

Mesalamine-Induced Lung Injury in a Patient with Ulcerative Colitis and a Confounding Autoimmune Background:

A Case Report

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Abstract

Two years after being diagnosed with ulcerative colitis, a 57-year-old man taking oral mesalamine experienced severe respiratory distress due to left lung pleuropneumonitis. Eight months later, severe respiratory distress recurred due to right lung pneumonitis. Extraintestinal manifestations of inflammatory bowel disease or mesalamine-induced pulmonary injury were considered in the differential diagnosis, which was complicated by a history of aseptic meningitis and evidence of an ongoing autoimmune response. The implications of the case are discussed.

Key Words: Inflammatory bowel disease, lung injury, autoimmunity.

Case Report

A 57-YEAR-OLD MAN was diagnosed with left-sided ulcerative colitis (UC) in October 1994. The disease was controlled with oral mesalamine. Flare-ups were accompanied by symmetrical arthritis of the hands and knees, and required high-dose parenteral steroids. Maintenance azathioprine was begun in March 1996 but discontinued seven

months later because of severe leukopenia. The patient's medical history was remarkable for aseptic acute meningitis in 1992; antinuclear antibodies (ANA) were first detected at that time. At presentation with UC, ANA were present in high titer (1:640) and found to react strongly with centromere protein B (CENP-B).

November 1996—First Admission

The patient complained of shortness of breath, cough, left-sided chest pain and fever (peak temperature, 39°C). His condition gradually worsened and after 2 weeks he was admitted to our intensive care unit (ICU) at the Ospedale Molinette. Physical examination revealed bronchial breath sounds and hepatomegaly. Pulmonary function tests indicated small airway obstruction

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and reduced CO₂ diffusion. Laboratory tests were unremarkable. Peripheral blood eosinophil count was normal. The P_aO₂ was 54 mm Hg, so oxygen was given. A computed tomographic (CT) scan showed condensed left lung parenchyma with basal atelectasis consistent with pleuropneumonitis (Fig. 1). The patient's condition was unaffected by wide-spectrum antibiotics, but he responded to a maximum standard dose of prednisone of 1 mg/kg/day. When the condition was stable, the hepatomegaly was investigated and a liver biopsy revealed cryptogenic cirrhosis without signs of biliary disease. The patient was negative for hepatitis A, B and C virus antigens. ANA were detected and the titer was 1:640. The patient denied alcohol abuse and was unaware of exposure to hepatotoxins. Upon steroid tapering, fever and pain rapidly returned and prednisone was again administered. The patient was discharged on a tapering prednisone dose of 35 mg/day. The mesalamine regime, initially prescribed at 800 mg twice a day, was increased to three times a day (Fig. 2).

July 1997—Second Admission

Seven months after discharge, the patient was admitted to our ICU for the second time because of right-sided chest pain, dry cough and fever. Blood tests revealed elevated erythrocyte sedimentation rate (ESR), C-reactive protein and fibrinogen. Immunological tests showed an ANA titer of 1:640, anti-double-stranded DNA antibodies and cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA). Total leukocyte and eosinophil counts were normal. Chest radiography showed right

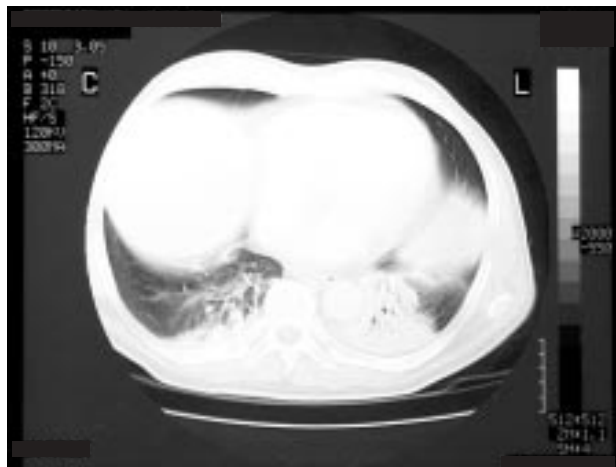


Fig. 1. Chest CT scan. Bilateral pleural reaction with an area of condensed parenchyma with air bronchogram suggesting pneumonia of the left lung.

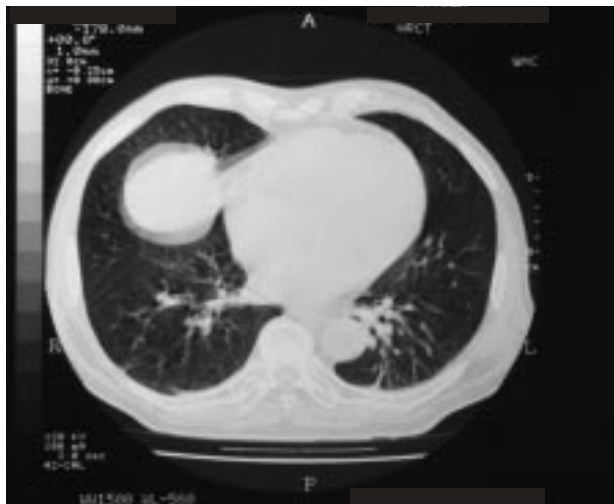


Fig. 2. Discharge chest CT scan. Significant clearance of the changes described above.

basal atelectasis and elevated diaphragm. Pulmonary embolism was ruled out by radionuclide scan. Culture of pulmonary lavage fluid was negative, so corticosteroids were given. Lung findings and hematological signs of inflammation cleared, and the patient was discharged. Prednisone was continued at 30 mg daily because of resting and exertional dyspnea.

October 1997

Multiple vertebral fractures were diagnosed and steroids were tapered. Daily cyclosporine was started.

November 1997

One month later, mesalamine and steroids were suspended, but cyclosporine was continued.

January 1998

Six weeks later, only mild exertional dyspnea persisted. Otherwise, the patient felt well and showed no signs of active UC. Nailfold capillaroscopy revealed alterations of vessel walls, aneurysms and microhemorrhages compatible with connective tissue disease, and prednisone was given. Cyclosporine was continued. ANA titer was 1:320.

September 1999

Cyclosporine was discontinued after 22 months of treatment; prednisone (10 mg/day) was continued.



Fig. 3. Chest X-ray film. An elevated right hemidiaphragm (probably secondary to hepatomegaly) and bibasilar hypoventilation are the main changes in this outpatient repeat radiograph.

September 2004

At the time of writing, chest X-rays no longer show most of the previous changes (Fig. 3). The patient has been weaned from prednisone; he has not experienced further acute respiratory difficulty since July 1997. Aside from dyspnea upon strenuous exercise, he leads an active life.

Discussion

Up to 40% of patients with inflammatory bowel disease (IBD) present with extraintestinal manifestations of IBD that may involve bone, the biliary system, eyes and skin (1). In recent reviews, Storch et al. (2) and Foster et al. (3) illustrated the difficulty presented by the differential diagnosis of pulmonary abnormalities in IBD. In these reports, fifty cases of mesalamine- or sulfasalazine-related pulmonary abnormalities were documented; they consisted primarily of eosinophilic pneumonia characterized by the appearance of clinical symptoms within months of drug administration and the disappearance of symptoms upon drug discontinuation. These cases usually do not require intensive steroid treatment.

The case presented here (summarized in Tables 1 and 2) differs in many ways from other similar

TABLE 1
Patient's Case History

Date	Condition	Medication
1994		
October	Active colitis	Local and oral mesalamine. Steroids.
1995		
July	Colitis relapse	High-dose oral steroids. Mesalamine.
1996		
March	Colitis relapse on steroid weaning	Azathioprine. Mesalamine. Prednisone 75 mg/day
July	Leukopenia	Azathioprine discontinued.
November	Left lung disease	High-dose parenteral steroids.
1997		
July	Right lung disease	High-dose parenteral steroids.
October	Dyspnea at rest Steroid toxicity	Mesalamine. Prednisone 35 mg/day.
November	Unchanged	Mesalamine discontinued. Prednisone tapering. Cyclosporine.
1998		
January	Exertional dyspnea	Prednisone tapering. Cyclosporine.
1999		
September	Improved	Prednisone 10 mg/day. Cyclosporine discontinued.
2000–2004		
September 2000 – September 2004	Good	Prednisone discontinued.

cases of IBD studied. First, pulmonary abnormalities appeared not months after, but two years after, mesalamine treatment began, a time lapse observed in only five other cases (2). Second, the patient improved after high-dose parenteral steroids, but his respiratory difficulties returned within hours of steroid withdrawal. Third, a positive c-ANCA test was found during maintenance treatment with mesalamine, an observation made in only three previous cases (2). For onset and course, our case is similar to the case of bronchiolitis obliterans described by Haralambou et al. (4). In our case, the pulmonary function tests suggested small airway obstruction, but lacked confirmation by lung biopsy. We conclude that this was an unusual

TABLE 2
Timecourse of Autoantibody Detection

Date	ANA ^a	Anti-ds DNA ^b	c-ANCA ^c
1996			
December	1:640	9	77
	1:640	9	75
1997			
March	1:640	ND	69
April	1:640	ND	<1.0
July	1:640	10	41
1998			
January	1:320	ND	<1.0
February	1:640	14	<1.0
March	1:640	10	<1.0
April	1:320	12	<1.0
June	1:640	ND	<1.0
July	1:640	ND	<1.0
September	1:640	ND	<1.0
August	1:640	13	<1.0
2000			
February	1:640	5	<1.0
March	1:640	5	<1.0
May	1:640	ND	<1.0

^a Antinuclear antibody titer

^b anti-double-stranded DNA antibodies; normal ranges 0–30 U/mL

^c cytoplasmic pattern, antineutrophil cytoplasmic antibodies; normal ranges 0–20 U/mL

ND = not done

case of drug-induced pulmonary dysfunction in UC, the 51st such case recorded, according to our estimates.

It has often been emphasized that UC has an immunological basis, with the extraintestinal manifestations part of the common pathogenic mechanism (5). The presence of autoantibodies in our patient is evidence of immune system dysregulation. ANA were detected at a titer > 1:640 in all but two of the 14 tests performed between December 1996 and May 2000, with a centromeric pattern upon indirect immunofluorescence confirmed on 9 occasions. In addition, the capillaroscopic results are consistent with an autoimmune disorder. The episode defined as aseptic meningitis may be evidence of autoimmune-mediated end-organ damage; one convincing case of sterile meningitis as a harbinger of systemic lupus erythematosus (SLE) has been reported (6).

These findings raise the question of whether or not an underlying autoimmune disorder, possibly a lupus-like syndrome, is responsible for the array of inflammatory manifestations exhibited by this patient since 1992. Favoring this hypothesis are the

following facts: (a) meningitis can herald SLE, (b) UC and SLE have been reported to coexist (7), (c) mesalamine can either cause or uncover SLE (8), and (d) the lungs are target organs in SLE (9). However, several points argue against a diagnosis of SLE for this patient, beginning with the fact that none of the classical criteria (10) are satisfied. Autoimmune lung disease in IBD often manifests itself as perinuclear-ANCA (p-ANCA)-positive vasculitis (2), but our patient was repeatedly p-ANCA-negative and he never showed signs of kidney dysfunction.

It remains difficult to determine the role played by cyclosporine treatment, prescribed at the time as a steroid-sparing agent. However, it seems reasonable to infer that mesalamine discontinuation alone prevented further disease recurrences. Since it remains unclear whether our patient is developing an ill-defined connective tissue disease (11) that facilitated or simply coincided with the recurrent pneumonitis, he is being kept under strict surveillance.

Conclusion

Inflammatory bowel disease should at times be viewed within the context of a more generalized immune imbalance affecting multiple organs, and not as an isolated pathological entity.

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