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BRIEF REPORT

Disseminated *Talaromyces marneffei* and *Mycobacterium abscessus* in a Patient With Anti-Interferon-γ Autoantibodies

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Anti-interferon (IFN)-γ autoantibodies are increasingly recognized as a cause of adult-onset immunodeficiency and increased risk for infections with intracellular pathogens. We report on disseminated *Talaromyces* (*Penicillium*) *marneffei* and *Mycobacterium abscessus* infection in a 72-year-old, human immunodeficiency virus noninfected, Thai man with anti-IFN-γ autoantibody. The patient was successfully treated with antimicrobial therapy and rituximab to control B cell-derived autoantibodies.

Keywords. anti-interferon-γ autoantibody; disseminated penicilliosis; *Mycobacterium abscessus*; *Talaromyces marneffei*.

A 72-year-old Thai man, from Northern Thailand, with a past medical history of diabetes mellitus and cerebrovascular accident with left hemiparesis, presented with cervical lymphadenopathy for 15 months. The patient was initially diagnosed with tuberculosis (TB) at a local hospital based on the histopathology finding of cervical lymph node fine-needle aspiration, which showed caseous granuloma formation. However, the tissue was negative for acid-fast bacteria (AFB) stain, and AFB culture was not performed. His initial chest x-ray revealed no definitive infiltration. He had been treated with a standard anti-TB regimen including isoniazid (H), rifampicin (R), pyrazinamide, and ethambutol for 2 months and continued with HR treatment with good adherence. During the 4th month of anti-TB treatment, he developed new cervical lymphadenopathy, low-grade fever, and erythematous patches at anterior chest wall. After completing 6 months of anti-TB treatment, he developed axillary lymphadenopathy and progression of the skin lesion. The patient was then referred for further evaluation at our hospital.

On admission, the patient's vital signs were within normal ranges. Multiple cervical lymph nodes and right axillary lymph nodes (3 cm in diameter) were palpated. Skin examination revealed erythematous plagues with crusted lesions at right cheek and upper chest area. The skin lesions were reminiscent of reactive dermatoses (Figure 1A and 1B). Laboratory data revealed a white blood cell count of 16 800/μL (neutrophil 72.5%, lymphocyte 10.6%, eosinophil 11.3%, monocyte 4%, basophil 1.6%), hemoglobin of 9 g/dL, and platelet of 390 000/μL. Laboratory results of liver and renal functions were unremarkable except for albumin of 1.9 g/dL. A third-generation human immunodeficiency virus (HIV) antibody assay was nonreactive. Computer tomography of the chest and abdomen revealed reticulonodular opacities in the right lower lung field and multiple enlarged intra-abdominal lymph nodes. Skin biopsy was performed and tissue pathology showed small-sized, yeast-like organisms with binary fission, predominant inflammatory cells: plasma cells and lymphocytes without papillary dermal edema (Figure 1C). The biopsied skin tissue culture revealed fungal organism growth consistent with *Talaromyces* (*Penicillium*) *marneffei* (Figure 1D). Bronchoalveolar lavage (BAL) was performed and revealed no endobronchial lesion. The BAL fluid with Gomori Methenamine Silver staining also showed multiple yeast-like organisms. However, the BAL culture did not recover any organisms. The treatment regimen for *T marneffei* infection was intravenous liposomal amphotericin-B for 2 weeks, followed by oral itraconazole (400 mg/day) for 10 weeks, and secondary prophylaxis (200 mg/day). A repeat cervical lymph node biopsy was performed, and tissue culture revealed growth of *Mycobacterium abscessus* confirmed by sequencing of the first 500 base pairs of the 16S ribosomal ribonucleic acid (RNA) gene. The minimal inhibitory concentration (MIC) of *M abscessus* isolate was further performed using the broth microdilution method. The MIC results were as follows: 8 μg/mL amikacin, >128 μg/mL cefoxitin, >4 μg/mL ciprofloxacin, >16 μg/mL clarithromycin, >16 μg/mL doxycycline, 32 μg/mL linezolid, and > 8/152 μg/mL trimethoprim/sulfamethoxazole. The treatment for *M abscessus* infection was intravenous amikacin plus imipenem-cilastatin for 28 days (initially as empirical regimens for non-TB treatment) follow by amikacin 3 times a week plus clarithromycin and ciprofloxacin (Table 1). Given the patient's clinical presentation with multiple intracellular pathogen infections, a cellular-mediated immune defect was suspected. A final diagnosis of anti-interferon (IFN)-γ

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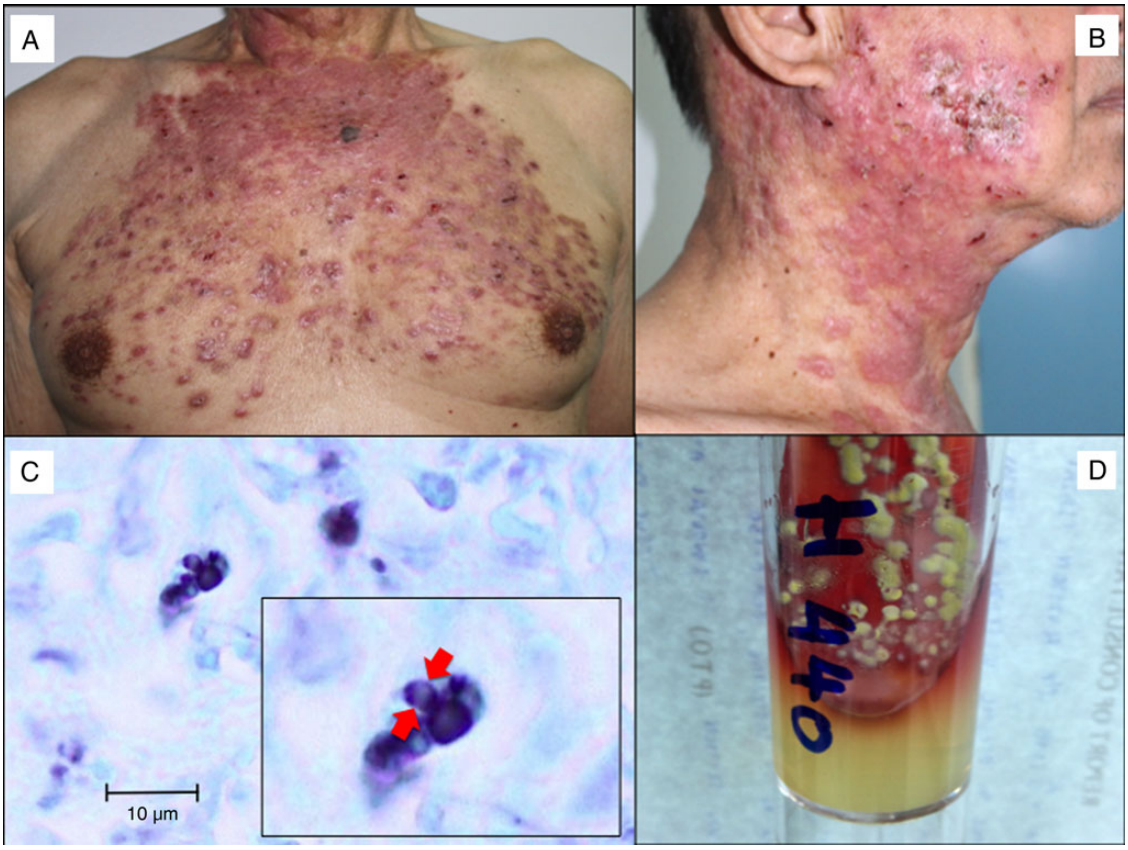

Figure 1. (A and B) Erythematous plaque with multiple crusted lesions at anterior chest wall and right side of head and neck. (C) Histopathology findings of biopsied skin lesion showed small-sized, yeast-like organisms sized 2–4 μm with binary fission (arrow), consistent with the characteristics of *Talaromyces marneffei* (Gomori Methenamine Silver stain: magnification, ×1000). (D) Yellow colony with distinctive red diffusible pigment on Sabouraud's dextrose slant, consistent with the characteristics of *T marneffei*.

autoantibodies was confirmed based upon on a positive anti-IFN-γ antibody assay (inhibition enzyme-linked immunosorbent assay [ELISA]), which was performed at the Cellular and Molecular Immunology Unit (Center for Research and Development of Medical Diagnostic Laboratories, Khon Kaen University, Khon Kane, Thailand) using a cytokine detection ELISA kit (BD Biosciences). After 6 months of treatment for *T marneffei* infection and 3 months of treatment for *M abscessus* infection, the patient developed new enlarged cervical lymph nodes without improvement of skin lesions and pulmonary infiltrates. He further received 1000 mg of methylprednisolone plus 375 mg/m^2 rituximab weekly to control B cell-derived anti-IFN autoantibodies. After 8 weeks of methylprednisolone and rituximab treatment, his skin lesions improved. Although *M abscessus* isolates from this patient had a low MIC only for amikacin, the patient developed renal toxicity and hearing loss from amikacin. An adjusted treatment regimen with linezolid was performed (Table 1). However, the patient also developed adverse effects from linezolid (thrombocytopenia) and ciprofloxacin (QT prolongation). Given the limited treatment options, he continued to receive clarithromycin plus ethambutol for *M abscessus* treatment for 14 months. Six months later, the patient received the second course of methylprednisolone plus rituximab. The patient responded well to the therapy with no new skin lesions and lymphadenopathy at least 9 months after all antimicrobial treatments were discontinued. The level of anti-IFN-γ autoantibodies titer had decreased from more than 1:10 000 (reference range <1:100) before the combined methylprednisolone and rituximab treatment to 1:5000 after 2 courses of the therapy (12 months after the first titers tested).

DISCUSSION

Anti-*IFN-γ* autoantibody is the emerging cause of adult-onset immunodeficiency syndrome, and this finding was first described in 2004 [1]. The disease is commonly found in Southeast Asia, and the patient age of onset is usually approximately 30–50 years [1]. Although the pathogenesis of these autoantibodies is still unclear, Patel et al [2] hypothesized that some infections may trigger the initial production of high-level *IFN-γ* autoantibody, and repeated infections leads to affinity maturation and increased specificity and activity of the autoantibody. A high titer of neutralizing anti-*IFN-γ* autoantibodies blocks *IFN-γ* activation and, in consequence, restrains *IFN-γ* interleukin-12

Table 1. Demonstrated Cases of Disseminated *Talaromyces* (*Penicillium*) *marneffei* Infection With Anti-IFN-γ Autoantibodies With Complete Patient Information[a]

References	Pruetpongpun et al [Current Report]	Tang et al [5][b]	Chan et al [6][c]	Kampitak et al [7]
Demographic data	72-year-old man, Thailand	45-year-old woman, Hong Kong	42-year-old woman, China	56-year-old man, Thailand
Comorbidity	- Diabetes mellitus - Previous cerebrovascular accident	- Hepatitis B carrier	None	- Epilepsy
Clinical manifestations	- Multiple lymphadenopathy (cervical and intra-abdominal) for 15 mo - Erythematous plague with multiple crusted skin lesions at the cheek and anterior chest wall for 11 mo - Low-grade fever for 11 mo	- Prolong fever, left upper lobe granuloma and submandibular lymphadenopathy for 2 yr - Multiple hilar and intra-abdominal lymphadenopathy and numerous lytic lesions at thoracic and lumbar spine for 1 yr	- Recurrent cervical lymphadenopathy for 6 yr - Fever, left elbow synovitis, multiple intra-abdominal and intrathoracic lymphadenopathy - Splenic microabscesses	- Prolong fever, cervical lymphadenopathy, and pulmonary infiltrates for 10 mo - Generalized skin rash over all extremities for 7 mo - Lumbosacral spondylitis for 5 mo - Panuveitis both eyes for 1 mo - Pulmonary infiltrates and multiple subcutaneous nodule at the abdominal wall
Diagnosis[d]	- Disseminated *Talaromyces marneffei* (lymph nodes and pulmonary infection)	Disseminated *T marneffei* (lymph nodes and pulmonary infection with positive serology)	*T marneffei* splenic abscess (positive serology)	Disseminated *T marneffei* (blood, subcutaneous nodule, pulmonary infection)
Coinfection[d]	- Disseminated *Mycobacterium abscessus*	- Disseminated *Mycobacterium avium-intracellulare* (bone marrow, lymph nodes, and spine)	- *Mycobacterium chelonae* infection (lymph nodes) - Disseminated *Mycobacterium kansasii* infection (synovium, and lymph nodes) - *Burkholderia pseudomallei* infection (positive serology)	- Disseminated *Mycobacterium intermedium* (blood, bone marrow, anterior eye chamber)
Specific treatment for infections	- For disseminated *T marneffei* infection - LAM-B 5 mg/kg per day for 2 wk, itraconazole 400 mg/day for 10 wk, and itraconazole 200 mg/day for 9 mo - For disseminated *M abscessus* infection (total treatment of 14 mo) - Imipenem/cilastatin plus amikacin for 1 mo - Amikacin (3 times/week), plus clarithromycin, ciprofloxacin for 4 mo - Amikacin (<3 times/ week), plus clarithromycin, ciprofloxacin, linezolid for 2 mo[e] - Clarithromycin plus ethambutol for 7 mo	- Amphotericin-B for 2 wk then itraconazole for 10 wk (no report of dose of treatment)	- Itraconazole, meropenem, amikacin, and tigecycline (no report of dose and duration of treatment)	- Itraconazole for 10 mo - Isoniazid, rifampicin, pyrazinamide, ethambutol, moxifloxacin, cotrimoxazole for 2 yr - Topical moxifloxacin and topical steroids
Treatment for anti-IFN-γ autoantibodies	- Rituximab plus methylprednisolone (indication for persistent/worsening lesions after 6 mo of *T marneffei* treatment and 3 mo of *M abscessus* treatment)	None	None	None
Outcome	No relapse after discontinue rituximab plus methyl prednisolone treatment for more than 6 mo	Recurrent cervical lymphadenopathy diagnosed as *Mycobacterium fortuitum* infection 2 yr later	Recurrent cervical lymphadenopathy diagnosed as *M chelonae* infection 2 yr later	Recurrent right pleural effusion diagnosed as *M intermedium* infection 1 yr later

Abbreviations: IFN, interferon; LAM-B, liposomal amphotericin B.

[a] Browne et al [1] also reported 7 patients with anti-IFN-γ antibodies and evidence of *Penicilliosis* from Thailand and Taiwan. Complete information on patients' treatment and outcome was not available.

[b] The study reported 7 other patients with anti-IFN-γ antibodies who had serological evidence of *Penicilliosis*, including 4 patients with *M chelonae* and/or *M kansasii* coinfection. Complete information on patients' treatment and outcome was not available.

[c] The study reported other patients with anti-IFN-γ antibodies who had serological evidence of *Penicilliosis* and *M chelonae* coinfection. Complete information on patients' treatment and outcome was not available.

[d] Infections were diagnosed based on cultures or histopathological results unless specified.

[e] The patient developed renal toxicity and hearing loss from amikacin as well as adverse effects from linezolid (thrombocytopenia) and ciprofloxacin (QT prolongation).

pathway. Patients with anti-*IFN-γ* autoantibodies are susceptible to infections associated with intracellular pathogens, including nontuberculous mycobacteria, nontyphoidal *Salmonella* spp, *Burkholderia* spp, varicella-zoster virus, cytomegalovirus, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *T marneffei* [1, 3].

Talaromyces marneffei is a facultative intracellular dimorphic fungus that causes disseminated infection in humans. Patients commonly present with fever, anemia, weight loss, hepatosplenomegaly, and skin lesion particularly described as generalized, centrally umbilicated maculopapular lesions. *Talaromyces marneffei* has been reported mostly in patients with acquired immune deficiency syndrome (AIDS) in Southern China and Southeast Asia [4–6]. In the era of antiretroviral treatment, *T marneffei* infection has been frequently reported in non-AIDS immunocompromised patients, such as solid organ and bone marrow transplant recipients and patients with autoimmune diseases, especially systemic lupus erythematosus and primary immune deficiency associated with anti-IFN-γ autoantibody [4]. The majority of patients reside or have a travel history to the endemic regions [4].

From the literature review, patients with anti-IFN-γ autoantibody-associated *T marneffei* infection usually presented with chronic disseminated infection involving pulmonary lymphadenopathy and had concomitant disseminated nontuberculous mycobacterial (NTM) infection (Table 1) [5–7]. The diagnosis of *T marneffei* infections were mostly made by histopathology findings consistent with (1) *T marneffei* invading the infected biopsied tissues, (2) the growth of the fungus in the culture specimens, or (3) evidence of positive serology. Some patients who did not receive specific treatment for anti-IFN-γ autoantibody were reportedly on relapse or developed new NTM infection. Rituximab is a monoclonal antibody directed against human CD20 on mature B cells. It has been used for off-label treatment of many diseases caused by autoantibodies, including pemphigus vulgaris, myasthenia gravis, and pure red cell aplasia [3]. Browne et al [3] previously demonstrated successful rituximab therapy in 4 cases of anti-IFN-γ autoantibody-associated refractory NTM disease, which was triggered by an increase of anti-IFN-γ autoantibody titers. However, there is a paucity of data on duration and long-term antimicrobial suppressive treatment and combined methylprednisolone and rituximab in these patients. Therefore, patients′ clinical diseases and autoantibody titers should be closely monitored. If a patient develops a new intracellular pathogens infection or increasing autoantibody titers from their baseline, methylprednisolone and rituximab treatment should be restarted. In this case, high suspicion of anti-*IFN-γ* autoantibody was included corrected demographic (from Thailand) and clinical presentation with *T marneffei* and *M abscessus* infection. The patient's levels of anti-IFN-γ autoantibody titers decreased, and he responded well after the 2 courses of combined rituximab and methylprednisolone. The combined methylprednisolone and rituximab were used as the specific treatment for anti-IFN-γ autoantibody due to a minimal response after antimicrobial therapy. Our patient was noted to have no clinical relapse at least 9 months after all treatments discontinued.

CONCLUSIONS

Talaromyces marneffei infections have been reported in patients with anti-IFN-γ autoantibody-associated adult-onset immunodeficiency from the endemic areas. Patients usually present with chronic disseminated infection and NTM coinfections. Despite good outcomes of antifungal therapy reported, relapsed new infections did occur. Combined methylprednisolone and rituximab therapy for controlling anti-IFN-γ autoantibody level may be used in refractory cases; however, their efficacy and duration of treatment need further evaluation.

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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