Disseminated Nontuberculous Mycobacterial Infection Associated With Acquired Immunodeficiency Due to Anti–Interferon γ Autoantibodies

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Fever of unknown origin (FUO) defined as community-acquired fever of ≥38.3°C lasting ≥3 weeks in immunocompetent individuals generally excludes fever among hospitalized patients or patients with human immunodeficiency virus infection or neutropenia. Due to recent advances in diagnostic technology, including sophisticated imaging tests, improved culture techniques, and molecular diagnostics, there has been increase in cases reported with pathogens previously considered uncommon. At the same time, the realization that new and subtle forms of immunodeficiency may present in adulthood has prompted practitioners to pursue immunological investigations earlier in the diagnostic workup of infections with unusual pathogens than was done previously. We present a case with FUO in which the isolation of an unexpected pathogen revealed an immunodeficient state that has been recently identified and has long term implications for the patient. We discuss the microbiological findings and laboratory investigations necessary to define the immune deficiency.

CASE REPORT

A 28-year-old Indian man who had been living in Australia for the preceding 3 years, presented to the hospital with a 2-month febrile illness characterized by headaches, abdominal pain, night sweats, and 30kg of weight loss. He reported no significant medical history, medication use, or allergies. At physical examination, he had a fever of 38.3°C and palpable right cervical lymphadenopathy. Initial laboratory testing revealed marked leukocytosis, neutrophilia, and eosinophilia (white blood cell, neutrophil, and eosinophil counts, 32.8 [reference range, 4.0–11.0] × 10^9/µL, 27.3 [2.0–8.0] × 10^9/µL, and 1.7 [0.0–0.5] × 10^9/µL, respectively).

Routine bacterial cultures of blood, urine, sputum and stool were unremarkable. Results of interferon (IFN) γ release assay testing (QuantiFERON-TB Gold) were indeterminate owing to lack of a mitogen response, and results of human immunodeficiency virus serology were negative. Cerebrospinal fluid sampling revealed pleocytosis (cell counts per µL: 693 erythrocytes, 52 polymorphonuclear leukocytes, 87 lymphocytes), an elevated protein level (0.65 mg/dL; reference range, 0.18–0.45 mg/dL), and a normal glucose level (3.0 mmol/L; 2.5–3.5 mmol/L). Computed tomography (CT) of the chest, abdomen, and pelvis revealed a right upper lobe pulmonary infiltrate and widespread lymphadenopathy. Bronchoscopy and bone marrow aspiration revealed neither infection nor cancer.

The patient's enlarged cervical lymph node was excised for Australia. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivative licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com.

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DISCUSSION

The clinical entity of adult-onset disseminated NTM infection resulting from anti–IFN-γ Abs is described in adults of Southeast or East Asian descent with a median age of 48 years [1, 3, 4]. Here we report the first case, to our knowledge, of anti–IFN-γ Abs arising in an individual of Indian origin. Genetic factors include a strong association with the HLA class II alleles DRB1*16 and DQB1*5, initially reported in a Taiwanese cohort, and DRB1*15, later reported in Thai patients [5–7]. We did not perform HLA analysis in our patient, but previous large-scale population studies have shown DRB1*15 as a common allele among individuals from Asian countries, including India, Taiwan, and Thailand [8].

Disseminated NTM infection is the most common infection in individuals with anti–IFN-γ Abs [5]. Frequently isolated organisms include Mycobacterium avium complex, M. abscessus complex, and Mycobacterium fortuitum [3]. Herpesvirus reactivations and certain bacterial infections, such as nontyphoidal Salmonella, have also been described [3]. M. abscessus complex comprises a group of rapidly growing and multidrug-resistant NTM, found widespread in the environment. Infection in humans can result in a range of different clinical manifestations, although skin and soft-tissue and pulmonary infections seem most common [9].

At present, there are no evidence-based guidelines regarding the specific treatment of this type of immunodeficiency. Previous uncontrolled case series include reports of treatment with intravenous immunoglobulin, plasmapheresis, cyclophosphamide, and exogenous IFN-γ to diminish the activity of anti–IFN-γ Abs [3]. Other case series have shown therapeutic benefit with the anti-CD20 monoclonal antibody rituximab [10, 11]. Our patient received 2 doses of rituximab over a 1-month period with continued antimicrobial therapy (10 months in total), after an initial period of 6 months of antimicrobial therapy alone to minimize the chance of recurrence.

In our patient, disseminated M. abscessus infection mimicked the typical clinical manifestations of disseminated tuberculosis and was initially treated as such. There is evidence suggesting that the QuantiFERON-TB Gold assay, which in this setting results in subnormal responses to mitogens, may serve as a screening tool for anti–IFN-γ Ab activity in similar presentations [12, 13]. The test can be especially useful in resource-poor settings where specialized assays to measure IFN-γ activity are not available. Collecting suitable tissue samples for diagnostic testing is also critical, and FDG positron emission tomography/CT allowed for a targeted biopsy to better direct management [14, 15].

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stained with CD14-PC5 to identify monocytes and incubated with control (autologous) plasma and patient plasma in 3 conditions: unstimulated, IFN-α stimulated (as an internal control), and IFN-γ stimulated. Cells were stained for intracellular phosphorylated STAT1 (pSTAT1) with anti-STAT1 conjugated to Alexa Fluor 488 (Becton Dickinson), fixed, and then analyzed with flow cytometry. Median fluorescence intensities (MFIs) for pSTAT1 in CD14+ gated monocytes for each condition are compared between unstimulated and stimulated. Red peak represents unstimulated cells; green peak, IFN-α-stimulated cells; and blue peak, IFN-γ-stimulated cells. Top plot (control plasma) shows increase in MFI, tabled under “MFI,” after stimulation with IFN-α and IFN-γ (blue and green peaks), and bottom plot (patient plasma) shows absence of pSTAT1 when stimulated with IFN-γ (blue peak), suggesting an inhibitor to IFN-γ in the patient’s plasma. This functional assay does not determine whether autoantibodies in the patient’s serum are targeting IFN-γ itself or IFN-γ receptors. Target-specific enzyme-linked immunosorbent assay was not performed for confirmation.

Figure 3. Flow cytometry of a functional assay for detecting anti–interferon (IFN) γ autoantibodies. Healthy control peripheral blood mononuclear cells were surface stained with CD14-PCS to identify monocytes and incubated with control (autologous) plasma and patient plasma in 3 conditions: unstimulated, IFN-α stimulated (as an internal control), and IFN-γ stimulated. Cells were stained for intracellular phosphorylated STAT1 (pSTAT1) with anti-STAT1 conjugated to Alexa Fluor 488 (Becton Dickinson), fixed, and then analyzed with flow cytometry. Median fluorescence intensities (MFIs) for pSTAT1 in CD14+ gated monocytes for each condition are compared between unstimulated and stimulated cells cultured in control and patient plasma. Red peak represents unstimulated cells; green peak, IFN-γ- and IFN-α–stimulated cells; and blue peak, IFN-γ–stimulated cells; and blue peak, IFN-γ and IFN-α stimulated cells; and blue peak, IFN-γ and stimulated cells cultured in control and patient plasma. Red peak represents unstimulated cells; green peak, IFN-γ– and IFN-α–stimulated cells; and blue peak, IFN-γ–stimulated cells. Top plot (control plasma) shows increase in MFI, tabled under “MFI,” after stimulation with IFN-α and IFN-γ (blue and green peaks), and bottom plot (patient plasma) shows absence of pSTAT1 when stimulated with IFN-γ (blue peak), suggesting an inhibitor to IFN-γ in the patient’s plasma. This functional assay does not determine whether autoantibodies in the patient’s serum are targeting IFN-γ itself or IFN-γ receptors. Target-specific enzyme-linked immunosorbent assay was not performed for confirmation.

References
1. Browne SK, Burbelo PD, Chetchotisakd P, et al. Adult-onset immunodeficiency in Thailand and Taiwan. N Engl J Med 2012; 367:725–34.
2. Shima K, Sakagami T, Tanabe Y, et al. Novel assay to detect increased level of neutralizing anti-interferon gamma autoantibodies in non-tuberculous mycobacterial patients. J Infect Chemother 2014; 20:52–6.
3. Valour F, Perpoint T, Sénéchal A, et al; Lyon TB study group. Interferon-γ autoantibodies. Healthy control peripheral blood mononuclear cells were surface stained with CD14-PC5 to identify monocytes and incubated with control (autologous) plasma and patient plasma in 3 conditions: unstimulated, IFN-α stimulated (as an internal control), and IFN-γ stimulated. Cells were stained for intracellular phosphorylated STAT1 (pSTAT1) with anti-STAT1 conjugated to Alexa Fluor 488 (Becton Dickinson), fixed, and then analyzed with flow cytometry. Median fluorescence intensities (MFIs) for pSTAT1 in CD14+ gated monocytes for each condition are compared between unstimulated and stimulated cells cultured in control and patient plasma. Red peak represents unstimulated cells; green peak, IFN-α-stimulated cells; and blue peak, IFN-γ-stimulated cells. Top plot (control plasma) shows increase in MFI, tabled under “MFI,” after stimulation with IFN-α and IFN-γ (blue and green peaks), and bottom plot (patient plasma) shows absence of pSTAT1 when stimulated with IFN-γ (blue peak), suggesting an inhibitor to IFN-γ in the patient’s plasma. This functional assay does not determine whether autoantibodies in the patient’s serum are targeting IFN-γ itself or IFN-γ receptors. Target-specific enzyme-linked immunosorbent assay was not performed for confirmation.
4. Aoki A, Sakagami T, Yoshizawa K, et al. Clinical significance of interferon-γ neutralizing autoantibodies against disseminated nontuberculous mycobacterial disease. Clin Infect Dis 2018; 66:1239–45.
5. Chi CY, Chu CC, Liu JP, et al. Anti-IFN-γ autoantibodies in adults with disseminated nontuberculous mycobacterial infection. Clin Microbiol Infect 2018; 24:159–65.
6. Suárez I, Lehmann C, Gruell H, et al. Repurposing QuantiFERON for detection of neutralizing interferon-γ autoantibodies in patients with nontuberculous mycobacterial infections. Clin Infect Dis 2017; 65:518–21.
7. Czaja CA, Merkel PA, Chan ED, et al. Rituximab as successful adjunct treatment in a patient with disseminated nontuberculous mycobacterial infection due to acquired anti-interferon-gamma autoantibody. Clin Infect Dis 2014; 58:e115–8.
8. Shankarkumar U. Complexities and similarities of HLA antigen distribution in Asian subcontinent. Indian J Hum Genet 2010; 16:108–10.
9. Lee MR, Sheng WH, Hung CC, et al. Mycobacterium abscessus complex infections in humans. Emerg Infect Dis 2015; 21:1638–46.
10. Browne SK, Zaman R, Sampao EP, et al. Anti-CD20 (rituximab) therapy for anti-IFN-γ autoantibody-associated nontuberculous mycobacterial infection. Blood 2012; 119:3933–9.
11. Wu UI, Chuang YC, Sheng WH, et al. Use of QuantiFERON-TB Gold In-tube assay in screening for neutralizing anti-interferon-γ autoantibodies in patients with disseminated nontuberculous mycobacterial infection. Clin Microbiol Infect 2016; 22:1124–6.
12. Lee MR, Sheng WH, Hung CC, et al. Mycobacterium abscessus complex infections in humans. Emerg Infect Dis 2015; 21:1638–46.
13. Suárez I, Lehmann C, Gruell H, et al. Repurposing QuantiFERON for detection of neutralizing interferon-γ autoantibodies in patients with nontuberculous mycobacterial infections. Clin Infect Dis 2017; 65:518–21.
14. Suárez I, Lehmann C, Gruell H, et al. Repurposing QuantiFERON for detection of neutralizing interferon-γ autoantibodies in patients with nontuberculous mycobacterial infections. Clin Infect Dis 2017; 65:518–21.
15. Lin KH, Wang JH, Peng NJ. Disseminated nontuberculous mycobacterial infection mimic metastases on PET/CT scan. Clin Nucl Med 2008; 33:276–7.
16. Meller J, Sahlmann CO, Scheel AK. 18F-FDG PET and PET/CT in fever of unknown origin. J Nucl Med 2007; 48:35–45.
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