

Pulmonary Noncaseating Granuloma Associated with Infliximab Crohn's Disease: The First Case Reported in China

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2. Key words

Crohn's disease; Pulmonary manifestation; Granuloma; TNF inhibitor; Infliximab.

1. Abstract

Crohn's Disease (CD) is a main kind of Inflammatory Bowel Disease (IBD) whose etiology is unclear but complex and the effective treatment is deficient. Since Tumor Necrosis Factor (TNF) inhibitor used to treat CD, greatly improvement has been seen in patients' clinical symptom and living condition. However, some complications have been emerged gradually. Here we report a CD patient who used to treated by In Fli Ximab (IFX) combined with non caseating granulomatous inflammation in lung lesion. As far as we know, the current study is the first to describe pulmonary granuloma associated with IFX in CD from China. The rare complication reminds that the extra intestinal granuloma of CD maybe related to anti-TNF alpha agent and physicians should keep awareness of its recurrence. It is essential to take the potential of TNF inhibitor induction of granulomas into account and prevent patients undergoing unnecessary TNF inhibitor treatment. Also, the safety and adverse reactions of TNF inhibitor should be evaluated prudently in a wider range.

3. Introduction

Tumor Necrosis Factor (TNF) is a kind of cytokine that associate with multiple diseases such as infectious disease, immune disease, tumor. It has been demonstrated that TNF inhibitor can effectively improve the clinical symptom and related laboratory data of autoimmune diseases through altering the immune response. Paradoxically, a series of cases of TNF inhibitor induced non caseating granulomatous inflammation in rheumatological conditions which involved multiple organs have been reported [1]. In all three kinds of TNF inhibitors, etanercept is more related with non caseating granuloma than the others [2]. The current study is, to our acknowledgement, the first to describe infliximab (IFX) induced non caseating granulomas in lung of a patient being treated for Crohn's disease in China. The safety and adverse event of anti-TNF alpha agent should be long-term monitored in the future.

4. Case Report

A 60-year-old woman with a history of 10-year CD presented with a history of fever, cough, shortness of breath, diarrhea and loss of appetite for 5 days. She had a pyrexia of 39 Celsius and coughed with white foam sputum accompanied by right chest pain. Ileo-

cecal CD had been diagnosed 10 years ago and the patient treated with infliximab (IFX), mesalamine, prednisolone, vitamins and nutritional treatment. She discharged after symptom control and take Azathioprine (AZA) for maintenance therapy. Five years later she underwent colectomy in other hospital and accepted blood transfusion during operation. She was a life-long non-smoker and her families were all in good condition.

On her admission, the physics examination was unremarkable despite a slightly rough breathing sounds in two lungs. Laboratory data showed a white blood account of $6.80 \times 10^9/L$ (88.8% neutrophils, 0.60% eosinophils, 0.10% basophil, 7.20% monocytes, 3.30% lymphocytes) and microcytic hypochromic anemia was taken into account for MCV 70.2 fl, MCH 22.6 pg, MCHC 322g. Blood test also showed an increase active of inflammation: ESR 45 mm/h; C reactive protein 19 mg/L; autoimmune related antibodies were all negative; Angiotensin Converting Enzyme (ACE) level was in normal range. Stool analysis showed Occult Blood Test (OBT), fungi and parasites were negative. Phlegm culture, blood culture and T-spot were negative. She was started on antibiotics quadruple therapy includes cefpodoxime, moxifloxacin, imipenem and cefoperazone, ambroxol and sodophylline used for pro-

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ductive cough and wheezing respectively. Unfortunately, the lung lesion was not improved obviously and further examination had been carried out. We found that she was a lifelong non-smoker and had no history of relevant lung diseases. Chest computed tomography revealed bilateral pleura thickness, consolidation in right middle lobe and small nodules in right upper lobe (Figure 1). She received immuno suppressants as long-term treatment and lead to a weak immune function, which pushed the differential diagnosis with infectious diseases into a dilemma and the lesion biopsy was imperative. Electronic bronchoscopy biopsy showed bronchitis in right middle lobe, mucosal inflammatory cells infiltration and several small granulomas (Figure 2). Broncho Alveolar Lavage (BAL) showed a small number of inflammatory cells and columnar epithelial cells. Pulmonary Function (PFT) test was normal and bronchial dilation test was negative. In consideration of granulomatous lung disease and organizing pneumonia was suspected, she was treated with methylprednisolone 40mg intravenous injection and then switched to oral methylprednisolone 16mg/12mg bid. Patients showed good compliance during the cortico therapy and no adverse effects such as central obesity, peptic ulcers, and infections occurred. Her symptoms had responded evidently and imaging manifestation had also improved. She was told to review chest CT regularly after discharge.

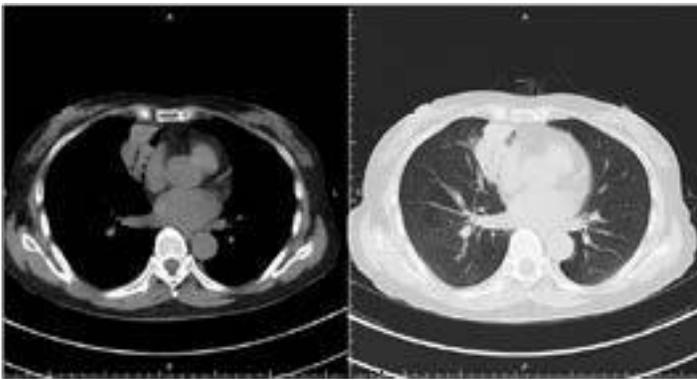


Figure 1: Chest computed tomography shows bilateral pleura thickness, consolidation in right middle lobe and small nodules in right upper lobe.

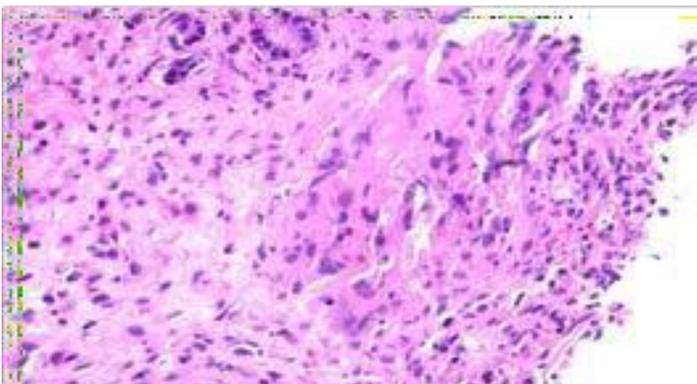


Figure 2: The pathological biopsy in lung lesions. Electronic bronchoscopy biopsy showed bronchitis in right middle lobe, mucosal inflammatory cells infiltration and several small granulomas

5. Discussion

TNF α has been recognized as an essential cytokine factor of inducing granuloma and the using of TNF α inhibitor could prevent the formation of granuloma therapeutically. Recent years, the form of granuloma has been described as a rare adverse reaction of anti-TNF α treatment repeatedly in rheumatic disease. Most cases were found non case ating granuloma in lung, hilar lymph node and skin lesion [1,3,4]. Other organs, such as bone marrow [5] and liver [6] have also been observed. These granulomas involved with multi-organs were all found between 1 to 69 months onset of the TNF α inhibitor therapy [1,4]. Among the commonly used TNF α inhibitors, it is etanercept (ETA) that more probably induces the extraintestinal granuloma than infliximab (IFX) and adalimumab (ADA) [1,3,4] and this discrepancy may caused by the different pharmacological mechanism. In conclusion, IFX could block TNF α in different points on its pathway while ETA leave a sum of TNF α in active form that participate in the forming of granuloma [7-10]. Meanwhile, it is seams that there is no correlation between the resolution of extra intestinal granuloma and the use of TNF α inhibitor, because of whether maintaining or interrupting the original TNF α inhibitor treatment or switch to another TNF α inhibitor can lead to the resolution of the pulmonary granuloma, and steroids is equally feasible [1,4].

Given that TNF α inhibitor is applied to CD later, fewer corresponding adverse reaction has been reported. Indeed, the mechanism by which TNF α inhibitors causes extra intestinal granuloma is not clear and clinicians generally lack of full understanding of it. To us acknowledge, it is the first case of pulmonary non case ating granuloma associated with IFX in China and there is only one pleural granuloma associated with IFX in CD has been reported before [2]. Our patient showed negative in infectious diseases and theratio of CD4/CD8 in BAL was normal, thus the diagnosis of tuberculosis or sarcoidosis was excluded. Besides adverse reaction of IFX we cannot find an appropriate cause to explain the pulmonary non case ating granuloma. This may suggest that when CD patients with a history of anti-TNF α agent medication shows extra intestinal granulomatous lesions, TNF α inhibitor associated adverse reaction should be considered. In addition, clinicians should be clear about the indications for TNF α inhibitors and the timing of optimal medication, thereby avoiding patients receiving unnecessary TNF α inhibitors treatment.

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