Journal of Crohn's and Colitis (2009) 3, 207–211

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SHORT REPORT

Pulmonary Crohn's disease: A rare extra-intestinal manifestation treated with infliximab ☆

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Received 26 January 2009; received in revised form 29 March 2009; accepted 30 March 2009

KEYWORDS
Crohn's disease;
Pulmonary extra-intestinal manifestation;
Infliximab

Abstract

Crohn's disease is a chronic inflammatory bowel disease often presenting with extra-intestinal manifestations. However, pulmonary involvement is quite rare. We report a case of Crohn's disease with pulmonary extra-intestinal manifestation (bronchiolitis obliterans organizing pneumonia-like changes) treated with infliximab. Furthermore, we present an overview of cases of inflammatory bowel disease with lung involvement, treated with tumor necrosis factor-α antagonists. In this case, when infliximab was given, a significant resolution of the pulmonary changes was achieved.
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1. Introduction

Inflammatory bowel disease (IBD) is a chronic disease affecting not only gastrointestinal tube, but also in approximately one third of cases also different extra-intestinal organs. The most frequently affected organs are skin, joints, eyes and liver.[1] Pulmonary involvement, however, is quite rare. The occurrence has been reported to be higher in ulcerative colitis (UC) than in Crohn's disease (CD) with only 0.4% of cases having CD.[2,3]

Infliximab, tumor necrosis factor-α (TNF-α) antagonist, has been well documented to be efficacious in the treatment of common extra-intestinal manifestations refractory to conventional immunosuppressive therapy.[1,4–7] However, there are only a few reports about efficacy of infliximab in pulmonary CD.[8–11]

This report presents a case of a 35-year-old woman with CD presenting with a pulmonary disease which was successfully treated with infliximab.

2. Case report

A 35-year-old woman was diagnosed with ileo-coecal CD in 1994 (age 24 years). In the same year the first ileo-coecal resection of 40 cm ileum was performed and followed by maintenance therapy with mesalazine 4 g daily. In 1998 the

Abbreviations: BOOP, Bronchiolitis obliterans organizing pneumonia; CD, Crohn's disease; IBD, Inflammatory bowel disease; UC, Ulcerative colitis; TNF-α, Tumor necrosis factor-α.

☆ Conference presentation: This case was presented at the clinical session of "rare cases" at UEGW Berlin 2006.

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doi:10.1016/j.crohns.2009.03.007

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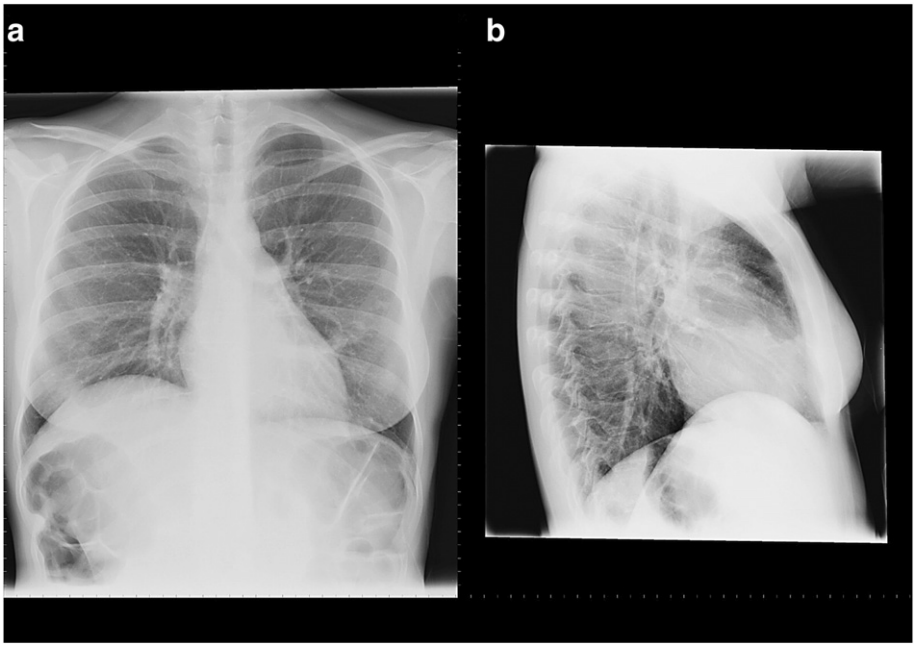

Figure 1 Chest X-ray, frontal (a) and side (b) films showing multiple bilateral pulmonary infiltrates.

patient underwent the second resection of 60 cm of neo-terminal ileum due to stenosis. Subsequently, azathioprine 150 mg daily was given and patient was maintained in complete clinical remission over the next 5 years. However, persistent hypoalbuminaemia and anemia were present in laboratory findings. In 2003 severe relapse of the disease occurred, characterized by continuous abdominal pain, diarrhea, weight loss, progression of anemia and hypoalbuminaemia. The ileo-colonoscopy revealed neo-terminal ileitis and left-sided colitis with stenosis of the anastomosis. A simple peri-anal fistula and multiple anal fissures occurred at the same time. Furthermore, the patient developed arthropathies. Topical corticosteroids, budesonide, later replaced by systemic corticosteroids were added to azathioprine in the following two years. In spite of the intensive anti-inflammatory therapy the disease was characterized as chronic continuous active, thus infliximab treatment was indicated. Prior to application of infliximab routine chest radiography was performed and unexpectedly revealed bilateral infiltrative opacities and patchy shadows of the lung (Fig. 1). Computed tomography (CT) confirmed the presence of bilateral peribronchial and perivascular nodular opacities, parenchymal infiltrates and pleural effusions (Fig. 2). The patient, however, did not present any clinical symptoms of lung disease.

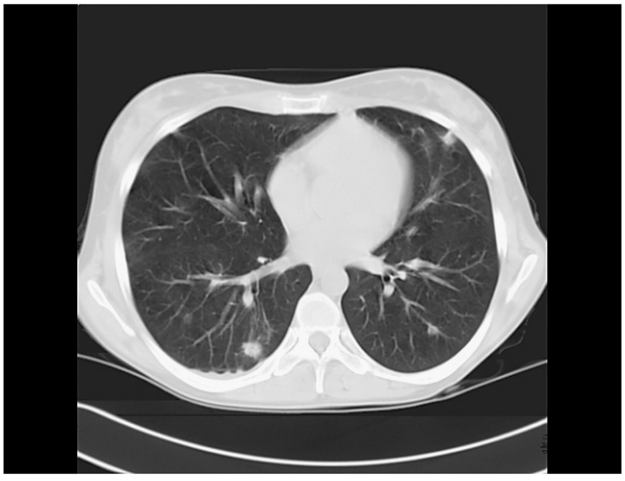

Figure 2 Non-contrast enhanced computerized tomography of the chest showing bilateral, non-segmental air-space consolidations in perivascular and peribronchial regions mainly distributed in lower peripheral segments of the lungs. The opacities were predominantly irregular and between 7-17 mm. A small right sided pleural effusion was present.

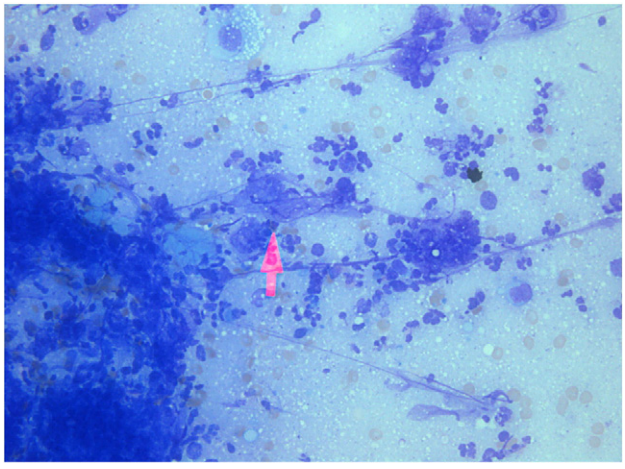

Figure 3 Cytology of lung fine needle aspiration showing numerous acute- and chronic inflammatory cells, including non-caseating granulomatous inflammation with multinucleated giant cells (Original magnification x 400, MGG stain).

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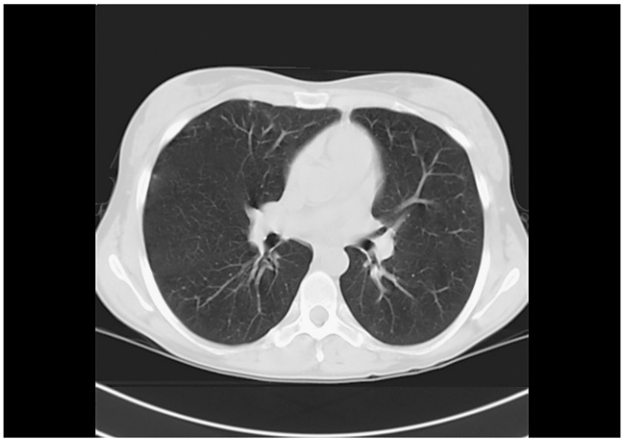

Figure 4 Non-contrast enhanced computerized tomography of the chest performed 2 months after induction of infliximab therapy, showing an almost complete resolution of pulmonary changes.

Infectious cause was excluded by negative cultivations of sputum for bacteria, fungi and mycobacterium. Furthermore, Mantoux test and PCR test for *Mycobacterium tuberculosis*, *Mycoplasma* and *Chlamydia* were negative. The pulmonary function test showed no abnormality. Serologic investigations regarding anti-neutrophil cytoplasmic antibodies (ANCA) and anti-*Saccharomyces cerevisiae* IgG and IgA antibodies (ASCA) were negative, excluding vasculitis. Angiotensin converting enzyme (ACE) inhibitor level was within the normal range excluding sarcoidosis. Drug-induced pulmonary changes were unlikely because of cessation of mesalazine several years ago. Ultrasound guided fine needle aspiration of a pulmonal nodule was preformed and showed the presence of non-caseating granulomatous inflammation with multinucleated giant cells (Fig. 3). It was concluded that the pulmonary findings were extra-intestinal manifestation of CD. Infliximab induction therapy (0, 2, 6 weeks) was given at a dose of 5 mg/kg and subsequent clinical remission and closure of perianal fistula was obtained. Control CT-scan of the thorax 2 months after the 3rd infusion revealed almost complete regression of pulmonary changes bilaterally (Fig. 4). The chest radiography, five years later was without any pathology.

3. Discussion

The lung involvement of IBD is considered to be a rare extra-intestinal manifestation. However, the true prevalence seems to be much higher due to a frequent occurrence of subclinical course.[3] A previously published study[12] has reported that CD patients often present with an asymptomatic inflammatory process when measured by lymphocytosis in induced sputum or metacholine test. Bronchial hyperresponsiveness has been demonstrated in 27% of CD patients.[12] Furthermore, high incidence of restrictive or combined restrictive and obstructive abnormalities has been described in pulmonary function tests in more than 50% of CD and UC patients.[13–15] Nevertheless, one has to be always aware of an increasing incidence of especially opportunistic infections due to a more intensive use of immunosuppressive therapy in the last period.[16] These often represent differential diagnostic challenge. In the present case, opportunistic infection was also initially considered as a highly possible cause of pulmonary changes because of long-term treatment with azathioprine.

The most common clinical symptoms are progressive dyspnoea, dry cough, fever, flu-like symptoms and pleuritis chest pain.[2] Our patient, however, did not present any clinical symptoms nor pathology was observed in functional tests and the findings were revealed accidentally on chest radiography prior to infliximab therapy.

Pulmonary IBD involves different pathologic entities. Storch et al.[3] have categorized them by disease mechanism into drug-induced disease, anatomic disease, over-lap syndromes, autoimmune disease, physiologic consequences of IBD, pulmonary function test abnormalities and non-specific lung disease. The diagnosis is based on chest radiograph, CT findings, bronchoalveolar lavage and definitively on characteristic histological features.[9,17–19] Neither lung biopsy nor bronchoalveolar lavage was performed in our patient because of subclinical disease course.

Although, we did not have histological confirmation, we considered that radiological features and findings of needle aspiration were indicative for bronchiolitis obliterans organizing pneumonia (BOOP)-like changes. BOOP is a lung disorder affecting small airways and lung parenchyma

Table 1 Summary of cases of patients with Crohn's disease and pulmonary involvement treated with tumor necrosis factor-α antagonist.

Author	Case	Treatment	Treatment outcome
Alrashid et al., 2001 (8)	1 case of Crohn's disease with bronchiolitis obliterans organizing pneumonia	Infliximab	Complete response
Gill and Mahadevan, 2002 (10)	1 case of Crohn's disease with pulmonary (noncaseating granulomas) and hepatic extra-intestinal manifestations	Infliximab	Complete response
Casey et al., 2003 (9)	1 case of Crohn's disease with bronchiolitis obliterans organizing pneumonia	Infliximab	Complete response
Silbermintz et al., 2006 (28)	1 pediatric patient with Crohn's disease and granulomatous pneumonitis, sclerosing cholangitis and pancreatitis	Infliximab	Complete response
Krishnan et al., 2006 (11)	2 pediatric Crohn's disease patients with noncaseating granulomas and one with bronchiolitis obliterans organizing pneumonia	Infliximab	Complete response

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with possible pleural involvement. It is not only associated with IBD, but also with other conditions such as connective tissue disease, myeloproliferative disorders and allogenic bone marrow transplantation.[20–22] Other causes of BOOP are inhalation injury and drugs such as acetylsalicylates, thiopurines and infliximab.[16,23] In the present case drug-induced lung disease was unlikely. Mesalazine was withdrawn several years before the diagnosis of pulmonary CD was established. An alternative cause of pulmonary findings was azathioprine treatment. Retrospectively it can be concluded that this was also unlikely, since the patient was still on azathioprine when the lung changes resolved.

The prognosis of pulmonary Crohn is generally favorable with a high response rate to therapy.[9] However, poor outcome has also been described mainly when the disease was associated with predisposing underlying conditions or drug induced.[21,22]

Corticosteroids are the most common drugs used in the treatment of pulmonary CD with a rapid improvement of symptoms in up to 90% of patients.[19,24] However, in 12–30% of patients relapse occurs after tapering or discontinuing of corticosteroids requiring dose increase or the drug re-administration.[25] Spontaneous improvement can also occur.[22]

Infliximab is efficacious for induction and maintenance of remission in both luminal and fistulizing CD.[26,27] The experience of infliximab therapy in more common extra-intestinal manifestations such as skin, joints, eyes and liver has already been well described.[4–7] However, the data about infliximab use in pulmonary IBD are sparse and based mainly on sporadic case reports. We found only 7 cases of CD patients with lung involvement treated with infliximab, while no reports about use of other anti-TNF-α agent have been described in published literature (Table 1).[8–11,28] Alrashid et al.[8] have reported a case of CD patient complicated with BOOP, effectively treated with infliximab. Gill and Mahadevan[10] have later described a case of CD patient presenting with hepatic and pulmonary lesions (noncaseating granulomas) which have resolved after infliximab therapy. Another study has reported a case of 3 children with CD lung lesions. Two of them have presented with noncaseating granulomas and one with BOOP. All children were treated with infliximab because of lack of response to conventional anti-inflammatory therapy and achieved a rapid clinical and radiologic improvement.[11] Casey et al.[9] have reported 4 cases of BOOP, where only one of the patients was treated with infliximab and obtained good response. In our case infliximab was primarily indicated for active luminal and perianal disease refractory to conventional anti-inflammatory treatment. Infliximab therapy resulted in improvement of both intestinal and lung changes, thus confirming its efficacy in pulmonary CD.

In conclusion, we report a rare case of pulmonary CD which was successfully treated with infliximab. This indicates the use of infliximab in extra-intestinal pulmonary manifestation in CD.

References

1. Juillerat P, Mottet C, Froehlich F, Felley C, Vader JP, Burnand B, et al. Extraintestinal manifestations of Crohn's disease. *Digestion* 2005;**71**:31–6.
2. Camus P, Colby TV. The lung in inflammatory bowel disease. *Eur Respir J* 2000;**15**:5–10.
3. Storch I, Sachar D, Katz S. Pulmonary manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2003;**9**:104–15.
4. Barrie A, Plevy S. Treatment of immune-mediated extraintestinal manifestations of inflammatory bowel disease with infliximab. *Gastroenterol Clin North Am* 2006;**35**:883–93.
5. Barrie A, Regueiro M. Biologic therapy in the management of extraintestinal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2007;**13**:1424–9.
6. Kaufman I, Caspi D, Yeshurun D, Dotan I, Yaron M, Elkayam O. The effect of infliximab on extraintestinal manifestations of Crohn's disease. *Rheumatol Int* 2005;**25**:406–10.
7. Siemanowski B, Regueiro M. Efficacy of infliximab for extra-intestinal manifestations of inflammatory bowel disease. *Curr Treat Options Gastroenterol* 2007;**10**:178–84.
8. Alrashid AI, Brown RD, Mihalov ML, Sekosan M, Pastika BJ, Venu RP. Crohn's disease involving the lung: resolution with infliximab. *Dig Dis Sci* 2001;**46**:1736–9.
9. Casey MB, Tazelaar HD, Myers JL, Hunninghake GW, Kakar S, Kalra SX, et al. Noninfectious lung pathology in patients with Crohn's disease. *Am J Surg Pathol* 2003;**27**:213–9.
10. Gill KR, Mahadevan U. Infliximab for the treatment of metastatic hepatic and pulmonary Crohn's disease. *Inflamm Bowel Dis* 2005;**11**:210–2.
11. Krishnan S, Banquet A, Newman L, Katta U, Patil A, Dozor AJ. Lung lesions in children with Crohn's disease presenting as nonresolving pneumonias and response to infliximab therapy. *Pediatrics* 2006;**117**:1440–3.
12. Bartholo RM, Zaltman C, Elia C, Cardoso AP, Flores V, Lago P, et al. Bronchial hyperresponsiveness and analysis of induced sputum cells in Crohn's disease. *Braz J Med Biol Res* 2005;**38**:197–203.
13. Herrlinger KR, Noftz MK, Dalhoff K, Ludwig D, Stange EF, Fellermann K. Alterations in pulmonary function in inflammatory bowel disease are frequent and persist during remission. *Am J Gastroenterol* 2002;**97**:377–81.
14. Munck A, Murciano D, Pariente R, Cezard JP, Navarro J. Latent pulmonary function abnormalities in children with Crohn's disease. *Eur Respir J* 1995;**8**:377–80.
15. Neilly JB, Main AN, McSharry C, Murray J, Russell RI, Moran F. Pulmonary abnormalities in Crohn's disease. *Respir Med* 1989;**83**:487–91.
16. Schleiermacher D, Hoffmann JC. Pulmonary abnormalities in inflammatory bowel disease. *Journal of Crohn's and Colitis* 2007;**1**:61–9.
17. Bouchardy LM, Kuhlman JE, Ball Jr WC, Hruban RH, Askin FB, Siegelman SS. CT findings in bronchiolitis obliterans organizing pneumonia (BOOP) with radiographic, clinical, and histologic correlation. *J Comput Assist Tomogr* 1993;**17**:352–7.
18. Carratu P, Dragonieri S, Nocerino MC, Trabucco SM, Lacedonia D, Parisi G, et al. A case of cryptogenic organizing pneumonia occurring in Crohn's disease. *Can Respir J* 2005;**12**:437–9.
19. Mahadeva R, Walsh G, Flower CD, Shneerson JM. Clinical and radiological characteristics of lung disease in inflammatory bowel disease. *Eur Respir J* 2000;**15**:41–8.
20. Kraft SC, Earle RH, Roesler M, Esterly JR. Unexplained bronchopulmonary disease with inflammatory bowel disease. *Arch Intern Med* 1976;**136**:454–9.
21. Lohr RH, Boland BJ, Douglas WW, Dockrell DH, Colby TV, Swensen SJ, et al. Organizing pneumonia. Features and prognosis of cryptogenic, secondary, and focal variants. *Arch Intern Med* 1997;**157**:1323–9.
22. Oymak FS, Demirbas HM, Mavili E, Akgun H, Gulmez I, Demir R, et al. Bronchiolitis obliterans organizing pneumonia. Clinical and roentgenological features in 26 cases. *Respiration* 2005;**72**: 254–62.
23. Weatherhead M, Masson S, Bourke SJ, Gunn MC, Burns GP. Interstitial pneumonitis after infliximab therapy for Crohn's disease. *Inflamm Bowel Dis* 2006;**12**:427–8.

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24. Omori H, Asahi H, Inoue Y, Irinoda T, Saito K. Pulmonary involvement in Crohn's disease report of a case and review of the literature. *Inflamm Bowel Dis* 2004;**10**:129–34.
25. Basarakodu KR, Aronow WS, Nair CK, Lakkireddy D, Kondur A, Korlakunta H, et al. Differences in treatment and in outcomes between idiopathic and secondary forms of organizing pneumonia. *Am J Ther* 2007;**14**:422–6.
26. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541–9.
27. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;**350**:876–85.
28. Silbermintz A, Krishnan S, Banquet A, Markowitz J. Granulomatous pneumonitis, sclerosing cholangitis, and pancreatitis in a child with Crohn disease: response to infliximab. *J Pediatr Gastroenterol Nutr* 2006;**42**:324–6.

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