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Case report

Two patients with new granulomatous lung lesions during treatment of Crohn's disease

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ABSTRACT

Two patients with granulomatous lung lesions thought to be related to Crohn's disease (CD) are reported. Patient 1 was a 43-year-old man who was diagnosed with CD at age 11 years. He developed a fever in the 38 °C, and a chest X-ray and CT scan showed infiltrates with air bronchograms in the right upper lobe and left lingular segment. Transbronchial lung biopsy (TBLB) revealed granulomatous lesions. Patient 2 was a 76-year-old woman who was diagnosed with CD at age 44 years. Chest CT showed infiltrates and nodular shadows in both lung fields. Video-assisted thoracoscopic surgery (VATS) in June 2012 revealed granulomatous lesions. Tuberculosis, fungal infections, drug-induced lung disorder, and sarcoidosis were ruled out as a cause of the granulomatous lesions in both patients. The aetiology was thought to be CD.

1. Introduction

Crohn's disease (CD) is a granulomatous inflammatory disease of unknown aetiology, but thought to involve abnormal immune function, with a predilection to develop in the small and large intestines [1,2]. Granulomatous lung lesions in CD have not previously been reported in Japan, and only 3 cases have been reported overseas [3]. Two rare cases of CD-related granulomatous lung lesions are reported, and the relevant literature is discussed.

2. Case reports

2.1. Patient 1

Patient 1 was a 43-year-old man who was diagnosed with CD in 1979 (age 11 years). He had been followed as an outpatient by the Department of Gastroenterology at our hospital. He underwent an ileocoecal resection in 1981 (age 13 years), partial small bowel resection in 1987 (age 19 years), and transverse colon strictureplasty in 1999 (age 31 years). Parenteral nutrition (elemental diet: Elental, Racol) was then started. Mesalazine (5-ASA) was started in 2006, and infliximab (an anti-TNF-α antibody drug) was started in 2007 (age 39 years). However, he continued to have severe active CD, and adalimumab (another anti-TNF-α antibody drug) was started in March 2011 (age 42 years). The patient's gastrointestinal symptoms were controlled, but he developed a dry cough in mid-November 2011 (age 43 years), followed by a fever (38 °C) in early December 2011, and he was evaluated by our department.

A chest X-ray and CT showed bilateral infiltrates with air bronchograms (Fig. 1). The patient was diagnosed with community-acquired pneumonia (WBC 4300/μL, CRP 0.07 mg/dL), and antibiotic therapy with ceftriaxone (CTRX) was prescribed. However, since the dry cough did not improve, the patient was admitted to our department in mid-December 2011 for further evaluation and treatment. Bronchoscopy was performed, and transbronchial lung biopsy (TBLB) of the right upper lobe revealed a non-caseating granuloma with multi-nucleated giant cells (Fig. 2).

As testing for the aetiology of the granulomatous lesions, a QuantiFERON-TB test was negative, a tuberculin reaction was negative, and acid-fast staining of the bronchoscopy specimens (bronchial lavage fluid, TBLB) was negative. Thus, tuberculosis was unlikely. Grocott staining, β-D glucan, and cryptococcal antigen

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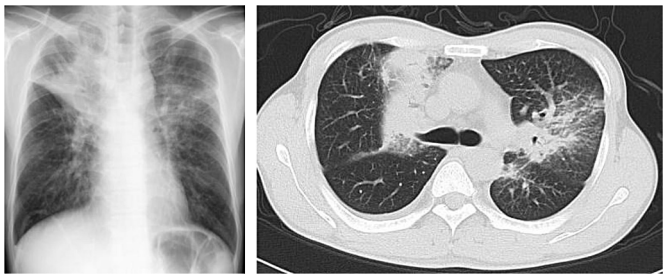

Fig. 1. Chest X-ray (left) and CT (right) taken in December 2011 show infiltrative shadows in the bilateral upper lobes.

testing of the TBLB specimens were negative, so a fungal infection was also unlikely. Aggressive therapy was not considered necessary, so the patient was followed as an outpatient. On a chest X-ray taken in July 2012, and on chest CT in August 2012, the infiltrate mainly in the right upper lobe had spontaneously disappeared (Fig. 3).

2.2. Patient 2

Patient 2 was a 76-year-old woman who was diagnosed with small intestinal CD in 1980 (age 44 years). She has been followed as an outpatient by the Department of Gastroenterology at our hospital. Salazosulfapyridine (5-ASA) was started in 1985 (age 49 years). She underwent a small bowel strictureplasty in 1992 (age 56 years), ileocoecal resection in 2003 (age 67 years), and then parenteral nutrition (Elental) was started.

The patient's gastrointestinal symptoms were well controlled, but she began to lose weight in September 2011 (10 kg weight loss/6 months). A CT scan in December 2011 showed thickened bronchiolar walls with multiple nodular shadows in peripheral bronchi of both lung fields, and bronchoscopy was performed in February 2012. The bronchoalveolar lavage (BAL) fluid showed predominant lymphocytosis (57%) and a CD4/CD8 ratio of 0.94. TBLB revealed no significant findings.

Chest X-ray and CT in May 2012 showed new infiltrates in the right lower and left upper lobes (Fig. 4). In June 2012, Video-assisted thoracoscopic surgery (VATS) of the lingula was performed, and histopathology showed an epithelioid cell granuloma with giant cells (Fig. 5). Since acid-fast cultures of the bronchial

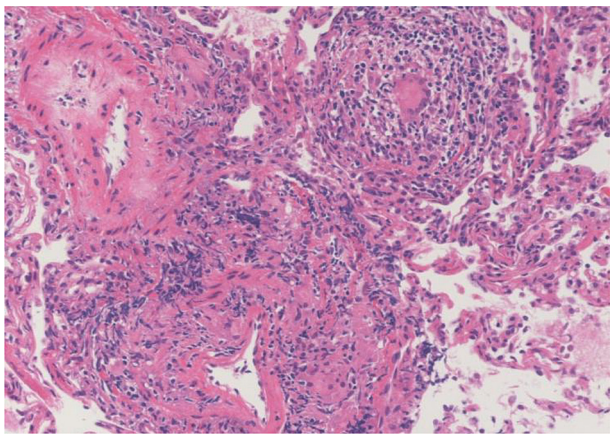

Fig. 2. Photomicrogram of transbronchial lung biopsy reveals non-caseating granuloma with multi-nucleated giant cells and lymphocytic infiltrate (haematoxylin-eosin, × 140).

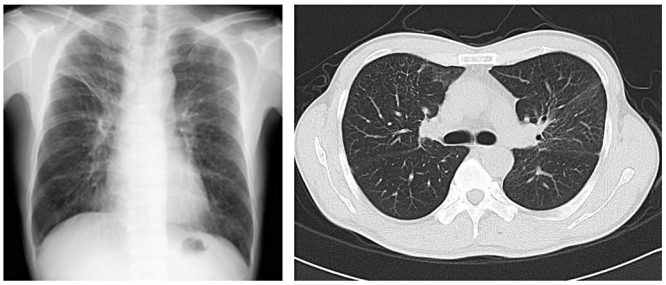

Fig. 3. Chest X-ray (left) and CT (right) taken in August 2012. The infiltrative shadow noted in Fig. 1 has disappeared spontaneously.

lavage fluid and lung biopsy tissue were negative, a mycobacterial infection was unlikely. Grocott staining, β-D glucan, and cryptococcal antigen testing were negative, so a fungal infection was also unlikely. Serum ACE was not elevated, the tuberculin reaction was negative, and the pulmonary hilar lymph nodes were not enlarged; thus, sarcoidosis was also ruled out. Drug treatment had not been switched during outpatient follow-up, so drug-induced pneumonia was also unlikely.

These findings were consistent with CD-related pulmonary lesions based on a diagnosis by exclusion and the histopathology. The patient developed dyspnoea on exertion, and treatment with tapering doses of prednisolone (PSL) starting at a dose of 40 mg/day was begun in July 2012. The exertional dyspnoea and imaging findings improved rapidly (Fig. 6).

3. Discussion

Crohn's disease (CD) was originally called regional ileitis and was first reported by Burrill B. Crohn MD at Mount Sinai Hospital (United States) in 1932 [4]. CD is characterized by chronic inflammatory granulomatous lesions of unknown aetiology that are associated with ulcerations and fibrosis. CD usually presents in younger patients with oedema and ulcerations in the small and large intestines, and intestinal strictures and fistulas often develop. CD most commonly affects the terminal ileum, but any site in the gastrointestinal tract may be involved [5]. Extra-intestinal complications of CD include joint complications (ankylosing spondylitis, sacroiliitis, peripheral arthritis), skin complications (erythema nodosum, pyoderma gangrenosum), ocular complications (episcleritis, scleritis, uveitis), hepatobiliary complications (primary sclerosing cholangitis), and pulmonary complications (organizing pneumonia) [6].

When granulomatous lesions develop in CD patients, granulomatous infections such as mycobacterial or fungal infections, drug-induced pneumonia, and sarcoidosis must be included in the differential diagnosis. Granulomas in CD are sarcoid-like granulomas,

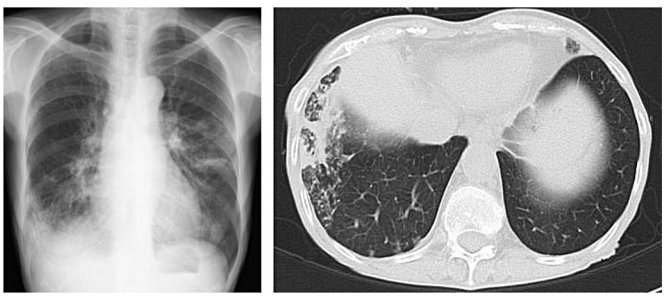

Fig. 4. Chest X-ray (left) and CT (right) taken on admission May 2012 reveals infiltrative and small nodular shadow in the right lower and left upper lobes.

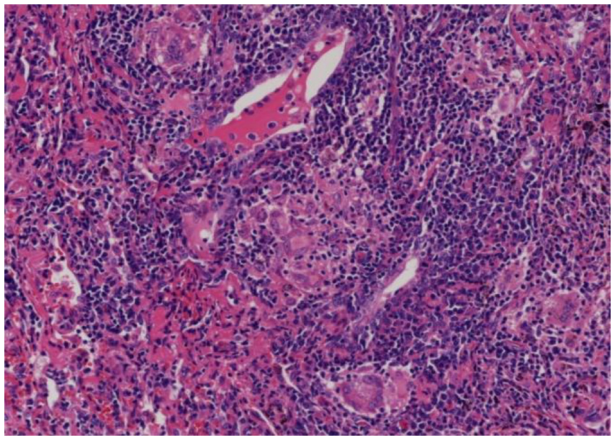

Fig. 5. Photomicrograph of biopsied lung tissue of case 2 reveals epithelioid cell granuloma with multi-nucleated giant cells and lymphocytic infiltrate (haematoxylin-eosin, × 140).

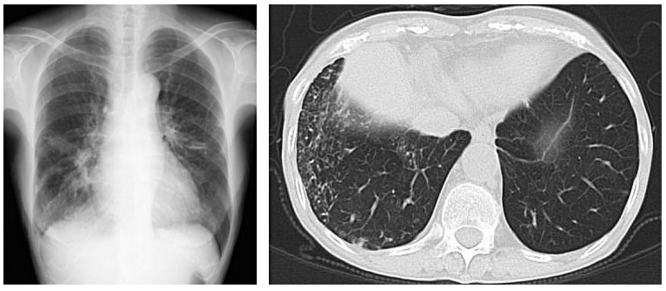

Fig. 6. Chest X-ray and CT of August 2012. The infiltrative shadow of the right lower and left upper lobes noted in Fig. 4 have improved.

and the differential diagnosis between these two diseases is particularly important. A diagnosis of sarcoidosis requires 2 or more of the following 6 findings indicating a systemic reaction: bilateral pulmonary hilar lymphadenopathy, elevated serum ACE levels, a negative tuberculin reaction, marked uptake on gallium^{67} citrate scintigraphy, lymphocytosis or an increased CD4/CD8 ratio in BAL fluid, and serum hypercalcaemia. Evaluation of these 6 items is important to exclude a diagnosis of sarcoidosis [7,8].

In patient 1 at the time of hospital admission, a QuantiFERON-TB blood assay was negative, acid-fast smear cultures of the bronchial lavage fluid were negative, and acid-fast staining of TBLB specimens was negative. Thus, tuberculosis was unlikely. Grocott staining, β-D glucan, and cryptococcal antigen testing of the TBLB specimens were negative, so a fungal infection was also unlikely. The only item meeting the diagnostic criteria for sarcoidosis was a negative tuberculin reaction, but because the QuantiFERON-TB test was also negative, this was thought to be of weak diagnostic significance, and sarcoidosis was ruled out. In addition, drug treatment had not been switched during follow-up, so drug-induced pneumonia was also unlikely. Based on a diagnosis of exclusion and the histopathology, the findings were consistent with CD-related pulmonary lesions.

In patient 2, the histopathologic examination revealed an epithelioid cell granuloma, multi-nucleated giant cells, and lymphocytic infiltration (Fig. 5). Acid-fast cultures of the bronchial lavage fluid and lung biopsy tissue were negative, so mycobacterial infection was unlikely. Sarcoidosis was also ruled out based on lack of elevation of serum ACE (15.5 IU/L) and a positive tuberculin reaction. Drug-induced lung disorder was also unlikely because the drug regimen had not been changed during outpatient treatment.

Three cases of granulomatous lung lesions in CD have been reported outside of Japan (a 13-year-old girl, a 14-year-old girl, and a 17-year-old boy). However, such cases have not been previously reported in Japan, so the present patients represent two rare cases. All 3 patients reported outside of Japan were young, had severe symptoms, and were being treated with infliximab (anti-TNF-α antibody drug). Regarding the present two cases in Japan, patient 1 (43-year-old man) was diagnosed with CD at age 11 years, and because of active gastrointestinal symptoms, infliximab (anti-TNF-α antibody drug) was started. Patient 2 (76-year-old woman) was diagnosed with CD at age 44 years, and she had a relatively satisfactory clinical course on nutritional therapy alone. If we consider the present 2 patients and the 3 patients reported from outside of Japan, 4 of these 5 patients developed CD at a young age and had highly active gastrointestinal symptoms [9]. Therefore, when lung lesions are seen in patients who developed CD during their youth and have highly active gastrointestinal symptoms, CD-related granulomatous lung lesions must be considered.

Conflict of interest

None.

Acknowledgements

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