Journal of Clinical Immunology (2019) 39:512–518
https://doi.org/10.1007/s10875-019-00652-1

ORIGINAL ARTICLE

Juvenile-Onset Immunodeficiency Secondary to Anti-Interferon-Gamma Autoantibodies

Woei-Kang Liew[1] · Koh-Cheng Thoon[2] · Chia-Yin Chong[2] · Natalie W. H. Tan[2] · Duo-Tong Cheng[2] · Bianca S. W. Chan[1] · Michelle S. Y. Ng[3] · Lena Das[1] · Thaschawee Arkachaisri[1] · Chiung-Hui Huang[4] · Jyn-Ling Kuan[5] · Louis Y. A. Chai[6,7] · Mark Jean Aan Koh[3]

Received: 11 May 2018 / Accepted: 27 May 2019 / Published online: 8 June 2019

Abstract

Immunodeficiency secondary to anti-interferon-gamma (anti-IFN-γ) autoantibodies was first described in 2004 as an acquired defect in the IFN-γ pathway leading to susceptibility to multiple opportunistic infections, including dimorphic fungi, parasites, and bacteria, especially tuberculosis and non-tuberculous mycobacterium (NTM) species. It has so far only been described in adult patients. We present 2 cases of disseminated NTM infections in otherwise immunocompetent children. A 16-year-old girl with Sweet's syndrome–like neutrophilic dermatosis developed recurrent fever and cervical lymphadenitis secondary to *Mycobacterium abscessus*. A 10-year-old boy with a history of prolonged fever, aseptic meningitis, aortitis, and arteritis in multiple blood vessels developed thoracic vertebral osteomyelitis secondary to *Mycobacterium avium* complex. Both patients were found to have positive serum neutralizing anti-IFNγ autoantibodies. Testing for anti-IFNγ autoantibodies should be considered in otherwise healthy immunocompetent hosts with recurrent or disseminated NTM infection. This represents a phenocopy of primary immunodeficiency which has been recently described only in adults. We report the first two cases of this phenomenon to affect children.

Keywords Anti-interferon-gamma autoantibodies · non-tuberculous mycobacteria · immunodeficiency

Introduction

Adult-onset immunodeficiency secondary to anti-interferon-gamma (anti-IFN-γ) autoantibodies was first described in 2004 as an acquired defect in the IFN-γ pathway leading to susceptibility to multiple opportunistic infections, including dimorphic fungi, parasites, and bacteria, especially tuberculosis and non-tuberculous mycobacterium (NTM) species [1–10]. It is an uncommon disease characterized by the presence of serum anti-cytokine autoantibody inhibitory to IFN-γ, a cytokine integral to cell-mediated defense against specific pathogens [1].

To date, this syndrome has been reported to affect only adults, mostly females, of predominantly East Asian origin, with presentation between 30 to 50 years of age [2, 4, 5, 10, 11]. Exceptionally, two recent case reports have described the disease in Caucasians [12, 13]. There have so far been no reports of this condition occurring in children or adolescents. We report two cases of children with disseminated NTM infection secondary to anti-IFN-γ autoantibodies.

✉ Mark Jean Aan Koh
Mark.Koh.J.A@singhealth.com.sg

1 Rheumatology and Immunology Service, Department of Paediatric Subspecialties, KK Women's and Children's Hospital, Singapore, Singapore

2 Infectious Diseases Service, Department of Paediatrics, KK Women's and Children's Hospital, Singapore, Singapore

3 Dermatology Service, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore, Singapore

4 Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

5 Genome Institute of Singapore, A*STAR, Singapore, Singapore

6 Division of Infectious Diseases, University Medicine Cluster, National University Health System, Singapore, Singapore

7 Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

Case 1

A 16-year-old Chinese girl presented with multiple painful nodules over her trunk and limbs, associated with intermittent high fever (Fig. 1). There was a history of recurrent painful oral ulcers lasting several weeks over the previous 10 years. She recalled a history of similar painful deep nodules at five years of age, which resolved after treatment with several months of oral colchicine prescribed by a private dermatologist. Physical examination revealed multiple, deep, tender, erythematous nodules on her trunk, upper and lower limbs, and several more superficial erythematous, juicy, "Sweet's syndrome-like" papules over her face, trunk, and limbs. There were several non-tender sub-centimeter lymph node swellings in bilateral post-auricular region. A systemic review of the other major organ systems, including the respiratory and gastrointestinal tract, was unremarkable.

Laboratory investigations showed raised inflammatory markers. The C-reactive protein (CRP) was 115.9 mg/L (normal, 0.0–5.0 mg/L) and erythrocyte sedimentation rate (ESR) was 59 mm/h (3–15 mm/h). The complete blood count showed a hemoglobin level of 11.9 g/dL (12.0–16.0 g/dL), white blood cell count of 10.95×10^9/L ($4.50–11.0 \times 10^9$/L), and platelet count of 235×10^9/L ($150–450 \times 10^9$/L). An infective screen including respiratory virus multi-plex PCR, anti-streptolysin O antibody titer (ASOT), Widal/Weil-Felix serology (WWF), melioidosis PCR, herpes simplex virus serology, rickettsia, and Mantoux test was unremarkable. Punch biopsy of a papular lesion showed neutrophilic and histiocytic infiltrates extending from the superficial to deep dermis, consistent with a neutrophilic dermatosis (Fig. 2a). Incisional biopsy of a deep nodule revealed thickening of the subcutaneous septa with involvement of the adjacent fat lobules by a mixed inflammatory infiltrate, consistent with septo-lobular panniculitis (Fig. 2b). Infective stains and tissue cultures for fungus and acid-fast bacilli (AFB) were negative on both skin biopsies. After clinical-pathological correlation, a diagnosis of Sweet's syndrome was made. Thorough investigations for inflammatory bowel disease, autoimmune diseases and hematological malignancies returned negative. The skin lesions

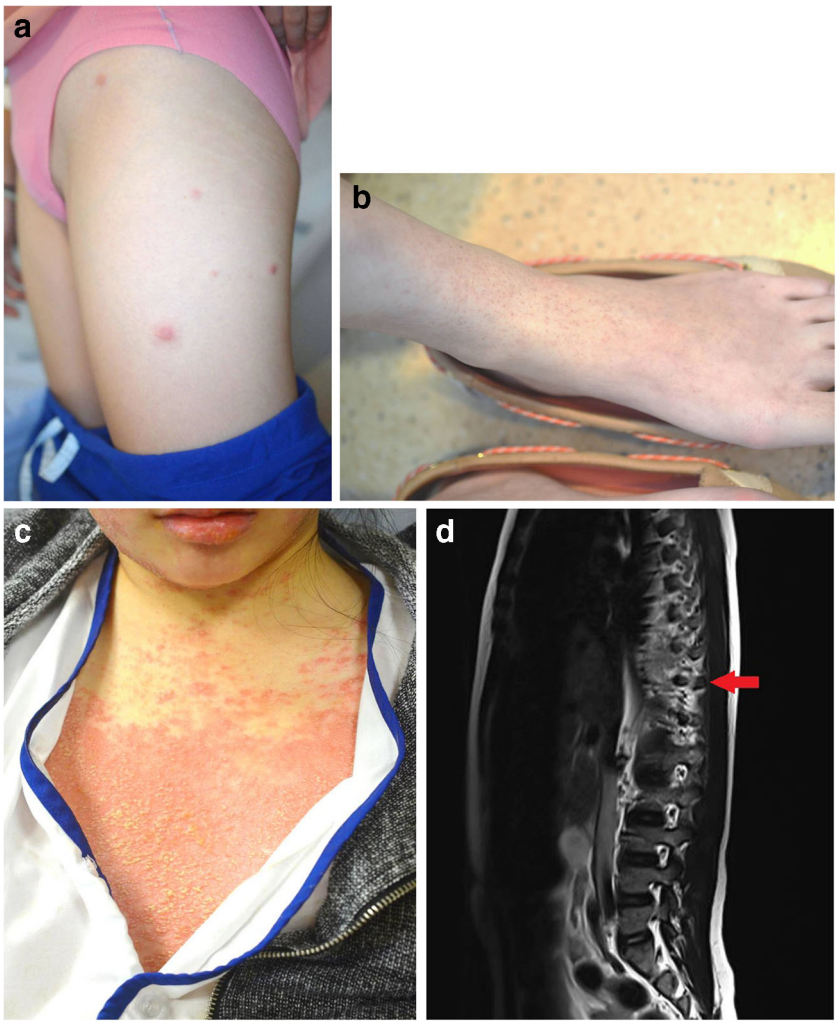

Fig. 1 **a** Case 1: Multiple tender erythematous Sweet's syndrome–like nodules over the left lateral thigh. **b** Case 1: Extensive flat erythematous pin-point papules. **c** Case 1: Generalized involvement with tiny pin-point pustules on background of erythema. **d** Case 2: MRI thoracolumbar image demonstrating complete collapse and enhancement of the T10 vertebral body with associated paravertebral soft tissue and epidural thickening and enhancement consistent with osteomyelitis

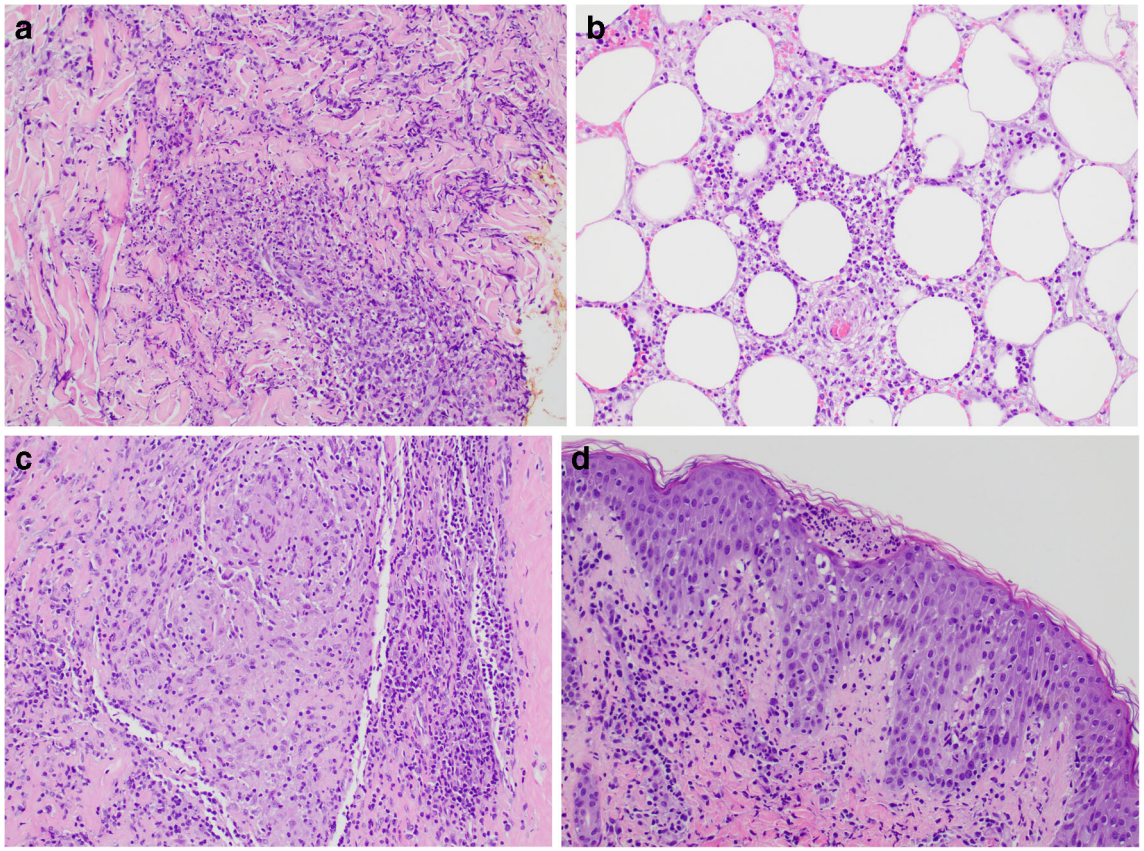

Fig. 2 **a** Case 1: Punch biopsy from a Sweet's syndrome–like papule showing neutrophilic and histiocytoid inflammatory infiltrate extending from the superficial to deep dermis, consistent with neutrophilic dermatosis. H&E × 20. **b** Case 1: Incisional biopsy of a nodule showing septolobular panniculitis by an admixture of neutrophils, lymphocytes, histiocytes, and occasional eosinophils. H&E × 20. **c** Case 1: Right cervical lymph node excisional biopsy showing architectural effacement with extensive fibrosis, regions of necrosis, and infiltration of histiocytes forming granulomas and multinucleated giant cells, consistent with necrotizing granulomatous infection. H&E × 20. **d** Case 1: Punch biopsy of a pustule showing spongiotic dermatitis with subcorneal pustules, consistent with AGEP. H&E × 20

improved with a tailing course of oral prednisolone (30 to 0.5 mg every other day) and oral colchicine (0.5 mg BD), and the disease remained quiescent.

She re-presented a year later with prolonged fever and multiple bilateral enlarged cervical lymph nodes of two months duration. The white cell count was raised at 23.35×10^9/L, with mainly neutrophilia. The CRP was 179.4 mg/L and ESR was 92 mm/h. Further infective serologies including human immunodeficiency virus (HIV), hepatitis B and C, cytomegalovirus, *Bartonella* and toxoplasma returned negative. Computed tomography (CT) scan showed multiple enlarged lymph nodes in the neck, thorax, and upper abdomen with no evidence of liquefaction or calcification. There was no evidence of pulmonary nodules or pleural effusion. Excision biopsy of an enlarged cervical lymph node showed necrotizing granulomatous inflammation on histology (Fig. 2c). Tissue culture of the same biopsy grew *Mycobacterium abscessus*. At the same time, the patient developed generalized non-pruritic, pin-point, and erythematous-to-brown papules, suggestive of lichen scrofulosorum (Fig. 1b). She declined biopsy of these new lesions. While awaiting results of the tissue culture, intravenous clindamycin was empirically started for lymphadenopathy. She developed acute generalized exanthematous pustulosis (AGEP) 10 days after commencement of clindamycin (Fig. 1c). A punch biopsy of the pustule showed subcorneal and intraepidermal neutrophilic collections, consistent with AGEP (Fig. 2d). Clindamycin was discontinued.

Further immunodeficiency evaluation was performed. Serum immunoglobulin levels showed IgG level of 13.66 g/L (6.60–15.3 g/L), IgA level of 3.26 g/L (0.50–2.90 g/L), and IgE level of 2893 IU/ml (18–100 IU/ml). Flow cytometry assay revealed mildly elevated CD3 T cells at 77.1% (64–73%) and CD4 T cells at 49.6% (30–36%), and mildly reduced Pan B CD20 cells at 12.9% (14–21%) and NK CD56 cells at 6.3% (11–53%). IFN-γ and IL-12 functional assays were performed with the patient's and healthy control's peripheral blood mononuclear cells (PBMC) stimulated in the absence of serum, with Bacillus Calmette-Guérin (BCG), in the presence or absence of IFN-γ (for the detection of IL-12) or IL-12 (for the detection of IFN-γ). The supernatant was collected at 18 h or 48 h for the detection of IL-12 or IFN-γ respectively, by ELISA. The patient's PBMC demonstrated

normal intrinsic IFN-γ and IL-12 production when tested in isolation (Fig. 3). Enzyme-linked immunosorbent inhibition assay was performed to measure the relative anti-IFNγ autoantibody titers through inhibition of recombinant IFNγ at varying serial dilution factors of the patient's plasma. Signal transducer and activator of transcription (STAT)-1 phosphorylation as a marker of intact IFNγ/IL-12 axis function were assessed by flow cytometry by incubating healthy control's peripheral blood mononuclear cells in the presence of patient's serum. She was tested positive for serum anti-IFNγ autoantibodies which were neutralizing (Fig. 4a, c).

The patient was started empirically on intravenous cefoxitin 12 g Q24H, intravenous amikacin 500 mg Q24H, and oral clarithromycin 500 mg BID. The *Mycobacterium abscessus* was susceptible to amikacin, linezolid, azithromycin, and clofazimine. Amikacin was stopped after 6 weeks due to rising serum creatinine levels (117 umol/L). After 6 weeks of treatment with the initial anti-tuberculous regimen, treatment was changed to a combination of oral linezolid and azithromycin for 6 months. On subsequent outpatient reviews, the cervical lymph nodes had reduced dramatically in size with minimal evidence of the initial rash. The serum levels of anti-IFN-γ antibodies were monitored and showed limited decline with disease quiescence (Fig. 4b, c). HLA typing of the patient yielded DQB1*04:05, DQB1*04:01:01G, DRB1*04:05:01, and DRB1*04:05:03.

Case 2

A 10-year-old Malay boy with a history of prolonged fever, aseptic meningitis, uveitis, erythema nodosum (EN)–like lesions, and aortitis and arteritis in multiple blood vessels was diagnosed presumptively with Takayasu arteritis and treated with weekly subcutaneous methotrexate and low-dose oral prednisolone. Infectious work-up, including acid-fast bacilli smears and cultures of cerebrospinal fluid, skin, urine, and bowel were negative. Skin biopsy on an EN-like lesion showed a septolobular neutrophilic panniculitis with absence of granulomas and vasculitis. Six months after the initial presentation, he complained of a new-onset of severe upper back pain for a few days. There was no associated fever, weakness, numbness, or derangement of bowel or bladder functions. Physical examination did not reveal any spinal tenderness on palpation and there were no neurological deficits. There were no enlarged lymph nodes or rashes. A systemic review of the major organs including respiratory and gastrointestinal tract was unremarkable.

Laboratory investigations showed raised inflammatory markers. The CRP was 39.7 mg/L and ESR was 61 mm/h. The full blood count showed hemoglobin of 11.5 g/dL, white cell count of 7.61×10^9/L, and platelet count of 334×10^9/L. A comprehensive infective screen including *Bartonella*, melioidosis, *Toxoplasma*, *Brucella*, fungal cultures, and blood cultures was unremarkable. X-ray imaging of the thoracolumbar spine did not reveal any pathological changes. In view of persistent pain, magnetic resonance imaging (MRI) of the thoracolumbar spine was performed which showed stable complete collapse and enhancement of the T10 vertebral body and posterior elements, with associated paravertebral soft tissue and epidural thickening and enhancement (Fig. 1d). These changes corresponded to an infective osteomyelitis of the T10 vertebra. An image-guided bone biopsy of T10 vertebra revealed severe inflammatory changes. Tissue culture of the biopsy sample grew *Mycobacterium avium* complex (MAC).

Further immunodeficiency evaluation was performed. Serum immunoglobulin levels showed raised IgG level of 18.94 g/L (6.60–15.3 g/L) and IgM level of 2.05 IU/ml (0.31–1.80 IU/ml), but normal IgA level of 1.92 g/L (0.50–2.90 g/L). Flow cytometry assay revealed mildly elevated CD3 T cells at 78% (65–72%), CD4 T cells at 43% (27–34%), and mildly reduced Pan-B CD20 cells at 7% (15–20%) and NK CD56 cells at 10% (11–24%). Antinuclear antibody (ANA) was negative. Anti-double-stranded DNA (dsDNA) antibody was raised at 45.78 IU/ml (< 25 IU/ml)

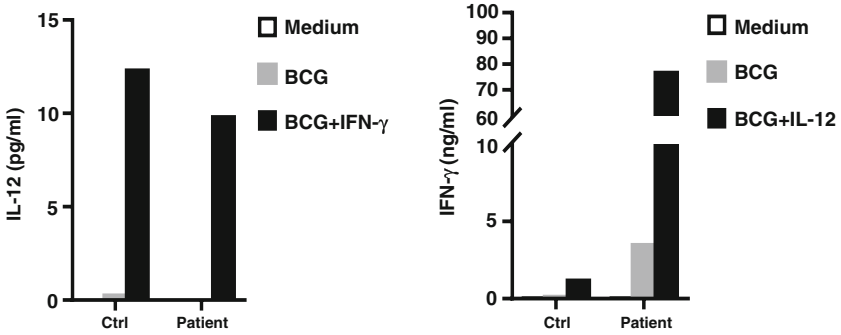

Fig. 3 Production of IL-12 and IFN-γ by case 1's peripheral blood mononuclear cells (PBMC). IFN-γ and IL-12 functional assays were performed with patient's and healthy control's PBMC stimulated in the absence of serum, with Bacillus Calmette-Guérin (BCG), in the presence or absence of IFN-γ (for the detection of IL-12) or IL-12 (for the detection of IFN-γ). The supernatant was collected at 18 h or 48 h for the detection of IL-12 or IFN-γ respectively, by ELISA

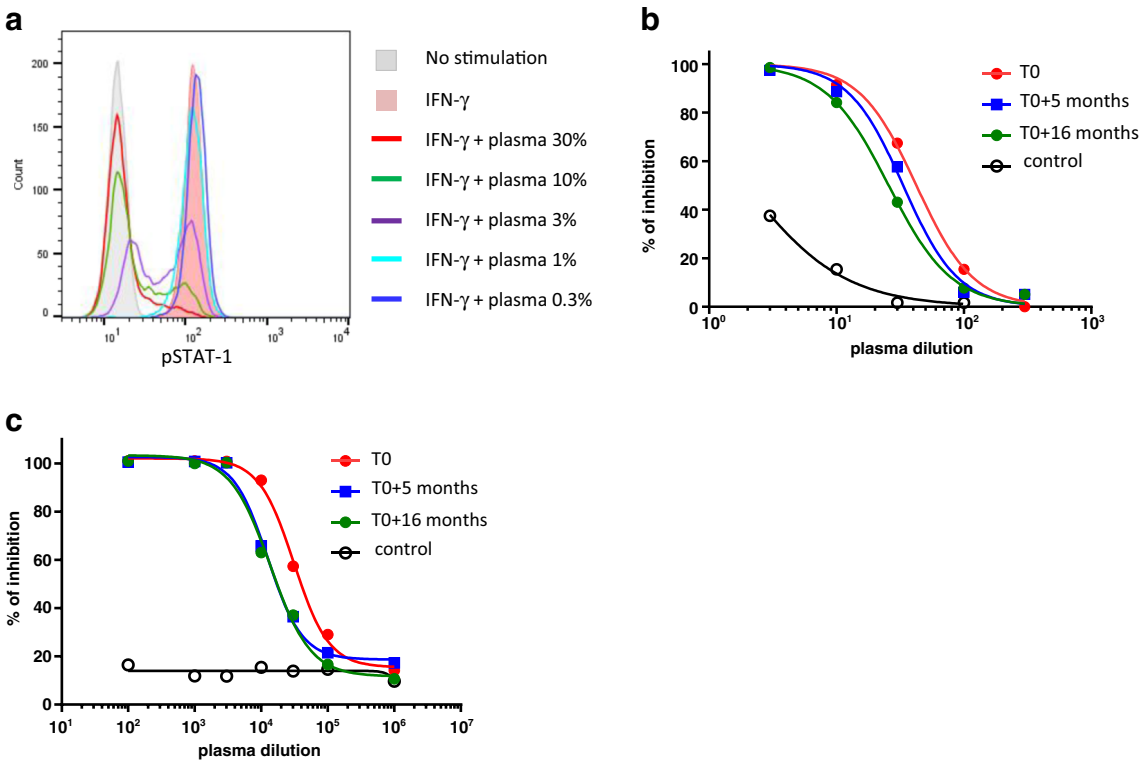

Fig. 4 **a**, **b** Inhibition of the STAT phosphorylation and **c** the detection of input IFN-γ by plasma samples of case 1. Enzyme-linked immunosorbent inhibition assays were performed to measure the relative anti-IFNγ autoantibody titers through inhibition of recombinant IFNγ input at varying serial dilution factors of the patient's plasma. Signal transducer and activator of transcription (STAT)-1 phosphorylation as a marker of intact IFNγ/IL-12 axis function was assessed by flow cytometry by incubating healthy control's peripheral blood mononuclear cells in the presence of patient's serum

but anti-Crithidia antibody was negative. IFN-γ and IL-12 functional assays were performed with the patients' PBMC and whole blood culture as described by the above methods. The patient's PBMC demonstrated normal intrinsic IFN-γ and IL-12 production when tested in isolation but this was completely suppressed by whole blood culture (Fig. 5). Serum anti-IFN-γ autoantibodies levels performed, with the same methodology as previous case, returned positive (Fig. 6).

Anti-NTM treatment was commenced with oral clarithromycin 275 mg Q12H, rifampicin 450 mg Q24H, and ethambutol 500 mg Q24H. The MAC was tested susceptible to clarithromycin. At 6-month review, there was clinical improvement and reduction of inflammatory markers. Repeat serum anti-IFN-γ antibodies showed fluctuating levels despite successful treatment and disease quiescence (Fig. 6a, b). The patient's HLA typing was DQB1*05:01:01G, DRB1*15:02:01 and DRB1*15:19.

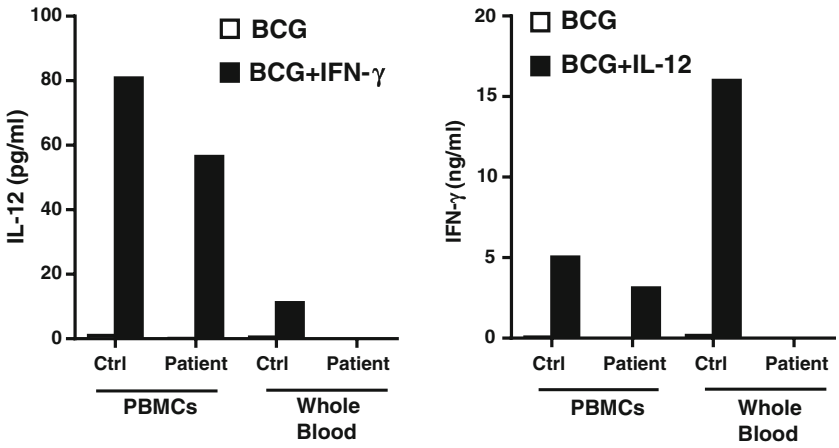

Fig. 5 Production of IL-12 and IFN-γ by case 2's PBMC (serum free) and whole blood cultures. The cells were stimulated with Bacillus Calmette-Guérin (BCG), in the presence or absence of IFN-γ (for the detection of IL-12) or IL-12 (for the detection of IFN-γ). The patient's PBMC demonstrated normal intrinsic IFN-γ and IL-12 production when tested in isolation but this was completely suppressed by whole blood culture

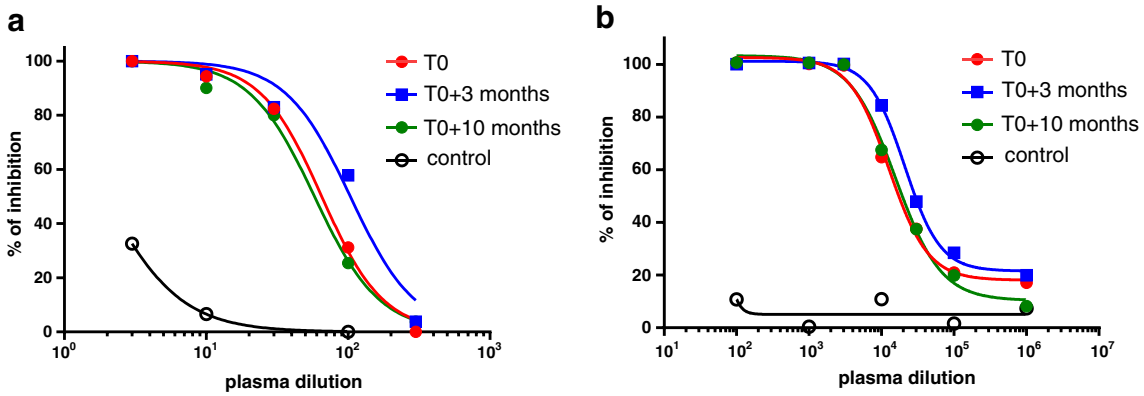

Fig. 6 **a** Inhibition of the STAT phosphorylation and **b** the detection of input IFN-γ by plasma samples of case 2. The relative anti-IFNγ autoantibody titers through inhibition of recombinant IFNγ at varying serial dilution factors of the patient's plasma was measured by ELISA as above. Signal transducer and activator of transcription (STAT)-1 phosphorylation as a marker of intact IFNγ/IL-12 axis function was assessed by flow cytometry by incubating healthy control's peripheral blood mononuclear cells in the presence of patient's serum

Discussion

IFN-γ, a key cytokine produced predominantly by T-helper-1 cells and natural killer cells, has a critical role in the cell-mediated immune cascade in response against invasion by intracellular pathogens, especially NTM species. The presence of pathological anti-IFN-γ autoantibodies with neutralizing capacity disrupts this pathway, impairing intracellular organism killing by macrophages, leading to disseminated NTM infections, which may be severe, progressive, and often difficult to treat.

In a study by Browne et al., screening for 41 anti-cytokine autoantibodies from a group of patients in Thailand and Taiwan demonstrated that only autoantibodies against IFN-γ correlated with disseminated opportunistic infection, with a large proportion (88%) caused by NTM species [4]. Various other studies have illustrated the distinctive role of IFN-γ in the control of NTM-specific infections [1–3, 5–10].

In reported cases, the most frequently isolated NTM species were the rapid growers, with *M. abscessus* being the commonest [4, 5, 14, 15]. Other NTM species isolated include *M. fortuitum* and *M. chelonae*, and slow growers, most commonly *M. avium* complex, *M. kansasii*, and *M. scrofulaceum* [4, 15]. Cervical lymphadenitis (81.8%) was the most common clinical manifestation in these patients [15]. Other common sites of infection include the lungs, bones, and joints.

Most children presenting with severe NTM infections have shown genetic defects in the IFN-γ/IL-12 axis—Mendelian susceptibility to mycobacterial disease (MSMD) [16]. In a review article by Filipe-Santos et al., as many as 13 different genetic defects involving the *IFN-γR1*, *IFN-γR2*, *Stat-1*, *IL-12Rβ1*, and *IL12-B* genes have been identified, and disease severity correlates with the amount of functional signaling [16]. The mean age at onset of mycobacterial infection in these patients is 13.4 years (range, 1.5 to 57 years). Mutations that cause complete receptor deficiencies typically result in a very severe disseminated infection with early onset and very poor prognosis with high mortality. The tissue lesions are widespread and typically show poorly delineated, lepromatous-like, multibacillary granulomas. These children are most commonly infected by BCG and NTM, notably rapid growers like *M. fortuitum*, *M. chelonae*, *M. smegmatis*, and *M. peregrinum*. Salmonellosis has been reported as the 2nd most frequent infectious disease in these patients, especially in patients with IL-12β1 deficiency [16].

In healthy persons, low-titers of naturally occurring anti-cytokine autoantibodies may be part of an immune regulatory response to inflammation and infection [5, 17]. It is unclear, however, what causes an overproduction of these autoantibodies that exhibit inhibitory effects at high-titers, nor do we understand their causal role in the disease [2–4]. The anti-IFN-γ autoantibody titers were monitored during the course of treatment and found not to correlate with disease activity in both patients. This has been similarly observed in our other patients [18]. A genetic origin is strongly suspected, given the racial predisposition in adults of East Asian origin. Association with HLA-DRB1 and HLA-DQB1 have been described [18, 19] but variant loci had been elicited in our patients. Interestingly, hypergammaglobulinemia was present in both our patients, with autoantibodies to ANA and dsDNA but no primary autoimmune disease. In addition, there were decreased levels of B lymphocytes in both our patients, suggesting possible underlying humoral defect and immune dysregulation.

Conclusion

A search for anti-IFN-γ autoantibodies should be carried out in cases of otherwise healthy immunocompetent hosts with recurrent or disseminated NTM infection, especially in patients of East Asian descent. Although previously only

reported to affect adults, our case clearly demonstrates that it can occur in the pediatric population. We propose that the previous disease nomenclature of "adult-onset immunodeficiency due to anti-IFN-gamma antibody" be changed to "Immunodeficiency Secondary to IFN-γ Autoantibodies" or "ISIGA Syndrome."

Funding information L.Y.A.C. has been supported by Clinician Scientist Award (CSA), Individual Research Grant (IRG), Bedside & Bench (B&B) grants, and the Training Fellowship Award from the National Medical Research Council (NMRC), Singapore. He also acknowledges the Synthetic Biology Research & Development Programme (SBP) from the National Research Foundation, Seed Fund grant from National University Health System and the Microbiome BIGHEART grant of the National University of Singapore.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

References

1. Dorman SE, Holland SM. Interferon-gamma and interleukin-12 pathway defects and human disease. Cytokine Growth Factor Rev. 2000;11(4):321–33.
2. Döffinger R, Helbert MR, Barcenas-Morales G, Yang K, Dupuis S, Ceron-Gutierrez L, et al. Autoantibodies to interferon-gamma in a patient with selective susceptibility to mycobacterial infection and organ-specific autoimmunity. Clin Infect Dis. 2004;38(1):e10–4.
3. Höflich C, Sabat R, Rosseau S, Temmesfeld B, Slevogt H, Döcke WD, et al. Naturally occurring anti-IFN-gamma autoantibody and severe infections with *Mycobacterium cheloneae* and *Burkholderia cocovenenans*. Blood. 2004;103(2):673–5.
4. Browne SK, Burbelo PD, Chetchotisakd P, Suputtamongkol Y, Kiertiburanakul S, Shaw PA, et al. Adult-onset immunodeficiency in Thailand and Taiwan. N Engl J Med. 2012;367(8):725–34.
5. Patel SY, Ding L, Brown MR, Lantz L, Gay T, Cohen S, et al. Anti-IFN-gamma autoantibodies in disseminated nontuberculous mycobacterial infections. J Immunol. 2005;175(7):4769–76.
6. Baerlecken N, Jacobs R, Stoll M, Schmidt RE, Witte T. Recurrent, multifocal *Mycobacterium avium-intercellulare* infection in a patient with interferon-gamma autoantibody. Clin Infect Dis. 2009;49(7):e76–8.
7. Kampmann B, Hemingway C, Stephens A, Davidson R, Goodsall A, Anderson S, et al. Acquired predisposition to mycobacterial disease due to autoantibodies to IFN-gamma. J Clin Invest. 2005;115(9):2480–8.
8. Koya T, Tsubata C, Kagamu H, Koyama K, Hayashi M, Kuwabara K, et al. Anti-interferon-gamma autoantibody in a patient with disseminated *Mycobacterium avium* complex. J Infect Chemother. 2009;15(2):118–22.
9. Tanaka Y, Hori T, Ito K, Fujita T, Ishikawa T, Uchiyama T. Disseminated *Mycobacterium avium* complex infection in a patient with autoantibody to interferon-gamma. Intern Med. 2007;46(13):1005–9.
10. Wongkulab P, Wipasa J, Chaiwarith R, Supparatpinyo K. Autoantibody to interferon-gamma associated with adult-onset immunodeficiency in non-HIV individuals in Northern Thailand. PLoS One. 2013;8(9):e76371.
11. Liu TT, Weng SW, Wang MC, Huang WT. Nontuberculous mycobacterial infection with concurrent IgG4-related lymphadenopathy. APMIS. 2016;124(3):216–20.
12. O'Connell E, Rosen LB, LaRue RW, Fabre V, Melia MT, Auwaerter PG, et al. The first US domestic report of disseminated *Mycobacterium avium* complex and anti-interferon-γ autoantibodies. J Clin Immunol. 2014;34(8):928–32.
13. Hanitsch LG, Löbel M, Müller-Redetzky H, Schürmann M, Suttorp N, Unterwalder N, et al. Late-onset disseminated Mycobacterium avium intracellulare complex infection (MAC), cerebral toxoplasmosis and Salmonella sepsis in a German Caucasian patient with unusual anti-interferon-gamma IgG1 autoantibodies. J Clin Immunol. 2015;35(4):361–5.
14. Kampitak T, Suwanpimolkul G, Browne S, Suankratay C. Anti-interferon-γ autoantibody and opportunistic infections: case series and review of the literature. Infection. 2011;39(1):65–71.
15. Chi CY, Lin CH, Ho MW, Ding JY, Huang WC, Shih HP, et al. Clinical manifestations, course, and outcome of patients with neutralizing anti-interferon-γ autoantibodies and disseminated nontuberculous mycobacterial infections. Medicine (Baltimore). 2016;95(25):e3927.
16. Filipe-Santos O, Bustamante J, Chapgier A, Vogt G, de Beaucoudrey L, Feinberg J, et al. Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. Semin Immunol. 2006;18:347–61.
17. Revoltella RP. Natural and therapeutically-induced antibodies to cytokines. Biotherapy. 1998;10:321–31.
18. Ku CL, Lin CH, Chang SW, Chu CC, Chan JF, Kong XF, et al. Anti-IFN-γ autoantibodies are strongly associated with HLA-DR*15:02/16:02 and HLA-DQ*05:01/05:02 across Southeast Asia. J Allergy Clin Immunol. 2016;137(3):945–8.e8.
19. Chi CY, Chu CC, Liu JP, Lin CH, Ho MW, Lo WJ, et al. Anti-IFN-γ autoantibodies in adults with disseminated nontuberculous mycobacterial infections are associated with HLA-DRB1*16:02 and HLA-DQB1*05:02 and the reactivation of latent varicella-zoster virus infection. Blood. 2013;121(8):1357–66.