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A case of disseminated nontuberculous mycobacteriosis and cerebellar toxoplasmosis with autoantibody to interferon-γ

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Abstract. Autoantibody against interferon-γ has recently been associated with a variety of opportunistic infections, particularly among Asians. We report the case of a 64-year-old Japanese woman who suffered from concomitant or sequential infections of the skin, lungs, bronchi, uterus, and bladder with nontuberculous mycobacteriosis, cerebellar toxoplasmosis, measles, herpes zoster, and vulvar herpes. Blood mononuclear cells from the patient displayed intact cytokine production in response to various stimuli and interferon-γ. High-titer anti-interferon-γ autoantibodies were detected in her serum. The atypical pathology hampered early diagnosis, but indeterminate results of an interferon-γ release assay could offer a simple clue suggesting the presence of autoantibody. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 308-316)*

Key words: NTM, toxoplasmosis, measles, herpes zoster, herpes simplex, autoantibody, interferon-γ

Introduction

The interferon (IFN)-γ/interleukin (IL)-12 pathway plays a crucial role in host defenses against mycobacterial infection (1). Recently, acquired generation of autoantibody against IFN-γ has been implicated in disseminated nontuberculous mycobacteriosis (NTM) and other opportunistic infections (2). We report herein the case of a patient with a high titer of anti-IFN-γ immunoglobulin (Ig) G who presented with disseminated NTM, cerebellar toxoplasmosis, and other infections.

Case Report

A 64-year-old woman presented with a forehead nodule in March 2007. Biopsy revealed nonspecific inflammatory tissues, but culture for acid-fast bacilli yielded positive results. The exact species

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was not identified and the lesion subsided with palliative therapy. She was subsequently referred to the respiratory division for left hilar lymph node enlargement and nodular shadows in the left lung in April 2008. The lesions were initially suspected to be metastatic, since she had undergone bilateral mastectomy with axillary lymph node dissection and postoperative irradiation for bilateral breast cancer (stage I) 1 year earlier. Hormonal therapy with anastrozole had been continued. She was affected by measles in June 2008, as verified by elevated serum IgM antibody titers against measles virus. Bronchoscopy performed in September 2008 revealed multiple endobronchial nodules in the left main bronchus (Fig. 1A). Pathological examination of the nodules demonstrated nonspecific granulation tissues without apparent granulomas. *Mycobacterium intracellulare* was later cultured from bronchial secretions recovered during bronchoscopy. The patient was started on clarithromycin (CAM), rifampicin (RFP), and ethambutol (EB) in October 2008, but was unable to continue the regimen due to adverse effects of facial blushing. At that time, indeterminate results were obtained for an interferon-γ release assay (QuantiFERON®-TB-Gold in Tube; Cellestis, Chadstone, Australia). The patient showed normal blood lymphocyte subpopulations and normal serum Ig levels. Anti-human immunodeficiency virus and anti-human T lymphotropic virus type 1 antibodies were not detected. The three-drug regimen of CAM, RFP and EB was restarted in December 2008.

Meanwhile, vertigo had developed in June 2008. Brain magnetic resonance imaging revealed a crescent shadow in the left cerebellum on gadolinium-enhanced imaging (Fig. 1B). The lesion expanded to both sides of the cerebellum with exacerbation of peripheral edema in January 2009. Cerebellar toxoplasmosis was diagnosed based on a markedly high antibody titer (>40,000 fold) against toxoplasma in serum. Treatment with acetylspiramycin (ACSPM) and sulfamethoxazol/trimethoprim (SMX/TMP) was started in February 2009. In March 2009, cerebellar lesions and pulmonary nodules were substantially improved, but treatment with CAM, RFP, EB, and ACSPM were stopped by April 2009 because of severe eruptions. Since new ground glass opacities appeared in the lung, video-assisted thoracic surgery was performed on the right upper lobe in April 2010. The pathological findings (Fig. 1C) were again the same as those for the endobronchial nodules. Although specific staining of tissue for acid-fast bacilli (Ziehl-Neelsen), fungus (Grocott), protozoans (Giemsa) and bacteria (Gram) yielded negative results, culture for acid-fast bacilli and polymerase chain reaction (PCR) testing for *M. avium* showed positive results.

In the meantime, ulceration and tumefactive lesion of the vulva occurred in March 2009. Bladder nodules, cervicovaginal swellings, and left inguinal lymph node enlargements developed sequentially from May to July 2010 (Fig. 1D). A specimen biopsied from the vaginal wall and secretions from an inguinal lymph node were positive for staining and culture of acid-fast bacilli. PCR for *M. avium* yielded positive results for both specimens. We therefore diagnosed this case as disseminated NTM complicated with cerebellar toxoplasmosis. CAM, RFP, and EB were restarted in August 2010, by which pulmonary and urogenital lesions promptly resolved. Cerebellar lesions also showed radiological remission, although dizziness has continued as a sequela. In addition, the patient experienced four episodes of vulvar herpes infection from December 2007 to January 2012.

Immunological analyses

Disseminated NTM and other infections in an elderly woman suggested some form of acquired immunodeficiency. Given that cases with severe NTM associated with anti-IFN-γ autoantibody have been reported (2-5), we measured anti-IFN-γ IgG autoantibody titers in serum using an in-house ELISA system (Fig. 2A). The patient's serum had an approximately 10,000-fold titer of anti-IFN-γ antibody compared with controls and other disease groups. Other autoantibodies against IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), tumor necrosis factor (TNF)-α, and TNF-β were not detected (not shown). Cytokine production including IFN-γ by blood mononuclear cells was similar for the patient and controls (not shown). Phosphorylation of signal transducer and activator of transcription 1 (STAT1) in response to IFN-γ was basically intact for the patient (Fig. 2B).

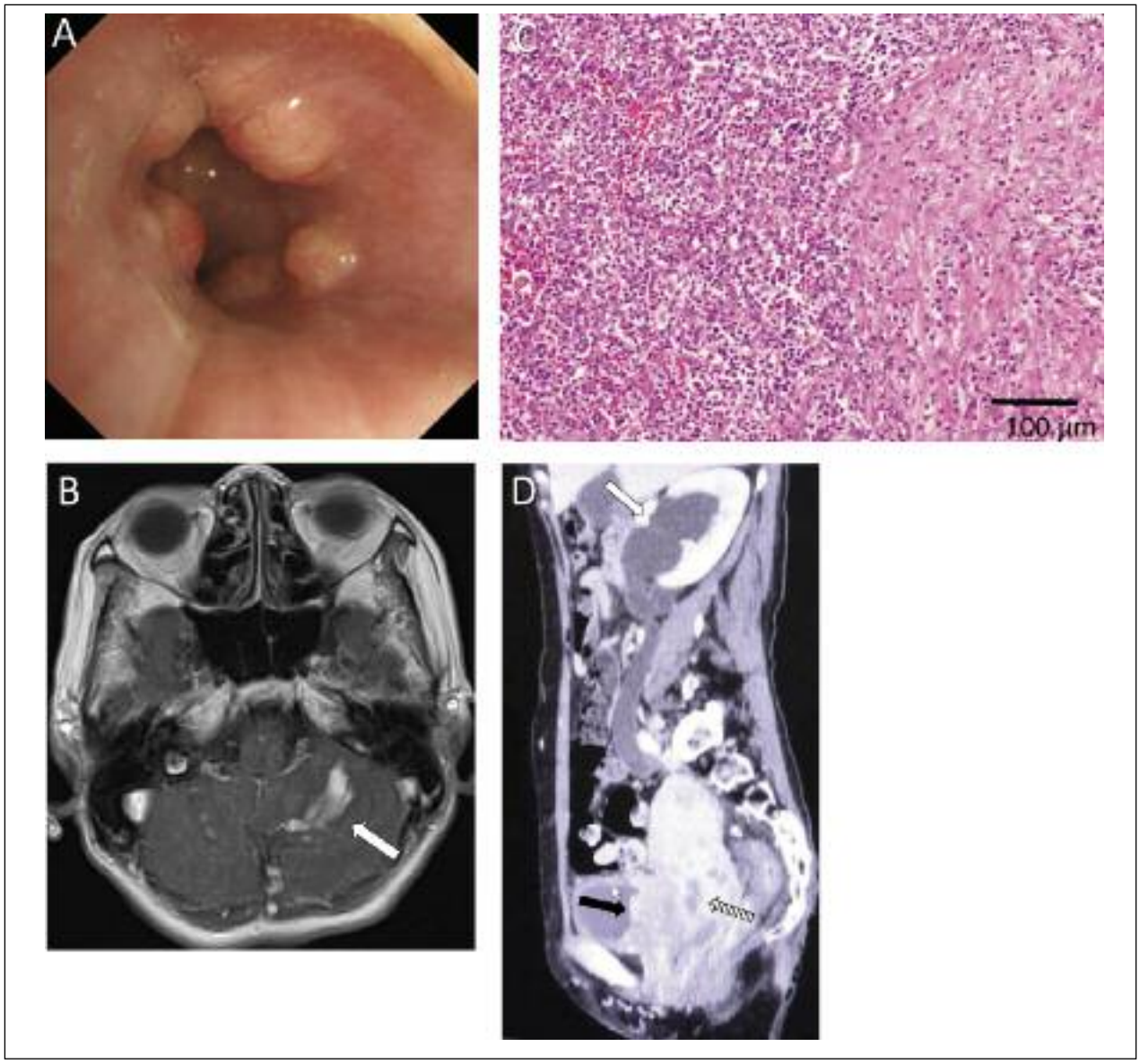

Fig. 1. A: Bronchoscopic view of the left main bronchus showing multiple hemispherical endobronchial nodules with bumpy surfaces. B: Brain MRI showed a crescent shadow in the cerebellum (white arrow) accompanied by peripheral high intensities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging. C: Pathology of the lung lesion obtained by video-assisted thoracic surgery. The photomicrograph of a nodular lesion in the right upper lobe shows fibroblastic proliferation with infiltration of neutrophils, eosinophils, and macrophages accompanied by fibrinous exudates in the surrounding alveolar spaces, indicating organizing abscess. D: Oblique sagittal computed tomography showing hydronephrosis of the right kidney (white arrow), dilated ureter, circumferential swelling of the uterine cervix and vagina (stippled arrow), and swollen posterior wall of the bladder (black arrow)

Discussion

This case was characterized by a wide variety of opportunistic and non-opportunistic infections, such as disseminated NTM, cerebellar toxoplasmosis, herpes zoster, recurrent vulvar herpes infection, and measles. Bronchial and urogenital NTM are extremely rare manifestations. Major genetic defects were considered most unlikely, since the patient was an elderly woman and cytokine production including IFN-γ by blood mononuclear cells remained intact. She also showed normal receptor expression of the

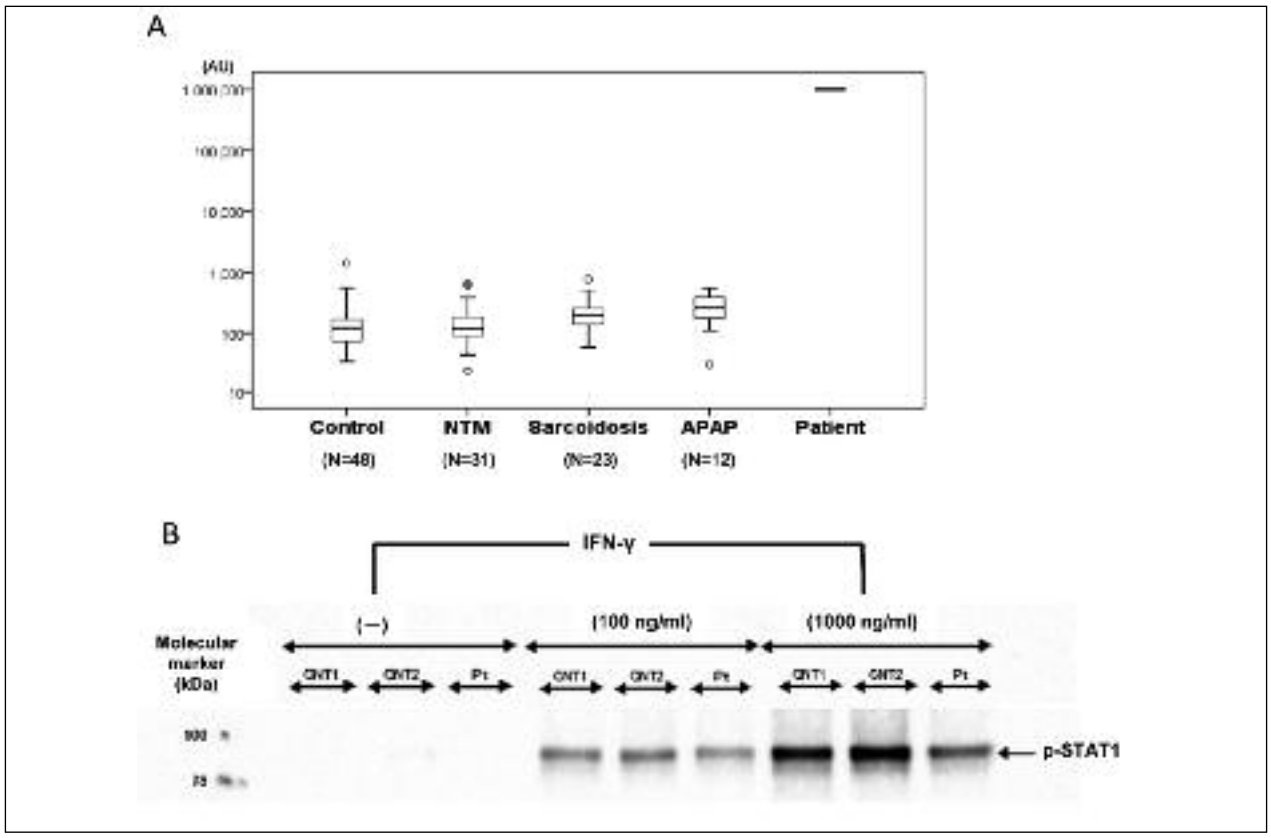

Fig. 2. A: Anti-IFN-γ IgG concentration in serum. Data are log-transformed and presented in box-and-whisker plots with ends of the whiskers representing the lowest datum still within the 1.5 interquartile ranges under the lower quartile and the highest datum still within 1.5 interquartile ranges above the upper quartile. Circles denote outliers. NTM, nontuberculous mycobacteriosis; APAP, autoimmune alveolar proteinosis; AU, arbitrary unit determined by our own reference sample. B: Phosphorylation of STAT1 by peripheral blood mononuclear cells induced by IFN-γ. CNT, control; Pt, patient; p-STAT, phosphorylated signal transducer and activator of transcription 1

IFN-γ/IL-12 pathway. The extremely high titer of autoantibody against IFN-γ thus seemed to be the sole immunological deficit responsible for the multiple infections (1, 6-9).

Early suspicion of disseminated mycobacteriosis was greatly hampered by the atypical pathological features without any apparent epithelioid cell granulomas. Similar phenomena have been observed for mice and humans (10, 11), suggesting an important role of IFN-γ for the formation of epithelioid cell granulomas. However, the indeterminate result from the IFN-γ release assay due to autoantibodies interfering with the detection of IFN-γ in post-culture plasma could serve as a simple clue suggesting the presence of autoantibody. Dissection of the pathways leading to the generation of autoantibody and exploitation of these findings for the treatment of mycobacterial and other infections represent critical issues for the future.

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