smears and cultures being negative.

A course of triple anti-tuberculous therapy was reinstituted but was again soon discontinued due to considerable transaminase elevations. Frequent therapeutic thoracentesis was necessary and on June 2004 steroids were withdrawn due to cushingoid features and poor results. In the following 5 months the patient's condition remained stable with need for frequent paracentesis and on October 2004 mantoux was again negative and immunological tests were normal with the exception of ANA in a speckled pattern at a titer of 1/320. It was then decided to attribute the effusions to CD per se and Infliximab was initiated (300 mg) on October 15th 2004. After the second dose of Infliximab no improvement was seen and the patient declined the alternative of an open surgical pleural biopsy or a thoracoscopy procedure. A new CT of the thorax on November showed multiple focal bilateral atelectases on middle–lower lung fields with no evidence of enlarged mediastinal nodes.

Until June 2005 the patient continued Infliximab (10 doses) with concomitant low-dose methylpredisolone (8 mg) and azathioprine 150 mg daily, with no obvious benefit and in need of frequent large volume paracentesis. Infliximab was discontinued at that time and methotrexate was added (25 mg/week in 2 divided doses). Therapy had no apparent result until September 2005 when methotrexate was discontinued due to hepatotoxicity. In the meantime (July) the patient suffered a minor respiratory infection treated with moxifloxacin 400 mg daily, during which a heart ultrasound revealed a small pericardial effusion, undetected in a follow-up study one month later. Since September 2005 the patient continued azathioprine plus low-dose methylpredisolone therapy (8 mg) with no apparent improvement in effusion size. Pleural fluid characteristics remained constant and cytology normal. Surprisingly enough, flow cytometry of a recent pleural fluid specimen revealed an almost complete predominance of CD4 lymphocytes (95%) with no signs of monoclonal proliferation.

3. Discussion

The differential diagnosis of a pleural exudative effusion is often a challenge for the clinician, given the multitude of possible etiologies involved and their frequently overlapping clinical and laboratory findings. In Crohn's disease the issue is further complicated by its unique, although rare associations already stated.

In our patient, a fistulous cause was readily excluded by the absence of empyema and associated pneumonia, while no fistulous tract was found on imaging. Mesalazine hypersensitivity pneumonitis-effusion was excluded in our patient without a lung or pleura biopsy, as there was no peripheral or pleural fluid eosinophilia and no improvement

was seen after therapy withdrawal, with adequate steroid therapy. Pulmonary embolism was readily excluded by imaging, normal d-dimmers and the absence of hemorrhagic exudate, being incompatible with the chronicity of the effusions. The clinically unfavorable possibility of infection by common bacteria, fungi and viruses was excluded by serological and microbiological testing. Accordingly, a subdiaphragmatic septic or inflammatory cause was readily excluded by clinical examination and imaging, as was Meigs syndrome. The diagnosis of Asbestosis was excluded in lack of historical and radiological clues. Metabolic causes were not supported by biochemical testing and no known pharmacological cause was determined, other than mesalazine.

On the other hand and on multiple examinations there was no clinical, imaging, laboratory endoscopic or cytological clue for a malignant cause of the effusion, (primary lung malignancy, malignant mesothelioma, metastatic carcinoma or lymphoma). The association of Crohn's disease and bowel lymphoma is a known fact.[24] Pleuritis due to an unrecognized extranodal lymphoma, although rare cannot be positively excluded in our patient, but seems improbable due to the chronicity of the case, the repeatedly negative cytology and incompatible flow cytometry. Accordingly, the very rare Primary Effusion Lymphomas have been reported only in association with advanced AIDS.

The possibility of tuberculous pleurisy was seriously examined in our patient, in view of recent reports of tuberculosis in azathioprine treated patients with CD.[13,25] Our patient was not aware of tuberculous contacts, had never traveled abroad in endemic areas, and had been vaccinated with BCG at the age of 10. She was afebrile with no constitutional symptoms and acute phase indices were normal, contrary to the usual presentation of Tb pleurisy, but developed some pleural thickening 5 months after diagnosis, a common finding in tuberculous pleurisy (Fig. 2). Mantoux test was negative in all 4 instances but under immunosuppressive therapy. Interestingly enough, mantoux has been reported positive in only 40% of the patients with isolated tuberculous pleural effusion.[27] Nevertheless an induration of 10 mm is formally required in our patient's group for a positive result,[26] while it was 0 mm in the first test and 4 mm (maximum) in the fourth test. Sputum smears and cultures were negative, but they have been reported positive in only 4% of the patients with isolated pleural effusion due to Tuberculosis. The negative smears and cultures of FOB and post-bronchoscopy specimens are a much more reliable result, although the sensitivity of this method in tuberculous pleurisy has not been reported. Pleural fluid smears and cultures were negative for acid fast bacilli, but this method diagnoses only 50% of the patients with tuberculous pleurisy.[28] Pleural fluid PCR was also negative and, as this method was reported to have a sensitivity comparable to pleural biopsy (77%) and high specificity (78–100%),[28] this is the strongest point against tuberculous pleurisy diagnosis, and partly overcomes our important omission of a pleura biopsy. The therapeutic criterion cannot be fully appreciated in our patient, given the short, discontinuous therapy period. Nevertheless we insisted on instituting anti-mycobacterial therapy in view of the foreseen initiation of Infliximab, but hepatotoxicity hampered our plan.

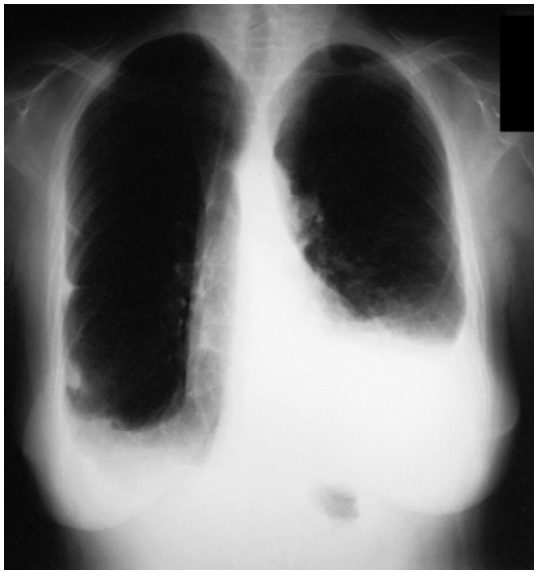

Figure 2 Chest X-Ray after therapeutic thoracentesis. Pleural thickening in right lower lung field.

Several cases of associations of CD with sarcoidosis have been reported in the literature and many investigators have stressed the clinical, microbiological, immunological and possible genetic, pathogenetic or even therapeutic similarities between the 2 entities.[15,16,29–32] In favor of such a coexistence in our patient was the first Mantoux test that could be interpreted as anergy and nephrolithiasis. On the other hand, nephrolithiasis is a common feature of CD and a common incidental finding, all the biochemical indices compatible with sarcoidosis were normal, and no lympadenopathy or extrapulmonary features of sarcoidosis were detected. There was also no improvement under adequate steroid-immunosuppressive therapy.

As far as collagen-vascular diseases are concerned, rheumatoid arthritis was excluded as a cause of the effusions based on lack of criteria for diagnosis[33] (only symmetrical arthritis) and seronegativity of rheumatoid factor. In spite of Ro-SSA positivity Sjögren's syndrome diagnosis cannot be supported in our patient in lack of any sicca findings or extraglandular involvement. Could she have some compatible form of vasculitis? Absence of skin lesions, renal involvement and negative ANCA do not support the diagnosis, but presence of migratory lung infiltrates is compatible, although it cannot be evaluated without a biopsy. Microscopic polyartiritis is not a favourable diagnosis, lacking the glomerulonephritis features and with negative p-ANCA. Churg–Strauss disease is not supported by lack of asthma, eosinophilia and with no lung biopsy. Our patient lacks the typical upper airway features, skin, orbital, heart and kidney involvement and c-ANCA positivity of Wegener Granulomatosis, another granulomatous disease with suggested common pathophysiology with CD.[34]

There has been an increasing number of reported associations between CD and Lupus syndromes. Older and recent reports have focused on the issue of drug-induced lupus due to sulfasalazine and mesalazine.[10,35] Our patient had few compatible clinical findings (arthralgias and pleuritis) and serological indices (positive ANA, negative anti-dsDNA), but also had negative anti-histone anti-bodies and persistence of the disease after mesalazine withdrawal,

excluding the diagnosis. No findings of Subacute Cutaneous Lupus were present other than Ro-SSA anti-bodies. Several other authors reported on cases of CD and Systemic Lupus Erythematosus (SLE) coexistence, with both diseases preceding the other at different cases.[17–23] In these cases, to the best of our knowledge there has never been a report of a pleural effusion. On reviewing our case we found four definite criteria positive for SLE diagnosis[36]: Non-erosive arthritis of 2 or more peripheral joints, serositis (pleuritis), history of seizures and an abnormal ANA titer persisting in time when mesalazine had been stopped. Although diffuse and homogenous patterns are more common in SLE, speckled patterns as in our case can also be seen. Other less crucial clinical and laboratory features of our case are consistent with SLE: Fleeting pulmonary infiltrates without purulent sputum are features of lupus pneumonitis; the low-normal value of C_4 is consistent but not characteristic of SLE as is a low C_3 component; the normal or near-normal value of CRP (but under immunosuppressives) during active disease is also consistent with the diagnosis of SLE. Of course one can comment on the absence of more common and typical features of SLE such as renal involvement, skin lesions and anti-dsDNA anti-bodies. However, clinical and laboratory features of the 2 entities frequently overlap, rarely creating a diagnostic problem at initial presentation. In our case the initial diagnosis of CD is not in doubt, but we cannot easily exclude the possibility of SLE coexistence, having 4 positive criteria.

Finally, there is a strong possibility of facing a rare isolated pulmonary manifestation of CD unrelated to therapy. There are few reports of such cases and definition of pleuritis as an extraintestinal manifestation of CD was always problematic due to the small patient number and the diagnosis made by exclusion.[3,37] Pleuritis was associated with a pericarditis in these cases and occurred during the quiescent phase of bowel disease (as apparently in our case). Contrary to our case, pleuritis resolved easily with steroids. The subacute presentation of pleuritis soon after steroid withdrawal (given for another extraintestinal flare of CD) also supports this diagnosis. The surprising feature in our patient lies on the unresponsiveness of the effusions to adequate anti-inflammatory therapy specific for CD, suggesting an unusual immunological activation, possibly involving other contributing mechanisms in addition to the TNF-a pathway. In favor of this profound immunological activation lies the detection of several autoimmune markers in both serum and pleural fluid and the evolution of pleural fluid flow cytometry towards a CD4-predominant population. We believe that these findings are important as they support a silent but unproven notion of many clinicians: that a definition of some autoimmune or inflammatory disorders (including CD) in strictly separated, non-overlapping entities, although helpful for teaching or statistical purposes, can be problematic in clinical management of specific patients. Furthermore, in CD the derangement of bowel mucosal barrier–regulatory immunological function can presumably lead to autoimmune extraintestinal disorders, similar but not identical with "classical" autoimmune entities. Maybe it is time to recognize these more rare disorders as part of a systemic immunological derangement of CD and implement therapeutic strategies individualized to each patient needs.

4. Conclusion

In brief, we have reported a case of a patient with longstanding CD in apparent remission of bowel disease, but unresponsive bilateral exudative pleural effusions during a 3 year follow-up period. During this time the effusions were associated with transient migratory infiltrates and localized pleural thickening. There was no therapeutic effect after mesalazine withdrawal, after 2 months of empirical anti-mycobacterial therapy and after 3 years of adequate continuous therapy for CD. The specificity of our observations in our patient lies in the rarity of isolated pleural effusion in quiescent CD and the overlapping clinical and laboratory autoimmune features.

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