Anti-interferon-gamma autoantibody related disseminated nontuberculous mycobacteriosis with pathological features of immunoglobulin G4-related disease

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ABSTRACT

A 72-year-old man who was diagnosed as pulmonary mycobacterium avium complex (MAC) disease had suffered from antibiotics resistant fever with left renal enlargement surrounded by inflammatory change and multiple osteolytic lesions on computed tomography (CT). The renal biopsied samples pathologically showed immunoglobulin G4 (IgG4) positive plasma cell infiltration and many acid-fast bacilli without granuloma formation. Nucleic acid identification test for MAC from the samples of vertebral osteolytic lesion was positive. In the autopsy samples from left kidney, epithelioid cell granuloma and Langhans giant cell with many acid-fast bacilli were shown pathologically. In addition to osteolytic lesions on CT study, these pathological findings were not consistent with IgG4-related disease (IgG4-RD). The diagnosis of disseminated nontuberculous mycobacteriosis was made, and plasma anti-interferon-gamma (IFN-γ) autoantibody was found as the cause of underlying immunodeficiency. Disturbed function of IFN-γ resulted in impaired ability of phagocytic cells against pathogens and leading to spread of infection. T-helper type 2 dominant immune response was induced by prolonged antigenic stimulation of mycobacteria, which might have contributed to form the pathological features of IgG4-RD.

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a systemic tumefactive organ involvement with elevated serum IgG4 concentration and pathological features of IgG4 positive plasma cell infiltration and storiform fibrosis [1]. Although the etiology is not clearly elucidated, T-helper type2 (Th2) and T- regulatory (Treg) dominant cytokine balance is assumed to contribute to this pathogenesis [2,3]. Mycobacterial infection also upregulates these cytokines, leading to increase IgG4 production [4].

Disseminated nontuberculous mycobacteriosis (dNTM) is a severe form of NTM infection mostly associated with a background of immunodeficiency. Neutralizing interferon-gamma (IFN-γ) autoantibodies were recently recognized as a cause of acquired immunodeficiency mainly in Asian population [5]. Mycobacterial infection complicated by IgG4-RD like clinical features have been reported. Th2 and Treg mediated response with decreased IFN-γ activity might contribute to this pathogenesis [6–9].

2. Case presentation

A 72-year-old man was referred to our hospital for persistent fever. His past medical history was hypertension, ossification of cervical posterior longitudinal ligament and hyperuricemia with no family history of serious infectious disorder. 30 months before, he was diagnosed as pulmonary mycobacterium avium complex (MAC) disease, and had taken anti-mycobacterial therapy of clarithromycin, rifampicin and ethambutol only for 3 months because of drug eruption. 17 months before, left renal swelling associated with increased surrounding fat density and osteolytic lesion in sacrum were revealed by computed tomography (CT). CT guided left renal biopsy was performed, which only showed acute and chronic inflammatory change histopathologically. 12 months before, middle and lower lobes of his right lung were resected as a clinical diagnosis of inflammatory pseudo tumor. The pathological features were obstructive pneumonia mainly composed of foamy histiocytes and lymphocytes with interstitial fibro-edematous change without granuloma formation. After partial pulmonary resection, only clarithromycin was continued for 9 months, subsequently stopped because of negative result in bacteriological cultures of sputum. One month before, he had abdominal pain and fever up, CT study presented known left renal swelling, multiple osteolytic...
changes of ribs, thoracolumbar vertebrae and pelvis in addition to existing sacral lesion, and no other obvious fever origin could not be detected. Left pyelonephritis was suspected, and several antibiotics were introduced, however resulted in poor response. After that, he was referred and admitted to our hospital. T-SPOT.TB test was negative, the serum prostate-specific antigen and angiotensin-converting enzyme were within normal ranges of 1.798 ng/mL and 20.5 IU/L. Result of blood culture was negative, and \textit{Klebsiella pneumoniae} was detected in urine culture. Other laboratory data and CT images on admission were presented in Table 1 and Figure 1. After admission, the serum creatinine level was progressively elevated necessary to introduce hemodialysis, while the serum CRP level had once decreased with antibiotic treatment, it increased again. To clarify the pathogenesis of fever and renal damage, we performed left renal biopsy again. Inflammatory cell infiltration mainly composed of plasma cells in the interstitium without granuloma formation, and many acid-fast stained bacilli were shown pathologically. IgG4-positive plasma cells markedly increased to the count of 110 microscopically in high power field (Figure 2), and IgG4/IgG ratio was 61%, these findings fulfilled some of the comprehensive diagnostic criteria of IgG4-RD [1].

Serum IgG4 and IgE levels were elevated to 258 mg/dL and 2900 IU/mL, respectively, which were also consistent with the clinical data of IgG4-RD. CT guided biopsy was underway at the osteolytic lesion of the thoracic vertebra, and the samples were applied to bacteriological examination. The result of MAC transcription reverse transcription concerted reaction test was positive, and mycobacterium avium was identified in culture by mycobacteria growth indicator tube. The diagnosis of dNTM was made, and clarithromycin and rifampicin were started. Soon after, his respiratory condition rapidly got worse with bilateral infiltration shadow on chest radiography (Figure 3) associated with progressing inflammatory reaction. Empiric therapies for bacterial and fungal infection with intravenous steroid were started concomitantly, however the patient finally died due to respiratory failure after a few days. The clinical course from admission is presented in Figure 4. After death, the autopsy had revealed diffuse alveolar damage with inflammatory cell infiltration including neutrophil, hyaline membrane, and intra-alveolar organization without granuloma and acid-fast bacilli in the pulmonary pathology (Figure 5), and epithelioid cell granuloma and Langhans giant cell with many acid-fast bacilli in the left kidney. Osteolytic lesions on CT and epithelioid granuloma formation pathologically revealed by autopsy were not consistent with IgG4-RD. In the autopsy from the mediastinal lymphnode, its basic structure was preserved and multi-nucleated giant cell was shown pathologically. In addition to no significant lymphnode swelling and hepatosplenomegaly, this pathological findings did not support the diagnosis of Castleman’s disease. Supposing acquired immunodeficiency as the background of dNTM infection, we examined plasma anti-IFN-\(\gamma\) autoantibody titer by using enzyme-linked immuno-sorbent assay, and quantitative analysis of signal transducer and activator of transcription 1 (STAT1) phosphorylation of mononuclear cells activated by IFN-\(\gamma\) in the serum [10]. The intensity of STAT1 phosphorylation was described as STAT1 phosphorylation index (STAT1-PI), which indicated the ratio to negative control. The IgG class IFN-\(\gamma\) autoantibody titer was elevated to 49.5 E.U, and STAT1-PI was inhibited to 41.8 compared to healthy control of 0.5 E.U and 365 respectively. These results confirmed having this neutralizing autoantibody.

| Table 1. Laboratory data on admission. |
|----------------------------------------|
| Urinalysis                            | Analine aminotransferase 38 U/L |
| density                               | Lactate dehydrogenase 154 U/L  |
| protein                               | Blood urea nitrogen 23.1 mg/dL |
| sugar                                 | Creatinine 1.39 mg/dL          |
| Ketone bodies                         | Sodium 134.6 mmol/L            |
| occult blood                          | Potassium 4.6 mmol/L           |
| Blood cell count                      | Chloride 102.3 mmol/L          |
| White blood cell                      | Calcium 8.7 mg/dL              |
| Monocyte                              | 2.0 %                         |
| Lymphocyte                            | 6.5 %                         |
| Red blood cell                        | 340 \(\times\) 10^4/\mu L     |
| Hemoglobin                            | 9.1 g/dL                      |
| Hematocrit                            | 28.8 %                        |
| Platelet                              | 48.3 \(\times\) 10^4/\mu L    |
| Total protein                         | 8.2 g/dL                      |
| Albumin                               | 2.0 g/dL                      |
| Total bilirubin                       | 1.2 mg/dL                     |
| Alkaline phosphatase                  | 430 U/L                       |
| Aspartase aminotransferase            | 39 U/L                        |
| Biochemistry                          | Serology                      |
| Albumin                               | C-reactive protein 20.63 mg/dL |
| Immunoglobulin G                      | Immunoglobulin A 459 mg/dL    |
| Immunoglobulin M                      | 155 mg/dL                     |
| Complement 3                          | 94 mg/dL                      |
| Complement 4                          | 23 mg/dL                      |
| 50\%hemolytic complement activity     | 24.2 U/mL                     |
| Virology                              | Human immunodeficiency virus antibody (–) |
| Human T-cell leukemia virus type I antibody (–) |

Changes of ribs, thoracolumbar vertebrae and pelvis in addition to existing sacral lesion, and no other obvious fever origin could not be detected. Left pyelonephritis was suspected, and several antibiotics were introduced, however resulted in poor response. After that, he was referred and admitted to our hospital. T-SPOT.TB test was negative, the serum prostate-specific antigen and angiotensin-converting enzyme were within normal ranges of 1.798 ng/mL and 20.5 IU/L. Result of blood culture was negative, and \textit{Klebsiella pneumoniae} was detected in urine culture. Other laboratory data and CT images on admission were presented in Table 1 and Figure 1. After admission, the serum creatinine level was progressively elevated necessary to introduce hemodialysis, while the serum CRP level had once decreased with antibiotic treatment, it increased again. To clarify the pathogenesis of fever and renal damage, we performed left renal biopsy again. Inflammatory cell infiltration mainly composed of plasma cells in the interstitium without granuloma formation, and many acid-fast stained bacilli were shown pathologically. IgG4-positive plasma cells markedly increased to the count of 110 microscopically in high power field (Figure 2), and IgG4/IgG ratio was 61%, these findings fulfilled some of the comprehensive diagnostic criteria of IgG4-RD [1]. Serum IgG4 and IgE levels were elevated to 258 mg/dL and 2900 IU/mL, respectively, which were also consistent with the clinical data of IgG4-RD. CT guided biopsy was underway at the osteolytic lesion of the thoracic vertebra, and the samples were applied to bacteriological examination. The result of MAC transcription reverse transcription concerted reaction test was positive, and mycobacterium avium was identified in culture by mycobacteria growth indicator tube. The diagnosis of dNTM was made, and clarithromycin and rifampicin were started. Soon after, his respiratory condition rapidly got worse with bilateral infiltration shadow on chest radiography (Figure 3) associated with progressing inflammatory reaction. Empiric therapies for bacterial and fungal infection with intravenous steroid were started concomitantly, however the patient finally died due to respiratory failure after a few days. The clinical course from admission is presented in Figure 4. After death, the autopsy had revealed diffuse alveolar damage with inflammatory cell infiltration including neutrophil, hyaline membrane, and intra-alveolar organization without granuloma and acid-fast bacilli in the pulmonary pathology (Figure 5), and epithelioid cell granuloma and Langhans giant cell with many acid-fast bacilli in the left kidney. Osteolytic lesions on CT and epithelioid granuloma formation pathologically revealed by autopsy were not consistent with IgG4-RD. In the autopsy from the mediastinal lymphnode, its basic structure was preserved and multi-nucleated giant cell was shown pathologically. In addition to no significant lymphnode swelling and hepatosplenomegaly, this pathological findings did not support the diagnosis of Castleman’s disease. Supposing acquired immunodeficiency as the background of dNTM infection, we examined plasma anti-IFN-\(\gamma\) autoantibody titer by using enzyme-linked immuno-sorbent assay, and quantitative analysis of signal transducer and activator of transcription 1 (STAT1) phosphorylation of mononuclear cells activated by IFN-\(\gamma\) in the serum [10]. The intensity of STAT1 phosphorylation was described as STAT1 phosphorylation index (STAT1-PI), which indicated the ratio to negative control. The IgG class IFN-\(\gamma\) autoantibody titer was elevated to 49.5 E.U, and STAT1-PI was inhibited to 41.8 compared to healthy control of 0.5 E.U and 365 respectively. These results confirmed having this neutralizing autoantibody.
3. Discussion

dNTM is a severe form of mycobacterial infection based on immune dysfunction in many cases, such as human immunodeficiency virus infection. Most patients with dNTM present generalized lymphadenitis or skin lesions, while renal involvement of our case is rare [11]. IFN-\(\gamma\) is a key cytokine in immunological defense system against mycobacterial infection [12]. Th1 cells sensitized to bacterial antigens activate macrophages by hyper-production of IFN-\(\gamma\), leading to phagocytosis and granuloma formation to eradicate and confine these pathogens [13]. Interleukin-12 (IL-12) secreted from phagocytic cells and IFN-\(\gamma\) mutually enhance this immune system against mycobacteria [14]. Neutralizing anti-IFN-\(\gamma\) autoantibodies were frequently reported in Asian adults with unexplained dNTM cases [5,15,16]. In patients with depressed IFN-\(\gamma\) function, the histological features of mycobacterial lesions demonstrate hypoplasia of granuloma, low epithelioid cell count [12,17], and many phagocytic cells such as histiocyte containing surviving pathogens [18]. Many acid-fast bacilli, no granulomas, and lympho-plasma cell dominant infiltration of biopsied renal histological findings supported the disturbed cellular immunity due to IFN-\(\gamma\) dysfunction.

IgG4-RD is an immune-mediated fibro-inflammatory disorder of organ enlargement with high serum IgG4 concentration and IgG4-positive plasma cell infiltration in the involved organs [1]. Immunoglobulin class switching depending on IL-4, 10, 13 and transforming growth factor-\(\beta\) (TGF-\(\beta\)), which act as Th2 and Treg response is considered

Figure 1. CT scan tested on admission showed left renal swelling surrounded by inflammatory change (arrow) (A), and osteolytic lesions in sacrum (arrow) (B), ribs, vertebrae and pelvis.

Figure 2. Biopsied samples from left kidney pathologically revealed marked plasma cell infiltration (A. Hematoxylin and Eosin staining, \(\times1000\)), mostly expressed IgG4-positive (B. Immunostaining of IgG4, \(\times400\)), and many acid-fast staining bacilli (C. Acid-Fast staining, \(\times1000\)).

Figure 3. Chest plain radiography showed bilateral infiltration shadow.
the basic immunological reaction of this disorder [3,19]. Most of the histopathological features of IgG4-RD are associated with Th2-dominant and upregulated Treg cells [20]. Increased these associated cytokine expression was proven in several involved organs of IgG4-RD [2,3,21]. Concerning the patient’s renal pathology, it showed increased IgG4/IgG ratio and IgG4 positive plasma cell count enough to meet the comprehensive diagnostic criteria for IgG4-RD. However, characteristic storiform fibrosis, so called Bird’s eye pattern could not be detected and diagnostic criteria for IgG4 related kidney disease was not fulfilled definitely.

Underlying pathophysiology of IgG4-RD like reaction associated with mycobacterial infection is speculated that surviving mycobacteria would activate Th2 cells [6–9]. Prolonged exposure to antigens would enhance serum IgG4 production [4,22]. Peripheral blood samples from patients of dNTM showed Th2 hyper-response and increase in serum IgG4 [23,24]. Persistent mycobacterial infection due to immunodeficiency caused by anti-IFN-γ autoantibodies might promote antigen-driven IgG4 secretion.

As another mechanism of IgG4 production, innate immunity was reported to play an important role [25]. Stimulation of toll-like receptor (TLR) and nucleotide-binding oligomerization domain and leucine rich repeat containing receptor (NLR) induces Th2 response to enhance IgG4 production and tissue fibrosis [26,27]. Persistent mycobacterial antigen exposure and subsequent innate immunity stimulation might have changed the immune balance toward Th2-dominant and formed IgG4-RD like histological features. In one study, epithelioid granuloma was noted in 1 case with a history of tuberculosis out of 114 IgG4-RD patients [28]. Therapies for dNTM with anti-IFN-γ autoantibodies have not been established, and antibiotic therapy alone is not enough to control in many cases. Some adjuvant therapies such as B-cell
depletion with rituximab were used to improve the clinical outcome in recent years [16]. In fact, long term combined anti-mycobacterial drugs should be considered in real clinical setting [29]. Direct cause of patient’s death was respiratory failure due to diffuse alveolar damage, which might have induced by spreading mycobacterial infection. Therefore, successive treatment of multiple anti-mycobacterial drugs had been required to improve the clinical course.

4. Conclusion

In conclusion, acquired immunodeficiency due to anti-IFN-γ autoantibodies should be considered in cases of dNTM, and IgG4-RD like pathological features could be found in the involved organs.

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Patient consent

We had signed informed consent for publication from the patient’s relative.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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