Granulomatous bronchiolitis with necrobiotic pulmonary nodules in Crohn's disease

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A 37-year-old man with extensive Crohn's disease of the stomach, small and large intestine for almost a decade developed respiratory symptoms and radiological findings suggestive of pneumonia that failed to resolve with antibiotic treatment. Computed tomography scanning of his lungs showed extensive changes with cavitated parenchymal nodules. Histological evaluation of an open lung biopsy showed granulomatous bronchiolitis and pulmonary necrobiosis. Treatment with steroids and immunosuppression resulted in complete resolution of his clinical symptoms of pneumonia and abnormal computed tomography imaging changes. Granulomatous bronchiolitis and necrobiotic nodules may be a manifestation of Crohn's disease in the absence of microbial agents, including mycobacteria or fungal agents. While a multiplicity of complex pulmonary changes may occur in Crohn's disease, their clinical recognition and precise pathological definition may be particularly important if treatment with a biological agent, such as infliximab, is being considered.

Key Words: Bronchopleural fistula; Crohn's disease; Granulomatous bronchiolitis; Infliximab; Necrobiotic pulmonary nodules; Pulmonary tuberculosis

The pulmonary changes in patients with chronic inflammatory bowel diseases have been well described in the past two decades, and were recently reviewed (1-4). Most often, these have been associated with ulcerative colitis (3,4), although significant pulmonary changes have also been rarely recorded in Crohn's disease (3,4).

In Crohn's disease, changes usually develop after the intestinal disease is well established, but in some patients, the pulmonary disease preceded the intestinal changes (5-7). Earlier reports also suggested overlap between pulmonary granulomatous disease in Crohn's disease and sarcoidosis (8-11), but newer classifications have categorized the pulmonary changes in Crohn's disease as either airway or interstitial disease (3,4). In some patients, mesalamine or other medications may be responsible, and differentiation of drug-induced versus disease-related changes may be difficult (12).

Cavitary lung lesions may also occur in Crohn's disease. Opportunistic infections with tuberculosis, *Pneumocystis carinii* and fungal infections should be considered, and aggressive

Bronchiolite granulomateuse, nodules pulmonaires nécrobiotiques et maladie de Crohn

Un homme âgé de 37 ans, atteint, depuis presque dix ans, d'une maladie de Crohn étendue, touchant l'estomac, l'intestin grêle et le côlon, a présenté des symptômes respiratoires, et les examens radiologiques évoquaient une pneumonie, mais celle-ci n'a pas réagi au traitement antibiotique. Une tomodensitométrie des poumons a montré des changements importants, accompagnés de nodules cavitaires du parenchyme. On a procédé à une biopsie du poumon à ciel ouvert, et l'examen histologique a révélé la présence d'une bronchiolite granulomateuse et d'une nécrobiose pulmonaire. Un traitement composé de stéroïdes et d'immunosuppresseurs a permis la disparition complète des symptômes cliniques de pneumonie et des changements anormaux révélés à la tomodensitométrie. Une bronchiolite granulomateuse, accompagnée de nodules nécrobiotiques peut être une manifestation de la maladie de Crohn en l'absence d'agents microbiens, y compris de mycobactéries et de champignons. La maladie de Crohn pouvant donner lieu à une multitude de changements pulmonaires complexes, il peut être particulièrement important de les reconnaître cliniquement et d'en préciser la nature histologique si un traitement à base d'agent biologique comme l'infliximab est envisagé.

immunosuppression may also predispose to cavitating malignancies, including lymphoma. In addition, vasculitis or metastatic Crohn's disease may cause cavitary lung lesions (13). Finally, necrobiotic pulmonary nodules may occur in patients with ulcerative colitis or predominantly Crohn's colitis (14,15).

CASE PRESENTATION

A 37-year-old man was referred in August 1993 for investigation of diarrhea, which had been present for over 10 years. In June 1993, an ischio-rectal abscess was drained at his community hospital. Later, periumbilical abdominal pain developed, associated with a 15 kg weight loss. An examination revealed a fatigued man with a weight of 69 kg. There was no fever but tenderness was present in the right lower quadrant. Laboratory studies revealed anemia (hemoglobin 110 g/L), a normal white blood cell count and thrombocytosis of 493,000. Sedimentation rate was 48 mm/h. Serum iron studies showed 2% saturation while serum albumin was reduced to

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30 g/L. Red cell folate, serum vitamin B₁₂, liver chemistry tests and renal function tests were normal. Fecal bacteriology and parasite studies were negative. Chest radiographs were normal but barium studies showed aphthoid ulcerations in the stomach with narrowing of the antrum and pylorus, thickened duodenal folds with diminished distensibility of the bulb, and irregular narrowing of the descending duodenum. Extensive ulceration and narrowing were present in the proximal jejunum and the distal 20 cm of the ileum, as well as the cecum and the ascending and transverse colon, which is consistent with multifocal involvement due to Crohn's disease. Endoscopy revealed a normal esophagus but gastric antral erosions were present along with linear and serpiginous duodenal ulceration; biopsies showed focally active gastritis with a gastric mucosal granuloma and a single focus of duodenal granulomatous inflammation. A flexible sigmoidoscopy and rectal biopsy were normal.

Initial treatment included a lactose-free diet, oral iron, omeprazole and oral mesalamine followed by an eight-week course of tapering prednisone.

By May 1994, his diarrhea and abdominal pain had resolved. His weight had increased by 6 kg. His hemogram was normal but his serum iron studies still showed only 7% saturation and serum albumin was 31 g/L.

Diarrhea reappeared in June 1995 and a flexible sigmoidoscopy showed scattered aphthoid ulcers in the rectum and sigmoid colon; a further course of oral prednisone was administered.

In March 1996, a colonoscopy showed ileal and cecal ulceration only. Biopsies showed nonspecific inflammatory changes but no granulomas.

In March 1997, diarrhea recurred with abdominal pain, vomiting and weight loss to 61 kg. Endoscopic studies of the upper and lower gastrointestinal tract showed gastric, duodenal and ileocecal ulceration. Instead of oral prednisone, budesonide controlled ileal release 3 mg twice a day was obtained through a compassionate release program (Astra Pharma, Canada), but it appeared to be ineffective in controlling symptoms over a period of six months.

From October 1997 to February 1998, a prolonged course of oral prednisone was provided. Repeated barium radiographic studies of his upper gastrointestinal tract showed a normal stomach but persistent strictures were present in the duodenum and ileum. Surgical treatment was refused and so metronidazole was initiated.

In early March 2000, cough, fever and further weight loss developed. Chest radiographs showed changes consistent with pneumonitis and his family physician prescribed azithromycin.

In June 2000, a helical computed tomography (CT) scan of the chest with contrast showed innumerable small nodular opacities in both lungs; the opacities were more numerous in the right upper and left lower lobes than elsewhere, and ranged in size up to 1 cm. Small areas of cavitation were seen in these opacities and an infectious etiology including fungal or tuberculous pulmonary disease was suggested. Serological studies for rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies (ANCA, including ANCA with a cytoplasmic staining pattern [c-ANCA]) and HIV were negative. A purified protein derivative test was negative. There was no known exposure to tuberculosis or histoplasmosis and no history of foreign travel or occupational exposure. There were

no clinical features or familial history to suggest an underlying or concomitant connective tissue disorder such as rheumatoid arthritis. Bronchoscopy revealed nonspecific findings and a transbronchial biopsy was negative. Pulmonary function studies showed changes of severe obstructive lung disease in a pattern consistent with advanced emphysema. Open lung biopsy showed granulomatous bronchiolitis and necrobiotic nodules (Figures 1 to 6). Acid fast and silver stains were negative. Cultures for mycobacteria and fungi were negative. During hospitalization, his intestinal disease worsened with recurrent abdominal pain and diarrhea. An ischiorectal abscess developed, necessitating surgical drainage. There was a persistent bronchopleural fistula from the biopsy site and chest tube drainage persisted for over two months.

Eventually, his chest tube was spontaneously expelled with a coughing episode and his fistula closed. His respiratory symptoms improved with a course of prednisone, and a follow-up CT scan showed resolution of the bronchiolitis and nodular changes. Subsequent treatment for his intestinal disease has included oral metronidazole, ciprofloxacin and azathioprine.

DISCUSSION

Pulmonary complications in patients with inflammatory bowel disease are becoming increasingly recognized. Even in the absence of symptoms or reported radiological changes, over 50% of Crohn's disease patients have been documented with altered lung function (16). Indeed, very recent studies in patients with Crohn's disease using high resolution CT scanning showed that all patients had one or more abnormalities detected with this modern imaging method (17). Pathological pulmonary changes in Crohn's disease may be categorized as airway or interstitial parenchymal disease, and include infectious, noninfectious and drug-induced causes. This patient had dramatic radiographic and helical CT scan findings of extensive cavitating pulmonary parenchymal disease confirmed histologically, with an open lung biopsy that showed granulomatous bronchiolitis and necrobiosis. The latter feature has been rarely recorded in Crohn's disease (14,15,18), usually with disease localized predominantly in the colon alone, or occasionally associated with pyoderma gangrenosum (19,20). In this patient, extensive multifocal involvement of the stomach, small intestine and colon with Crohn's disease was defined without other extraintestinal changes, including dermatological complications.

In this patient, the duration of the lung disease before its eventual recognition and diagnosis was unknown, but may have been occult and prolonged because of intermittent courses of oral corticosteroids used to treat his intestinal symptoms over many years. In some patients with noninfectious pulmonary pathology in Crohn's disease, treatment with corticosteroids has been associated with resolution of the lung disease, and in this patient, may have indirectly and unknowingly ameliorated pulmonary changes. Eventually, in the absence of ongoing corticosteroids, respiratory symptoms became clinically evident, which led to more detailed pulmonary investigations and a precise diagnosis.

Although there is evidence from case studies that use of corticosteroids or other forms of immunosuppression may be useful to manage the necrobiotic pulmonary lesions in Crohn's disease, definition of cavitating pulmonary nodules raises the possibility of underlying pulmonary tuberculosis or another ubiquitous infectious agent. In this setting, the decision to use

Figure 1) Non-necrotizing granuloma with a central scar. Pigment-laden macrophages are also present (hematoxylin and eosin stain, original magnification $\times 40$)

Figure 2) Bronchiolitis with destruction of some of the wall (hematoxylin and eosin stain, original magnification $\times 160$)

Figure 3) Bronchiolitis obliterans organizing pneumonia with mixed inflammation (hematoxylin and eosin stain, original magnification $\times 40$)

immunosuppressive therapy is difficult. Here, infliximab therapy was also considered but it was thought not to be a safe option. There are a number of studies now documenting subsequent development of serious infections, including fatal tuberculous disease, histoplasmosis and other infections (21-23) as well as

Figure 4) Stellate scar with a collection of giant cells in the centre (hematoxylin and eosin stain, original magnification $\times 40$)

Figure 5) Neutrophilic inflammation and destruction of alveolar walls typical of necrobiotic lesion (hematoxylin and eosin stain, original magnification $\times 40$)

Figure 6) Higher power of necrobiotic lesion with central neutrophils, together with inflammation surrounding the blood vessel, possibly a secondary vasculitis (hematoxylin and eosin stain, original magnification $\times 100$)

sterile pulmonary granulomas (24) following infliximab treatment. In contrast, there are also rare cases of resolution of noninfectious pulmonary disease (25,26) with infliximab therapy. These apparently contradictory reports serve as a reminder that our understanding of the effects and risks of

tumour necrosis factor- α inhibition remain limited and, despite recent reports of adverse events in large clinical experiences (27,28), still require further elucidation and longer term monitoring.

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