

## Letters to the Editor

### A Combination of Two rare Granulomatous Diseases

#### *Asociación de dos enfermedades granulomatosas raras*

To the Editor:

Sarcoidosis is a multisystemic granulomatous disease that affects middle-age adults with a greater proportion of women and certain ethnic groups. It has a very variable incidence, between 10.9 in white Americans and 35.5 per 100,000 in afro-Americans. It can affect different organs, although the most frequent form is pulmonary affection. Histologically, granulomas are observed, although they are not exclusive of this pathology. On rare occasions, it is associated with other rare diseases such as primary biliary cirrhosis, also characterized by the formation of granulomas.<sup>1,2</sup>

We present the clinical case of a 60-year-old man, an active smoker (with a total accumulated dosage of 5 pack-years), who consulted with his physician due to chest pain with pleuritic characteristics and dry cough. He has arterial hypertension in treatment with nimodipine and prior cerebrovascular disease. Physical examination revealed the presence of hypoventilation on respiratory auscultation. Blood analysis showed gamma-glutamyl transpeptidase 203 UI/L, alanine transaminase 242 UI/L, with normal bilirubin values. Chest radiography presented a bilateral interstitial pattern predominantly in the upper lobes. High-resolution computed tomography of the thorax demonstrated a 1.2-cm right axillary lymphadenopathy, mediastinal lymphadenopathies smaller than 1 cm, some of them calcified in bilateral hilar and subcarinal locations and ground-glass increase in density with thickening of the peribronchovascular interstitium with bilateral and diffuse micronodular morphology (fig. 1). The flow-volume curve and plethysmography showed no alterations. Carbon monoxide diffusion was 87%, and 76% when corrected for alveolar volume. Bronchoscopy detected no alterations in the bronchial tree. Bronchoalveolar lavage revealed a cellularity with 88% macrophages, 8% lymphocytes and 2% eosinophils. CD4 samples analyzed showed 78% CD4 lymphocytic population, 6% CD8 and 3% lymphocytes. Microbiological studies were negative. Transbronchial biopsies demonstrated interstitial-pattern pneumonitis with inflammatory infiltrate, that expanded the interstitium and in some areas formed granulomatous lesions constituted by epithelioid histiocytes that were accompanied by foreign body-type giant cells, some of which converged without central necrosis and had peribronchiolar and perivascular distribution without images of vasculitis. All of this was compatible with non-necrotizing granulomatous inflammation suggestive of pulmonary sarcoidosis. The study was completed with an abdominal ultrasound, where we observed a diffuse increase in hepatic echogenicity with autoimmunity markers that detected high titers of antinuclear (more than 1/160) and M2 antimitochondrial (more than 1/320) antibodies.

Primary biliary cirrhosis (PBC) is an uncommon autoimmune progressive hepatic disease. It more commonly affects middle-aged

women. In the immunological study, the presence of antimitochondrial antibodies is typical, with a specificity of 100%. On occasions, they coexist with other autoimmune diseases (such as Raynaud's disease, systemic sclerosis and Sjögren's syndrome).<sup>2</sup> There are three cases published where PBC and sarcoidosis coexist, with the particularity that the predominant affection of the latter is cutaneous, either pruritus or erythema nodosum.<sup>4</sup> The case provided presents neither typical age nor sex. The overlapping of both diseases makes diagnosis difficult. Symptoms can be varied, from cough to dyspnea and skin eruptions.<sup>5</sup>

The association has been tried to be explained from the physiopathological viewpoint. Both diseases have granulomas that show accumulation of T CD4 cells in the center and CD8 in the periphery. In sarcoidosis, there is peripheral lymphopenia due to accumulation of CD4 lymphocytes compared with the CD8 of the tissue, resulting in an increase of CD4/CD8. In PBC, there is a similar accumulation of lymphocytes in the tissues, but in late stages of the disease there is a disproportionate increase of cytotoxic cells caused by a decrease of CD4 lymphocytes.<sup>2</sup>

PBC is suspected mainly due to dermatological symptoms in 88% of the cases,<sup>2</sup> pruritus being the most frequent. In the blood analysis, a pattern of cholestasis is observed and it is confirmed by the presence of M2 antimitochondrial antibodies and biopsy of liver tissue.<sup>2</sup> It has been demonstrated that ursodeoxycholic acid improves the biochemical and histological manifestations of PBC; this effect is greater the earlier the onset. The efficacy is reduced when there are manifestations of hepatic cirrhosis.<sup>2</sup> Corticosteroids in PBC also improve the histological y biochemical parameters, but their use can be limited due to their side effects.<sup>3</sup> Out of the cases published, in



**Figure 1.** Chest high-resolution computed tomography showing increase in ground glass density with thickening of the peribronchovascular interstitium with diffuse and bilateral micronodular morphology.

one the initial treatment was with methotrexate with worsening of the hepatic function, therefore the patient ultimately received a liver transplant. In the second case, treatment was begun with ursodeoxycholic acid with poor evolution at the pulmonary level. Methotrexate and hydroxychloroquine were therefore added for its control. Finally, in the last case, single treatment was initiated with corticosteroids with poor hepatic evolution, requiring transplantation. The clinical case that we present has been treated with corticosteroids and ursodeoxycholic acid with good control of the disease to date.

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## Usefulness of the Presence of Trophozoites in Pleural Fluid in the Diagnosis of Amoebic Empyema and Liver Abscess

### Utilidad de la visualización de trofozoitos en líquido pleural en el diagnóstico de empiema y absceso hepático amebianos

To the Editor:

*Entamoeba histolytica* (*E. histolytica*) is an uncommon cause of liver abscess, affecting immigrants or travellers to endemic areas,<sup>1</sup> although indigenous cases have been reported in our country.<sup>2</sup> The exact incidence of pulmonary alterations in patients with hepatic amebiasis is unknown, although it has been estimated that there can be clinical or radiological pulmonary findings in 50% of the cases. One-third of said alterations include inflammatory reactions (pleural effusion and pneumonitis), and there is frequently rupture of the abscess to the airway, pleural cavity or both.<sup>3</sup>

We present the case of a patient with liver abscess and right pleural effusion. The identification of *E. histolytica* in the pleural liquid allowed us to make a diagnosis of amoebic empyema and amoebic liver abscess, even though the microbiological study of the pus drained from the abscess had come back negative for bacteria and parasites.<sup>4</sup>

The patient is a 57-year-old man who is a professional bullfighter and travels to Ecuador annually. He arrived at the ER due to symptoms evolving over the previous three weeks of fever (39 °C) with shivering. These symptoms began while in Ecuador after having been there for two weeks, and a fortnight before his return to Spain. In recent days, the fever was accompanied by dry cough and pain on the right side and ipsilateral hypochondrium. Physical exploration showed an axillary temperature of 37.5 °C, hypoventilation in the right lung base and painful hepatomegaly at one fingerbreadth. Hemogram: 14.350 leukocytes/mm<sup>3</sup> (72.3% neutrophils), hemoglobin 10.8 g/dl with normal MCV and MCH and 599,000 platelets/mm<sup>3</sup>. Biochemistry: urea 28 mg/dl, creatinine 0.79 mg/dl, total protein 6 g/dl, GOT 36 IU/l, GPT 78 IU/l, alkaline phosphatase 283 IU/l, GGT 278 IU/l, total bilirubin 0.84 mg/dl, LDH 129 IU/l, VSG 110 mm/h and CRP 147 mg/l. Chest radiograph showed evidence of elevation of the right hemidiaphragm with ipsilateral pleural effusion in limited quantity. The abdominal ultrasound showed a liver abscess of 9.5 × 9 cm in the posterior segments of the right hepatic lobe. A percutaneous drain was placed and maintained for 11 days, while antibiotic therapy was initiated with

con piperacillin/tazobactam at a dose of 4/0.5 g IV/8 h. The culture of the pus and the analysis for parasites were negative. In successive days, the patient was afebrile, although the non-productive cough and general malaise continued. Treatment with metronidazole IV 750 mg/8 h was added due to the suspicion of amoebic abscess. Diagnostic thoracocentesis revealed pleural liquid that was melicerous in appearance with 7,200 cel/mm<sup>3</sup> (PMN 75%), protein 4.91 g/dl, LDH 615 mU/ml, glucose 0.95 g/l, pH 7.31, ADA 27.5 mU/ml, and presence of trophozoites of *E. histolytica*. Indirect immunofluorescence for *E. histolytica* was positive at 1/512. A pleural drain tube was placed and removed four days later. The patient's symptoms remitted. Oral treatment was continued at 750 mg/8 h for two weeks, followed by paromomycin 30 mg/kg/day for 10 days. On the follow-up CT done two weeks later, persistence of the residual cavity was observed in the right hepatic lobe (3 x 2.8 cm in diameter), with no evidence of pleural effusion.

The previously described case suggests that when given a liver abscess with associated pleural effusion in which the patient history show suspicions for amoebic etiology, both diagnostic thoracocentesis and the investigation of trophozoites in the pleural liquid can be useful, especially if the culture and the investigation for parasites in the pus of the liver abscess are negative.<sup>4</sup> This would be of special interest if the clinical evolution was unfavorable with antimicrobial treatment and percutaneous drain of the liver abscess<sup>5</sup> since, as happened in our patient, a correct diagnosis allowed for continued treatment with metronidazole, already initiated empirically,<sup>1,3</sup> and the placement of a pleural drain tube, as is recommended for the treatment of amoebic empyema.<sup>4</sup>

Although the most frequent access pathway to the pleural space of *E. histolytica* is the transdiaphragmatic rupture of an amoebic liver abscess, the trophozoites can also reach the pleural space through the blood or lymphatic flow.<sup>6</sup> Therefore, imaging tests, as happened in our case, may not show signs of diaphragmatic perforation.

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