Journal of Clinical Immunology (2018) 38:460–463
https://doi.org/10.1007/s10875-018-0509-8

LETTER TO EDITOR

Autosomal Dominant IFN-γR1 Deficiency Presenting with both Atypical Mycobacteriosis and Tuberculosis in a BCG-Vaccinated South African Patient

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Received: 5 February 2018 / Accepted: 8 May 2018 / Published online: 18 May 2018

Keywords Mendelian susceptibility to mycobacterial disease · IFN-γ immunity · Ttuberculosis · South Africa · IFNGR1 · Mycobacterium other than tuberculosis

To the Editor,

Mendelian susceptibility to mycobacterial disease (MSMD) refers to a group of primary immunodeficiency disorders (PIDs) that characteristically cause susceptibility to mycobacterial infections by a range of mycobacteria and to systemic non-typhoidal salmonellosis [1, 2]. MSMD sufferers are also vulnerable to the more pathogenic *Mycobacterium tuberculosis* (TB) [3]. To date, the disruption of IFN-γ immunity has been reported in all genetic etiologies of MSMD [2, 4, 5]. The prevalence of MSMD is currently unknown in South Africa and is almost certainly masked by the enormous TB/HIV epidemic [1, 6]. Poor awareness of PID adds to the lack of or late diagnosis. Age of onset of MSMD reported from regions of lower prevalence of TB is typically in infancy with disseminated infection by weakly virulent mycobacteria such as Bacillus Calmette–Guérin (BCG) or atypical mycobacterial species. MSMD clinical presentation and the virulence of the infecting organism in highly endemic regions have only rarely been reported on [2, 7].

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10875-018-0509-8) contains supplementary material, which is available to authorized users.

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Here, we describe a girl of South African mixed ethnicity (with genetic contributions from Khoesan, Bantu-speaking Africans, European, and Asian ancestors [8]) of non-consanguineous parents who was referred at age 9 years from an orthopedic facility to the Pediatric Rheumatology Service, Tygerberg Hospital. She was severely wasted and wheelchair bound with chronic arthritis of her left ankle. She had not responded to extended antibacterial treatment for suspected staphylococcal septic arthritis nor completed 6 months of standard anti-tuberculous treatment. Her sputum was positive for Ziehl–Neelsen (ZN) stain for acid-fast bacilli (AFB), but culture-negative. Owing to the lack of response, she had been started just prior to referral on an 18-month treatment for suspected drug-resistant TB, with initial ZN-negative sputum but subsequent positive cultures of both TB and non-tuberculous mycobacteria (MOTT)—resembling *Mycobacterium avium* subsp. *intracellulare* (MAI)—from sputum and neck lymph nodes. These had been PCR-confirmed, with corresponding adjustment of therapy. Granulomatous tissue had been identified on histology of the ankle joint, but no AFB were seen, and culture was negative for TB. She had been vaccinated with Bacillus Calmette–Guérin (BCG) at birth, as evidenced by scarring on her upper arm. At 6 months, according to maternal history, she had been treated for pulmonary TB in a rural hospital of the Eastern Cape Province of South Africa. There was no relevant history of other infections, no family history of recurrent infections with either TB, MOTT, or *Salmonella*. The patient has three, healthy, live siblings. The family lived in an informal settlement on the outskirts of Cape Town.

On examination at presentation to the rheumatology clinic, there was no evidence of syndromic features, specifically none of ectodermal dysplasia. The patient was severely wasted with a weight of 19.8 kg (3rd centile for age) and length 142 cm (25th centile) at age 9 years. Severe monoarthritis of the left ankle joint was noted, which prevented the patient from walking unassisted. Despite 6 weeks of intensive antibiotic treatment for presumed septic arthritis (*Staphylococcus aureus* cultured from a tissue biopsy) and 6 months of TB therapy, there was poor response of both the arthritis and still severe wasting. She was started on a five-drug regime for MAI as soon as a culture-positive sputum sample was obtained for a non-TB organism presumed MAI.

On baseline investigation, HIV ELISA test was negative. The erythrocyte sedimentation rate (ESR) was 115 mm/h and remained elevated on repeated determinations. She had normal lymphocyte subset and total numbers. Neutrophils were elevated: 14.34 (N 1.4–5.2 × 10 > 9/L), immunoglobulins were normal, and neutrophil burst showed normal response. There was no record of a tuberculin skin test (TST) on the initial workup of the patient. Lymphocyte proliferation response to phytohemagglutinin (PHA), concanavalin A (ConA), and pokeweed mitogen was normal. Lymphocyte proliferation response to protein A and *Candida* stimulation was reduced compared to adult control. A commercial IFN-γ release assay was not locally available at the time. On chest X-ray (Fig. 1a), there was an evidence of scattered lytic lesions in the humerus and clavicle. Multiple abnormal uptake areas or "hot spots" were reported on radio-nucleotide bone scan (Fig. 1b).

The patient gradually improved on her treatment for MOTT in the time leading up to a defined diagnosis. However, she defaulted follow-up at age 12 before further consideration of specific treatment options for MSMD. She re-entered medical care aged 15 years with admission to a neighboring academic hospital, with left leg chronic pain, weight loss, and night sweats. CT scan showed multiple small radio-dense lesions in liver, brain, bones, and lungs (Fig. 1b). Bone biopsy culture confirmed MAI. She was again started on 18 months of MOTT therapy and antibiotic prophylaxis. She defaulted from care until a further relapse of her symptoms. Challenges with compliance and accessing care despite intensive counseling have prevented optimal management including surveillance and prophylactic antibiotics for TB and potential adjunctive treatment strategies such as IFN-γ therapy.

The study was approved by the Health Research Ethics Committee of Stellenbosch University (study no. N08/09/264). The mother granted informed consent, and this included the genetic evaluation of the affected individual, her brother, and her half-sister. Additionally, informed consent was also obtained from both parents as well as two healthy control individuals. The study adhered to the ethical guidelines as set out in the Declaration of Helsinki, 2013 [9].

Cells from the patients responded modestly to IFN-γ by whole blood assay [10] and EMSA, whereas their response to IL-12 and IFN-α was normal, highly suggestive of a defect in IFN-γ signaling pathway (Supplementary Table 1 and Supplementary Fig. 1). Sanger sequencing of all exons of *IFNGR1* in the family members identified a de novo heterozygous four base pair deletion in exon 6 of IFN-γR1 at nucleotide 818 (818del4) in the affected individual (Supplementary Fig. 2). This mutation has previously been identified in individuals with MSMD and is responsible for an impaired response to IFN-γ [11] due to the accumulation of IFN-γR1 at the cell surface (Supplementary Fig. 3), lacking the recycling motif and leading to a dominant negative effect on the WT. This mutation was the first identified hotspot of small deletion in humans, discovered in patients with MSMD, and was previously identified in patients with TB [12, 13]. Together, these results suggest that the patient has AD IFN-γR1 deficiency leading to a poor response to IFN-γ and TB.

The case we present here represents the first confirmed diagnosis from South Africa of a mutation of a MSMD gene, with recurrent infection with TB and other less pathogenic mycobacteria. The infection with both environmental and typical mycobacteria as well as negative HIV status focusses attention on a genetic etiology. Despite the high prevalence

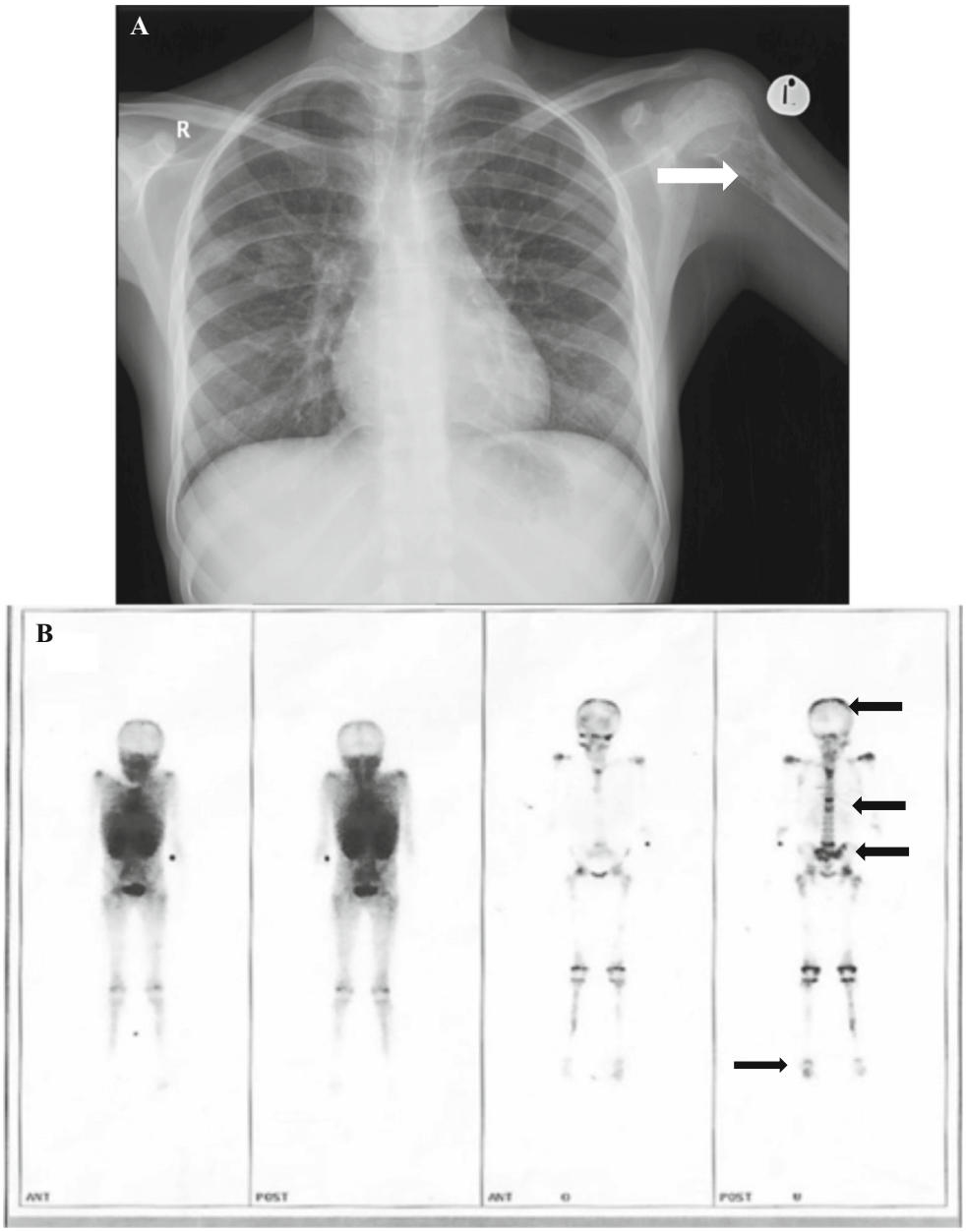

Fig. 1 **a** Chest X-ray of the patient. White arrow indicates lytic lesions in the humerus. **b** Bone scan of the patient. Multiple small radio-dense lesions demonstrated in the bones (indicated by the black arrows)

of TB or in fact especially in areas of high TB prevalence, genetic causes of TB should be considered. Genetic predisposition in these high infection pressure settings will elucidate the intricate pathways of the immune response to TB. Therefore, a genetic cause should be considered in all children and adults HIV negative with severe, persistent, unusual, or recurrent mycobacterial disease.

Acknowledgments Our gratitude goes to the patient and her family members who participated in the study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the South African Medical Research Council.

Authorship Contributions The work presented in the article was carried out in collaboration between all authors. CK, PvH, EGH, MM, MU, BG, NdV, RN, and ME are part of the Primary Immunodeficiency Diseases Genetic Network (PIDDGEN) at Stellenbosch University. CK, PvH, EGH, MM, MU, JP, JB, MM-V, LA, J-LC, SB-D, and ME made substantial contributions to the conception or design of the work. CK, BG, MU, MM, RG, NdV, JB, MM-V, LA, J-LC, SB-D, and ME made significant contributions to the interpretation of data. JB, MM-V, LA, J-LC, and SB-D performed all laboratory experiments. CK, BG, MM, and ME drafted the manuscript. All authors critically revised the final manuscript. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding Information This research was partially funded by the South African government through the South African Medical Research Council (CK, PvH, and EGH) and the South African National Research Foundation. Stellenbosch University also supported this work.

The Laboratory of Human Genetics of Infectious Diseases is supported by grants from the National Institute of Allergy and Infectious Diseases (NIAID) grant numbers R37AI095983, and R01AI089970, the National Centre for Research Resources and the National Centre for Advancing Sciences (NCATS) of the National Institutes of Health grant number UL1TR001866, The Rockefeller University, the St. Giles Foundation, the European Research Council (ERC-2010-AdG-268777), Institut National de la Santé et de la Recherche Médicale, University Paris Descartes, Laboratoire d'Excellence Integrative Biology of Emerging Infectious Diseases (ANR-10-LABX-62-IBEID), and by the French National Research Agency (ANR) under the "Investissement d'avenir" program (grant ANR-10-IAHU-01), ANR-GENMSMD (ANR-16-CE17-0005-01) and TBPATHGEN (ANR-14-CE14-0007-01).

Compliance with Ethical Standards

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

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