Opportunistic skin infection in adult-onset immunodeficiency due to anti-interferon-gamma autoantibody: a case report and literature review

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ABSTRACT:

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An acquired anti-interferon-gamma autoantibody syndrome is a well-recognized entity presenting in non-HIV and previously healthy patients, resulting in susceptibility to severe and recalcitrant intracellular opportunistic infections. Here we describe a case of HIV-negative, interferon-gamma-autoantibody–positive, Thai male who presented with disseminated *Mycobacterium abscessus* infection with a history of tuberculous lymphadenitis, genital herpes simplex and *Salmonella group B* infection and was treated with antimicrobial therapy in combination with rituximab.

Key words: anti-interferon-gamma autoantibody, opportunistic infections, rituximab

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An acquired anti-interferon-gamma autoantibody syndrome is a well-recognized entity presenting in non-HIV and previously healthy patients, resulting in susceptibility to severe and recalcitrant intracellular opportunistic infections such as disseminated nontuberculous mycobacteria (NTM), *Salmonella spp, Cryptococcus neoformans,* herpes simplex virus, and varicella zoster virus infection, etc. This disease is caused by the neutralizing capacity of anti-interferon-γ autoantibodies(anti-IFN-γ Ab) that interfere with the IFN-γ-IL-12 pathway and also diminishes the production of interleukin-2 (IL-2) and tumor necrosis factor–α (TNF-α) by T cells, similar to that seen in chronic infection[1]. Subsequently, this leads to an impairment of immune function, particularly against intracellular organisms[2].

In this case report, we describe a case of HIV-negative, IFN-γ-Ab–positive, Thai male who presented with disseminated *Mycobacterium abscessus* infection with history of tuberculous lymphadenitis, genital herpes simplex and *Salmonella group B* infection and was treated with antimicrobial therapy in combination with rituximab.

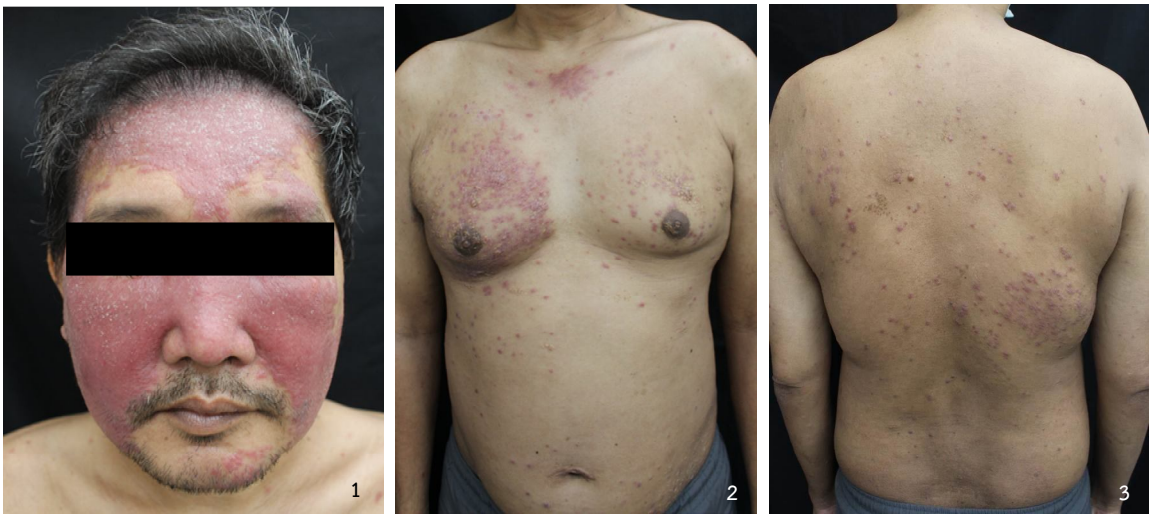

Figure 1,2,3 Clinical features of skin manifestations, large well-defined erythematous infiltrative plaques on face, and multiple well-defined erythematous infiltrative papules and plaques and scar-like lesions on chest and back

Case report

A 49-year-old man from Pathumthani province presented to a private hospital with a three-year history of bilateral cervical lymphadenopathies and a small red rash on his face. A lymph node biopsy was performed and

revealed granuloma with central necrosis. He was diagnosed with tuberculous lymphadenitis and received oral isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months. Shortly after, he developed a rash which was thought to be due to an adverse drug reaction, and thus the medications were stopped and changed to intravenous streptomycin, oral ethambutol, and levofloxacin for 8 months. His lymphadenopathies resolved but the rash on his face continued to progress. A facial skin biopsy showed nodular infiltration with histiocytes, few Langhans giant cells, and mixed cell granuloma. Both the AFB staining and mycobacterial culture were negative. A diagnosis of lupus vulgaris was made and he received several drug regimens including oral ethambutol, clarithromycin, ciprofloxacin, and intravenous amikacin, all without improvement.

Two years later, his facial rash progressed from initially a few erythematous papules to infiltrative plaques and developed into extensive multiple erythematous papules and plaques with scar-like lesions on chest wall and back (Fig. 1, 2, and 3). He presented to our hospital and a skin biopsy was taken from the face and chest wall. The histopathology showed superficial and deep perivascular mixed cell infiltration composing of lymphocytes, neutrophils, histiocytes, giant cells, and granuloma without caseous necrosis in the dermis and was negative for AFB, mAFB, PAS and GMS staining (Fig. 4 and 5). Non-tuberculous mycobacterium was detected by PCR and and the tissue culture grew *Mycobacterium abscessus*. A CT scan of the chest and abdomen revealed several tiny pulmonary nodules as well as hepatosplenomegaly with multiple small hypodense lesions within the liver and spleen. The patient was diagnosed with disseminated *Mycobacterium abscessus* infection. After reviewing the past medical history, it came to light that two months prior to this admission, the patient also had a history of *Salmonella group B* septicemia and genital herpes simplex viral infection.

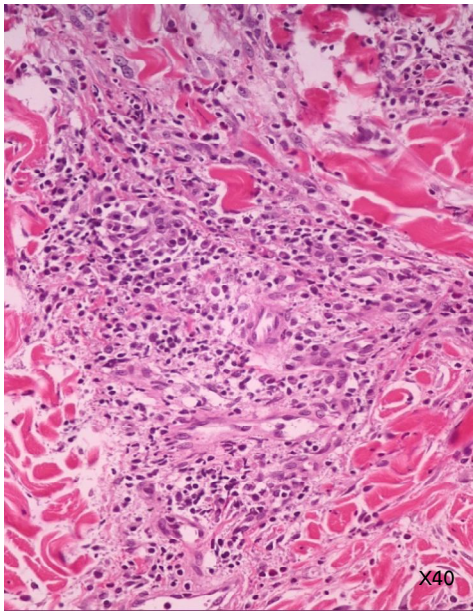

Figure 4 Histopathology, H&E, mix cell granulomas without caseous necrosis

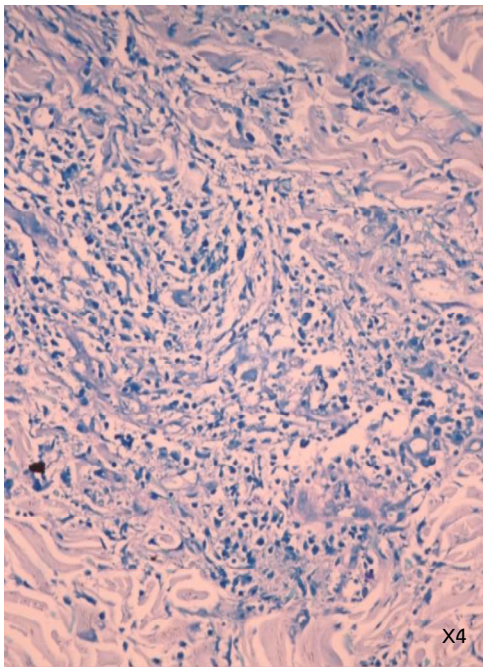

Figure 5 Histopathology, AFB, negative for acid fast bacilli

Laboratory testing for anti-HIV antibodies was negative. The immunoglobulin level and PPD test were normal. However, the patient was found to have a high concentration of anti-IFN-γ Ab (50% inhibition at titer 1:400,000) by ELISA technique. His white blood cell was 27,200/uL (neutrophil 74%, lymphocyte 13%). He was treated with a combination of intravenous imipenem 2 gm/day, intravenous amikacin 100 mg/day, oral clarithromycin 500 mg/day and oral levofloxacin 750 mg/day for 1 month which was changed to intravenous imipenem 2 gm/day, intravenous amikacin 100 mg/day, oral doxycycline 200 mg/day as per drug sensitivity testing. After 3 months of treatment, the patient showed significant clinical improvement and imipenem was discontinued. However, 2 weeks after discontinuation of imipenem, there was a flare-up of the rash at the same sites, and the c-reactive protein (CRP) rose from 37.45 to 51.12 mg/L. Consequently, intravenous imipenem was restarted, and oral azithromycin 500 mg/day was added on for another 2 months. The patient continued to show a good clinical response and the CRP decreased to 9.13 mg/L. Consequently, we initiated intravenous rituximab 700 mg weekly. After a month of treatment with rituximab and antibiotics, the rash improved drastically, while levels of anti-IFN-γ Ab and CPR significantly decreased (50% inhibition at titer 1:100,000 and 4.09 mg/L respectively). Thus, intravenous amikacin and imipenem were stopped, and the patient continued taking oral azithromycin and doxycycline.

Discussion

An acquired immunodeficiency due to anti-IFN-γ Ab is a well-known entity which affects non-HIV and previously healthy patients, particularly the Asian populations, leading to susceptibility to severe and recalcitrant intracellular opportunistic infections. The most common pathogen causing opportunistic infections in this disease is NTM, followed by *Burkholderia spp, Salmonella spp,*

Mycobacterial tuberculosis complex, Cryptococcus neoformans, Histoplasma capsulatum, Talaromyces marneffei, Human papillomavirus, herpes simplex virus and, Varicella zoster virus[2-5]. Cutaneous manifestations are the common presentation of the syndrome, and are classified into reactive skin diseases and infective skin diseases. The former includes neutrophilic dermatoses such as acute generalized exanthematous pustulosis, Sweet syndrome, pustular psoriasis, and pyoderma gangrenosum and non-neutrophilic dermatoses such as diffuse plane xanthoma, erythema nodosum, and leukocytoclastic vasculitis, etc. *M.abscessus* infection is the most common cause of infective skin disease in acquired immunodeficiency due to anti-IFN-γ Ab[2,5-7]. Acquired immunodeficiency status of the disease is caused by the neutralizing capacity of anti-IFN-γ Ab. IFN-γ, which is produced by T cells, activates macrophages and dendritic cells, causing them to phagocytose and kill intracellular organisms, and to produce IL12 to activate T cells and natural killer cells. Therefore, any interference with the IFN-γ-IL-12 pathway leads to defective function against intracellular organisms. Chronic infection results in chronic antigenic stimulation leading to subsequent T cell exhaustion which diminishes the production of IL-2 and TNF-α, further impairing the immune function[1]. To date, the cause of antibody production remains unknown, and there is currently insufficient data to link certain HLA alleles with anti-IFN-γ Ab[5]. Although some reports have previously shown that the autoantibody level and neutralizing capacity were not associated with the clinical course or disease severity amongst patients[8], one recent report showed that the concentration of anti-IFN-γ Ab significantly correlated with the treatment outcome[5].

Infection in anti-IFN-γ Ab syndrome can be severe and difficult to treat. In cutaneous atypical mycobacterium infection, a combination of ≥3 antibiotics with ≥4 months is the standard of treatment, with previous reports describing a mean remission time of 20-52 weeks[9,10]. In refractory cases with high-titers of anti-IFN-γ Ab, aggressive antimicrobial therapy alone may not be sufficient to achieve a sustained response. Rituximab, an anti-CD20 monoclonal antibody, has been used off-label for the treatment of diseases caused by pathogenic autoantibodies and could be an adjunctive treatment to antibiotics, as in our case. Rituximab causes a depletion of plasmablasts and B cells, leading to decreased antibody production and thus minimising the antibodies' neutralizing capacity[11]. Intravenous cyclophosphamide in combination with systemic corticosteroid has been shown to lead to clinical improvement and reduce the titer of anti-IFN-γ Ab, making it a promising

alternative adjunctive immunotherapy in recalcitrant patients who cannot afford rituximab[12]. Clinical improvement have also be demonstrated in treatments with intravenous immunoglobulin despite little efficacy in the suppression of autoantibody levels[13].

In conclusion, we reported a case of a previously healthy, HIV-negative, and anti-IFN-γ-Ab -positive, Thai male who presented with disseminated *Mycobacterium abscessus* infection with history of tuberculous lymphadenitis, genital herpes simplex and *Salmonella group B* septicemia. This patient responded well to a combination of antimicrobial therapy, however his rash returned after discontinuation of intravenous imipenem. We thought that this rash was unlikely to be a drug reaction as the rash continued to flare up at the same sites despite withholding antibiotics and slowly responded upon re-starting medications. According to minimally and slowly response to 6–month standard antimicrobial therapy, a 1-month course of rituximab was added to the standard antibiotic regimen. After the addition of rituximab, there was a dramatic fall in antibody titer which correlated with favorable clinical response. Thus, we recommend that as well as observing the clinical symptoms and signs, the antibody titer should be monitored during follow-up to evaluate disease activity.

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