Case Report

Bullous Pemphigoid and Disseminated *Mycobacterium abscessus* Infection in a Patient with Anti-IFN-γ Autoantibody: The First Case Report

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Disseminated non-tuberculosis mycobacteria (dNTM) infection is an uncommon but critical infectious disease. This infection occurs almost exclusively in immunocompromised patients, and treating such an infection is a challenge for clinical physicians. Recently, adult-onset immunodeficiency with anti-IFN-γ autoantibody has been recognized as an immunodeficiency disease, particularly in the Asian population, and patients with anti-IFN-γ autoantibody became more susceptible to dNTM infection. Notably, the skin reaction may be the primary or secondary manifestation in patients with dNTM infection and anti-IFN-γ autoantibody. Here, we report a 67-year-old woman without systemic diseases presented to our hospital with bullous pemphigoid and disseminated *Mycobacterium abscessus* infection and anti-IFN-γ autoantibody was identified in further immune test.

Key words: anti-IFN-γ autoantibody, disseminated non-tuberculosis mycobacteria, *Mycobacterium abscessus*, bullous pemphigoid

Introduction

Non-tuberculous mycobacteria (NTM) species are mycobacterial species other than those belonging to the *Mycobacterium tuberculosis* complex. NTM are generally widely distributed in the environment and are less virulent to human. However, severe infection such as disseminated non-tuberculous mycobacterial (dNTM) may occur in patients with advance immune system defects.[1] Recently, adult-onset anti-IFN-γ autoantibody was recognized as an unusual but emergent immunodeficiency disorder and was associated with dNTM infection. In addition to dNTM infection, patients with anti-IFN-γ autoantibody may develop dermatosis and co-infection with other microorganism.[2] Identifying underlying anti-IFN-γ autoantibody is important for

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clinical physicians because of higher risk of relapse of infection in these patients. Bullous pemphigoid is an uncommon but important blister disorder. The disease has a chronic, frequent relapsing course and significantly effects on patient's quality of life and prognosis.[3] The association between bullous pemphigoil and anti-IFN-γ autoantibody has not been described before. Here, we reported the first case with anti-IFN-γ autoantibody presentation with bullous pemphigoid and disseminated *Mycobacterium abscessus (M. abscessus)* infection.

Case Report

A 67-year-old woman presented to our hospital with skin eruption and multiple enlarged lymph nodes for 1 month. Her medical history revealed that she was hospitalized twice in the past three months owing to bilateral leg cellulitis and a right inguinal rapidly growing mass after intravenous antibiotics injection in another hospital. In addition, she had an episode of herpes zoster on the right lower abdominal wall at around the same time.

Since one month ago, progressive generalized mild tender lymph nodes developed on the bilateral neck, axillae, and inguinal areas. In addition, painful erythematous induration over palms and similar but milder lesions on the right leg and buttock were noted (Fig. 1A and B). Other accompanying symptoms included intermittent fever, decrease in body weight by 7 kg within two months, and right wrist pain. Laboratory tests showed a white blood cell count of 25.5 × 10^3 mL with 88% mature neutrophil, hemoglobin of 9.4 g/dL, platelet count of 339 × 10^3 mL, C-reactive protein of 113.6 mg/L, creatinine of 1.0 mg/dL, alanine transaminase of 41 unit/L, and blood sugar of 142 mg/dL. The results of chest radiographs and urine analysis were unremarkable.

Non-contrast and contrast computed tomography showed multiple enlarged lymphadenopathies at the right submandibular region,

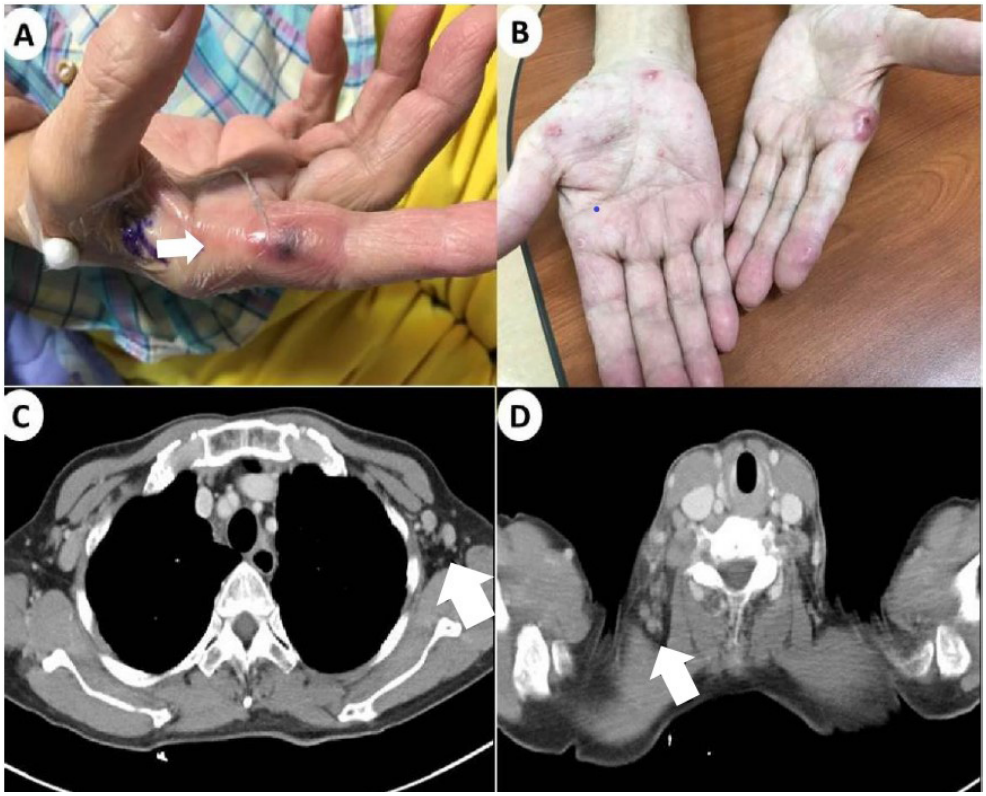

Fig. 1 Images of bullous pemphigoid and disseminated Mycobacterium abscessus infection, (A) and (B) showing painful erythematous induration lesions on the hands, (C) and (D) showing contrast chest computed tomography images of enlarged lymph nodes at the left axillae and right lateroposterior neck (arrow) .

right lateroposterior neck, bilateral supraclavicular to subclavicular region, bilateral mediastinum, subcarina, bilateral axillae, perigastric region of the upper abdomen and mesenteric root region, retroperitoneum, and bilateral parailiac region (Fig. 1C & D). Lymphadenopathy related to infection or neoplasm and the urticaria stage of bullous pemphigoid were tentative diagnosis by the clinical physician and dermatologist. Thus, right axilla excisional lymph node and skin biopsy was undertaken further. Lymph node biopsy revealed acute lymphadenitis characterized by necrosis, cell debris, and neutrophils without microorganism identified using acid fast staining and periodic acid Schiff staining. Skin biopsy revealed bullous pemphigoid characterized by focally disrupted epidermis and marked inflammatory infiltrate containing mainly neutrophils in the upper dermis and C3 deposition along basement membrane. Lymph culture was negative for bacteria and fungi, but *M. abscessus* growth was observed. Skin culture was negative for bacteria and fungi as well as Mycobacterium. The diagnosis of bullous pemphigoid and disseminated *M. abscessus* infection was made.

Additional immune system and viral examinations were performed; normal results were obtained for the human immunodeficiency virus Ag/Ab combo test, hepatitis B antigen, hepatitis C antibody, CD4 cell counts, autoimmune profiles including antinuclear antibody, anti-double stranded DNA, and rheumatoid factor, but the patient was positive for anti-IFN-γ autoantibody.

For disseminated *M. abscessus* infection, the following antimicrobials were prescribed: tigecycline 100 mg loading followed by 50 mg intravenously every 12 hours, amikacin 500 mg every 12 hours, imipenem 500 mg every 6 hours, and azithromycin 500 mg orally once daily. For bullous pemphigoid, the patient was prescribed prednisolone 10 mg three times a day. Lymph nodes and skin eruption both regressed. She was discharged and followed up in the outpatient department.

Discussion

NTM infection has become an emergent infectious disease in recent years. The increase in its incidence might be attributed to an increase in immunocompromised host population and advancement in diagnosis technology.[4] *M. abscessus* is one of the rapidly growing NTM and is commonly present in the environment, such as in water and soil. Pulmonary infection is the most common clinical manifestation of *M. abscessus* infection in patients with or without underlying diseases, but lymphadenitis, skin diseases, and disseminated infections may also occur. Treating *M. abscessus* is a challenge because this pathogen is usually resistant to classic anti-tuberculosis agents and many other antibiotics. A combination of at least two antimicrobial agents such as macrolides (clarithromycin or azithromycin), aminoglycosides, fluoroquinolones, imipenem, and doxycycline for 6 – 12 months is recommended.[4]

Our patient was previously healthy and presented with generalized lymphadenopathy, and disseminated *M. abscessus* infection was diagnosed based on the culture sampling from the lymph node. Because dNTM usually occurs in immunocompromised hosts, several immunological tests were ordered which confirmed the presence of anti-IFN-γ autoantibody in our patient. Adult-onset immunodeficiency with anti-IFN-γ autoantibody is a rare but emergent immunodeficiency disorder mainly involving patients from Southeast Asia, including Taiwan.[5-7] Patients with anti-IFN-γ autoantibody are more susceptible to dNTM due to markedly suppressed IFN-γ in response to mycobacteria. The mechanism of the production of anti-IFN-γ autoantibody remains unclear, but the development of anti-IFN-γ autoantibody might be associated with genetic factors such as the human leukocyte antigen class.[2,6] Recognizing anti-IFN-γ autoantibody in patients is essential

for clinical physicians because these patients are at a higher risk of relapse of infection, and therapies such as monoclonal rituximab might be adjunct treatment.[8-9]

Reactive skin lesions which include Sweet's syndrome, lobular panniculitis, erythema nodosum, and generalized pustular eruptions have been reported to be associated with anti-IFN-γ autoantibody.[5] The skin reaction is believed to be related to alterations in cytokine levels due to the presence of anti-IFN-γ autoantibodies.[10] To the best of our knowledge, we demonstrated the first case with anti-IFN-γ autoantibodies presentation with bullous pemphigoid and dNTM infection. Bullous pemphigoid is an uncommon autoimmune disorder and typically affects elderly patients. The clinical features of bullous pemphigoid may be variable in some cases, particularly during the early phase of the disease or with atypical variants in which typical blisters may be absent. The diagnosis of bullous pemphigoid is based on clinical suspension, histopathological findings, and positive direct immunofluorescence microscopy.[3] Similar with other dermatosis, the mechanism of the association between bullous pemphigoid and anti-IFN-γ autoantibody and mycobacterial infection is unclear. Genetic factors and triggers of infection might contribute to bullous pemphigoid development. Further investigation is warranted to clarify the association.

In conclusion, we reported the first case of bullous pemphigoid and disseminated *M. abscessus* infection in a patient with anti-IFN-γ autoantibody. Clinical physicians should be alert to the possibility of an underlying dNTM infection and anti-IFN-autoantibody in patients presenting bullous pemphigoid and lymphadenopathy.

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