Anti-interferon-gamma autoantibody syndrome and opportunistic skin infections: a case report and literature review

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ABSTRACT:

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In adulthood, patients with acquired anti-interferon-gamma (anti-IFN-γ) autoantibody syndrome usually suffer from recurrent and recalcitrant disseminated non-tuberculous mycobacterial (NTM) diseases with or without other opportunistic infections. We describe a case of HIV-negative, IFN-γ antibody positive, Thai adult who presented with disseminated *Mycobacterium avium complex* co-infection with cutaneous *Talaromyces marneffei and Mycobacterium abscessus* lymphadenitis.

Anti-IFN-γ autoantibody syndrome should be considered in the differential diagnosis of HIV-negative adults who present with unusual, severe, or recurrent skin infections caused by NTM or other opportunistic pathogens, especially in Asian patients.

Key words: anti-IFN-γ autoantibodies, Opportunistic infections, Mycobacteriosis, Talaromycosis

บทคัดย่อ :

อาริสา แก้วเกษ พัดชา พงษ์เจริญ รายงานผู้ป่วยและทบทวนวรรณกรรมเกี่ยวกับกลุ่มโรคที่มีแอนติบอดีต่ออินเตอร์เฟอรอนแกมมาและการเกิดการติดเชื้อฉวยโอกาสทางผิวหนัง วารสารโรคผิวหนัง 2561; 34: 192-199.

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ผู้ป่วยวัยผู้ใหญ่ที่มีแอนติบอดีต่ออินเตอร์เฟอรอนแกมมาในภายหลังมักเจ็บป่วยจากการติดเชื้อไมโครแบคทีเรียที่ไม่ใช่วัณโรค ซึ่งมักเป็นชนิดแพร่กระจายและดื้อต่อการรักษาซ้ำๆ ซึ่งอาจเกิดร่วมกับการติดเชื้อฉวยโอกาสอื่นๆ รายงานฉบับนี้เป็นการรายงานผู้ป่วยไทย ที่ไม่ได้ติดเชื้อเอชไอวี และตรวจพบว่ามีแอนติบอดีต่ออินเตอร์เฟอรอนแกมมา และมีการติดเชื้อ ***Mycobacterium avium complex*** ชนิดแพร่กระจาย ร่วมกับการติดเชื้อ ***Talaromyces marneffei*** ที่ผิวหนัง และติดเชื้อ ***Mycobacterium abscessus*** ที่ต่อมน้ำเหลือง

ดังนั้นควรนึกถึงกลุ่มโรคมีแอนติบอดีต่ออินเตอร์เฟอรอนแกมมาเป็นหนึ่งในการวินิจฉัยแยกโรคของผู้ป่วยวัยผู้ใหญ่ ที่ไม่ได้ติดเชื้อเอชไอวีและมาด้วยการติดเชื้อทางผิวหนังที่มีความรุนแรง และเป็นซ้ำๆที่เกิดจากเชื้อไมโคแบคทีเรียที่ไม่ใช่วัณโรค หรือจากเชื้อฉวยโอกาสอื่น โดยเฉพาะในผู้ป่วยชาวเอเชีย

คำสำคัญ: แอนติบอดีต่ออินเตอร์เฟอรอนแกมมา, การติดเชื้อฉวยโอกาส, การติดเชื้อไมโคแบคทีเรีย, การติดเชื้อทาราโรไมโคซิส

Introduction

Adult-onset immunodeficiency with acquired anti-interferon-gamma (anti-IFN-γ) autoantibodies has been recognized recently in the Southeast Asian region. Patients usually suffer from infections like recurrent disseminated non-tuberculous mycobacterial (NTM) diseases, talaromycosis (formerly penicilliosis), extraintestinal nontyphoidal salmonellosis, and burkholderiosis.[1] The precise mechanism of production of anti-IFN-γ autoantibodies remains unknown but it results in the neutralization of IFN-γ activity by the autoantibody and lead to immunodeficiency[2]

Herein, we describe a case of previously healthy adult Thai patient who presented with disseminated NTM and *Talaromyces marneffei* co-infections who were diagnosed with anti-IFN-γ autoantibody syndrome.

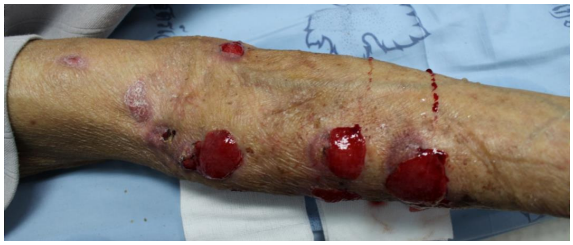

Figure 1 Multiple ulcerated nodules with hemorrhagic crust in sporotrichoid pattern on the right arm.

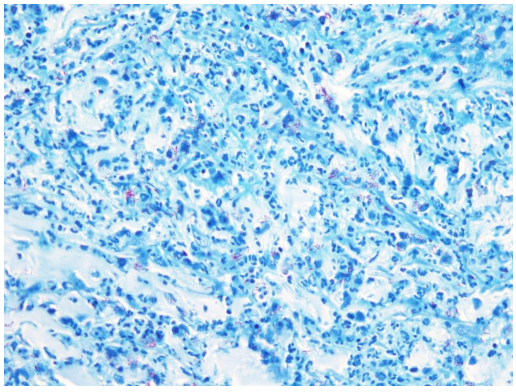

Figure 2 Skin biopsy from right arm revealed positive staining for acid fast bacilli (AFB) on a Ziehl-Neelsen stain.

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Case report

A 65-years-old man from Nan province presented with a two-year history of prolonged fever, generalized malaise, weight loss, and an ulcerative nodule with purulent discharge on the right side of neck. He had no other previous illnesses. The pus culture was negative result for aerobic bacteria. Serology for meiliodosis (*Bukholderia pseudomallei*) was positive (1:160) and he was treated with intravenous ceftazidime for seven days and then switched to oral doxycycline and co-trimoxazole. Unfortunately, he developed Steven-Johnson syndrome on the 17^{th}day of oral antibiotics. Therefore, he was changed to oral amoxicillin/clavulanate for 5 months. Despite this, his clinical state was essentially unchanged.

One year later, he developed multiple skin abscesses along right arm in a sporotricoid pattern. [figure 1] He was treated empirically with several antibiotics but with no apparent improvement. One month later, he was admitted to our hospital with acute dyspnea and a non-productive cough.

A chest and abdomen CT scan showed a left lower lung abscess with a small liver abscess. A right arm skin biopsy was positive staining for acid fast bacilli (AFB) on a Ziehl-Neelsen stain [figure 2] and the tissue culture grew *Mycobacterium avium complex* (MAC). PCR for mycobacteria was negative as were fungal and routine bacterial cultures. A diagnosis of disseminated MAC infection was made and he was treated with a combination of oral azithromycin 500 mg/d, isoniazid 300 mg/d, rifampicin 600 mg/d, pyrazinamide 1,500 mg/d and ethambutol 1,200 mg/d (AIRZE) for 2 months and then the regimen was change to azithromycin 500 mg/d, ethambutol 1,200 mg/d, rifampicin 600 mg/d (AER) for 5 months.

After four months of treatment, the right arm skin lesions completely resolved and a chest and abdomen CT showed resolution of the lung abscess (becoming a pneumatocele) and complete disappearance of the liver abscess. Laboratory testing for anti-HIV antibodies was negative, and his $CD4^+$ and $CD8^+$ lymphocyte counts, immunoglobulin concentrations, PPD and candida skin tests were all normal. However, he had high concentrations of anti-IFN-γ autoantibodies (73% inhibition at titer 1:10,000) detected by ELISA technique.

One month later (while still taking AER), he developed new erythematous infiltrative plaques and small ulcers on left arm and left axillary and inguinal lymphadenopathy. A skin biopsy showed a nodular and granulomatous dermatitis with focal ulcer and small abscesses in the upper dermis and *Talaromyces marneffei* grew in culture. Aerobic bacterial culture and PCR for mycobacteria were negative. The tissue culture from inguinal lymph node grew

Mycobacterium abscessus. He was treated with intravenous imipenem 2 g/d and amikacin 750 mg/d in combination with oral azithromicin 500 mg/d and ethambutol 1,200 mg/d for one month and then changed to oral ciprofloxacin 1,500 mg/d, ethambutol 1,200 mg/d and azithromicin500 mg/d with clinical improvement until now. He also received oral itraconazole 400 mg/d for the treatment of *Talaromyces marneffei* for 3 months then decrease the dose to 200 mg/d for another 18 months with clinical improvement. Post treatment, his anti-IFN titer increased from 71% inhibition to 83% inhibition at a titer of 1:10,000.

Discussion

We report the previously healthy adult patient from northern Thailand with adult onset of disseminated *Mycobacterium avium complex* co-infection with cutaneous *Talaromyces marneffei and Mycobacterium abscessus* lymphadenitis**.** These pathogens are rare in immunocompetent individuals and are reported as opportunistic infections especially in individuals with AIDS.[3,4]

The patient had previously been healthy into adulthood, whereas primary immune deficiencies tend to present early in life. We first excluded secondary T-cell immunodeficiencies by performing serology for HIV, $CD4^+$, $CD8^+$ T cell subsets, PPD and candida skin tests. All tests revealed normal results. Neither patient was on or had received immunosuppressive drugs. The patient tested positive for autoantibodies against to IFN-γ in high concentrations.

The IFN-γ-IL-12 axis plays a crucial role in the protection against intracellular pathogens, especially non-tuberculous mycobacteria as well as others opportunistic organisms.[5,6] IL-12, produced by antigen presenting cells, stimulates natural killer (NK) and T cell to produce IFN-γ. IFN-γ can activate macrophages to phagocytose and kill intracellular pathogens [7] Therefore, the patients who have autoantibody to IFN-γ will impair ability in killing of intracellular pathogen by macrophage.[8] In addition, high titer of autoantibody to IFN-γ also have ability of inhibiting IL-12 production.[9]

Recently, there have been an increasing number of reports of acquired autoantibodies to IFN-γ in adults, especially in Southeast Asians and Chinese.[10] In studies from Thailand and Taiwan, neutralizing anti-IFN-γ antibodies were detected in 88% of adults with multiple opportunistic infections.[2] The precise mechanism of production of autoantibody to IFN-γ is unknown but genetic factors are suspected to be involved. One study found that interferon-γ autoantibodies in adults with disseminated NTM infections and herpes zoster reactivation were associated with HLA-DRB1*16:02 and DQB1* 05:02 alleles[9] Another study which compared HLA genotyping between 32 patients with

antibody to IFN-γ autoantibody syndrome and 38 controls found the association of this syndrome with HLA-DRB1* 05:01, HLA-DRB1*16:02, HLA-DQB1* 05:01 and HLA-DQB1* 05:01 alleles.[11]

Disseminated opportunistic infections in individuals with anti-IFN-γ autoantibodies are characteristically difficult to treat. In addition to standard aggressive antimicrobial therapy, the patients with persistent, progressive, or severe anti-IFN-γ autoantibody-associated infections may need adjunctive therapy such as IFN-γ, immunoglobulin and plasmapheresis. However, they have limited success in these patients with IFN-γ autoantibody syndrome [12-15]

Rituximab is an antibody directed against the CD20 B cell surface protein that mediates antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).[16] It has been reported as a promising adjunct treatment with NTM infections in patients with antibody to IFN-γ autoantibody syndrome.[12] Browne et al. reported four patients with refractory NTM disease who were successfully treated with rituximab resulting in a reduction in autoantibody titer, improvement in IFN-γ signaling, and sustained disease remission.[12] Czaja et al. also reported the successful treatment with rituximab in one patient who had persistent disseminated *Mycobacterium abscessus* infection and the reduction of the inhibition of IFN-γ signaling after treatment[17] Pruetpongpun et al. also observed similar positive result in a patient with anti IFN-γ autoantibody syndrome who received rituximab for his disseminated *Talaromyces marneffei* co-infection with *cutaneous Mycobacterium abscessus*. They found the decrease of autoantibody titer after only two courses of rituximab treatment.[18] However, our patient was treated with antimicrobial alone without rituximab because of financial problem and result in rising of anti IFN-γ autoantibody titer. Therefore, we closely follow-up the clinical and the antibody titer because disease relapse is associated with an increasing of the autoantibody titer.[12,19]

In conclusion, we experienced the HIV negative patient who presented with opportunistic infections usually associated with AIDS and other severe immunocompromised diseases. The patient had autoantibodies to IFN-γ. Therefore, clinicians should search for unusual immunocompromised diseases like IFN-γ autoantibody syndrome in such patients who are HIV negative. The antibody titer should be monitored during follow-up to evaluate disease activity and recurrence and the titer may be increase while continue long-term antimicrobial treatment alone as in our patient. Therefore, considering adjunctive treatment such as

rituximab may be useful in disease control especially in refractory cases.

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