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LETTER TO EDITOR

Recurrent *Salmonella typhi* Infection and Autoimmunity in a Young Boy with Complete IL-12 Receptor β1 Deficiency

Ankur Kumar Jindal[1] · Deepti Suri[1] · Sandesh Guleria[1] · Amit Rawat[1] · Sumit Garg[2] · Amanjit Bal[2] · Jean-Laurent Casanova[3,4,5,6,7] · Jacinta Bustamante[3,4,6,8] · Surjit Singh[1]

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To the Editor

Mendelian susceptibility to mycobacterial diseases (MSMD) is a group of rare primary immunodeficiency (PID) diseases characterized by defects of IL-12/IFN-γ pathway. The defect predisposes an individual for infections with unusual intracellular organisms typically mycobacteria and salmonella [1, 2]. Autoimmune manifestations only rarely develop in these patients [3–8]. We report one such patient with IL-12 receptor β1 defect who had recurrent *Salmonella typhi* infection, leukocytoclastic vasculitis, and autoimmune hemolytic anemia.

Index boy was symptomatic since the age of 1 month. He was being treated at a local health care facility before referral. At 1 month of age, he was diagnosed to have Bacillus Calmette–Guérin (BCG) lymphadenitis. He also had recurrent episodes of dysentery, oral thrush, and purulent ear discharge. At 6 years of age, he started developing multiple pus discharging sinuses in the right leg and forearm. This was managed as tubercular osteomyelitis but no organism was isolated at this time. This treatment led to the healing of the sinuses and formation of scars. He was born out of a non-consanguineous marriage in India with no suggestive family history of recurrent infections or autoimmunity. He presented to us at 10 years of age with diarrhea and fever for 20 days. On examination, he had pallor, multiple healed scars over the right leg, right dorsum of the foot and right forearm (Fig. 1a), and hepatomegaly. The rest of the examination was unremarkable. A clinical possibility of PID was considered. Laboratory investigations showed hemoglobin 64 g/l, white blood cell count 14.2×10^9 cells/L (Polymorphs$_{83\%}$/Lymphocytes$_{10\%}$/Monocytes$_{7\%}$), absolute lymphocyte counts 1.42×10^9 cells/L, platelet counts 424×10^9/L, C-reactive protein 106 g/l ($N < 6$), and erythrocyte sedimentation rate 64 mm in the first hour. Stool culture and blood culture grew *Salmonella typhi* (sensitive to ceftriaxone). Blood and stool culture did not grow any mycobacteria. Immunological investigations are summarized in Supplementary Table 1. The flow cytometric expression of IL-12Rβ1 on stimulated lymphocytes was markedly reduced as compared to control. Molecular analysis confirmed a previously described homozygous nonsense mutation in the IL-12RB1 gene (c.962C > A, p.S321*). Mother, father, and younger brother were found

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✉ Deepti Suri
surideepti@gmail.com

[1] Department of Pediatrics, Allergy Immunology Unit, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[2] Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[3] Laboratory of Human Genetics of Infectious Diseases, Institut National de la Santé et de la Recherche Médicale, Paris, France

[4] Imagine Institute, Paris Descartes University, Paris, France

[5] St. Giles Laboratory of Human Genetics of Infectious Diseases, The Rockefeller University, New York, NY, USA

[6] Pediatric Hematology-Immunology Unit, Necker Hospital for Sick Children, AP-HP, Paris, France

[7] Howard Hughes Medical Institute, New York, NY, USA

[8] Center for the Study of Primary Immunodeficiencies, Necker Hospital for Sick Children, Paris, France

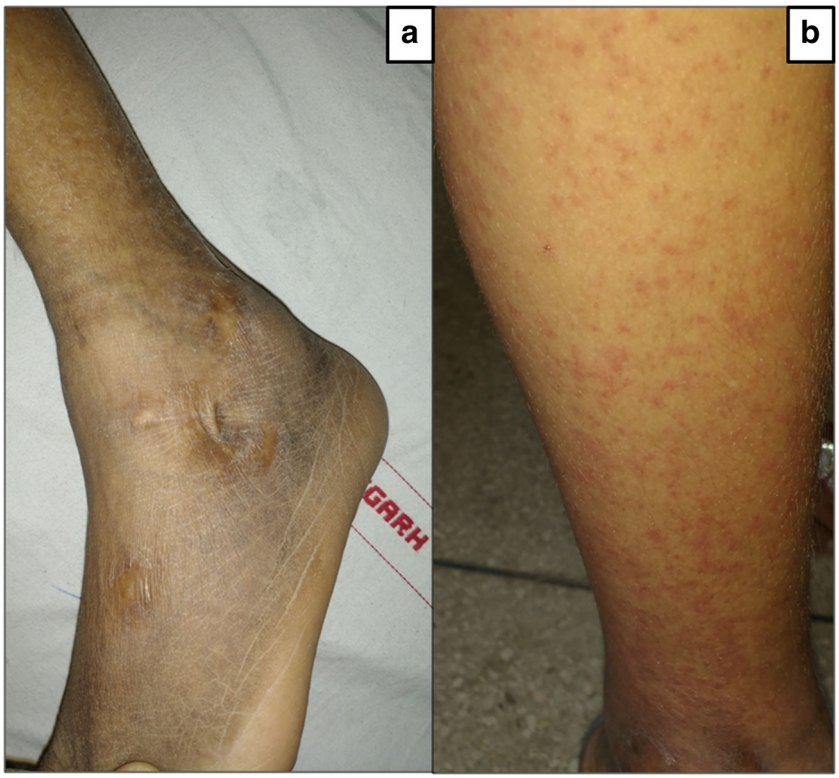

Fig. 1 **a** Healed scarred lesions over the left foot. **b** Palpable purpuric lesions over the legs

to be carriers for the same mutation at heterozygous state. He was initiated on intravenous ceftriaxone (100 mg/kg/day in two divided doses). However, he continued to have loose stools with passage of blood and mucus. He underwent colonoscopy that showed patchy erythema in the proximal rectum and distal sigmoid colon with deep ulceration, mucosal heaping, and pseudo polyps. Biopsy specimen from rectum showed cryptitis and crypt abscesses that were reported to be consistent with inflammatory bowel disease (IBD) (Supplementary figure 1A, B, C, and D). Stain for acid-fast bacilli was negative. He showed gradual recovery and intravenous ceftriaxone was given for a total of 21 days. He was discharged on oral azithromycin prophylaxis (5 mg/kg/day). He remained clinically well for the next 6 months. He had another episode of loose stools and fever. Blood and stool cultures were sterile. He was re-initiated on intravenous ceftriaxone that was given for 21 days. During this diarrheal illness, he also developed erythematous and palpable purpuric lesions over both legs (Fig. 1b) associated with swelling of both ankle joints and painful subcutaneous swelling over the dorsum of both feet. Histopathological examination of skin biopsy showed leukocytoclastic vasculitis but direct immunofluorescence showed no immune deposits. He had normal blood pressure; urine showed no red blood cells or protein; hepatitis B surface antigen and IgM hepatitis C serology were non-reactive. In view of the persistence of skin lesions, arthritis, and swelling over the dorsum of the feet despite treatment of his diarrheal illness, he was given oral prednisolone (2 mg/kg/day) for 2 weeks followed by gradual tapering over the next 6 weeks. This led to complete resolution of skin rash, arthritis, and subcutaneous swelling over the feet. He was also initiated on cotrimoxazole prophylaxis (5 mg/kg/day of trimethoprim component). He remained clinically well for the next 6 months. However, he again developed *S. typhi* bacteremia and was treated with oral cefixime (20 mg/kg/day in two divided doses) for 8 weeks. He was also noticed to have persistent anemia and peripheral blood smear examination showed features suggestive of hemolysis (target cells, macro-ovalocytes, spherocytes, stomatocytes, and elliptocytes). Direct Coombs test (DCT) was positive (2+ anti-IgG positive; C3d negative), thereby suggesting a warm antibody-mediated autoimmune hemolytic anemia (AIHA). Antinuclear antibody (ANA) was positive (2+ nucleolar pattern on indirect immunofluorescence, 1:40 dilution). He was initiated on oral prednisolone (1 mg/kg/day) for AIHA. His hemoglobin improved on therapy and prednisolone was gradually tapered after 8 weeks of therapy. He was also planned for IFN-γ therapy, but due to its non-availability in the country, it could not be given. He was reinitiated on a higher dose of cotrimoxazole prophylaxis (10 mg/kg/day of trimethoprim component).

Interleukin-12Rβ1 defect is the most common genetic etiology for MSMD. Approximately 237 cases of IL-12Rβ1 have been reported so far in the literature [1, 2, 9, 10]. Only two children reported so far had *Salmonella typhi* infection presenting as typhoid fever [10]. The index case had probable BCG adenitis and mycobacterial osteomyelitis. He also had

Table 1 Review of reported cases with IL-12Rβ1 deficiency and autoimmunity

S. no.	Author, year and country	Age (years)/ Sex	Mutation	Autoimmune manifestations	Autoimmune markers	Infection that potentially triggered autoimmunity	Treatment for autoimmunity	Outcome
1	Kutukculer, 2006, Turkey [5]	8 years, F	R173P	Leukocytoclastic vasculitis; C3 and IgM deposits	ANA, ANCA and ENA negative	*Mycobacterium chelonae* and *Salmonella enteritidis*	None	Responded to treatment of infection
2	Sanal et al, 2006, Turkey [13]	5 years, M	r.783 + 1G>A; aberrant splicing of the RNA (skipping of exon 8 or exon 5 and exon 8), resulting in premature stop codon	Skin vasculitis	NA	Group D Salmonella	NSAIDS	Responded to treatment of infection
3	Filiz et al, 2014, Turkey [4]	4 years, F	Intron 8 (783+1G>A)	Leukocytoclastic vasculitis	ANA, ANCA and RF negative	*Salmonella enteritidis*	None	Responded to treatment of infection
4	Khamassi et al, 2015, Tunisia [6]	3 years, M	1791+2T >G (premature stop codon)	Leukocytoclastic vasculitis; C3, C1q, IgM, IgG and IgA deposit	ANA, ANCA negative	*Salmonella enteritidis*	None	Responded to treatment of infection
5	Ling et al, 2016, Israel* [7]	12 years, M	large deletion encompassing exons 8–13	SLE and interstitial lung disease	ANA and ENA negative, positive anti dsDNA, DCT and IgG anticardiolipin antibody	None	Corticosteroid	Died due to septic shock
6	Ling et al, 2016, Israel* [7]	7 years, M	large deletion encompassing exons 8–13	Photosensitive dermatitis and leukocytoclastic vasculitis (IgM and C3 deposits)	low C1q complement, positive ANA, RF and DCT	None	Photoprotection	Responded to photo protective measures
7	Göktürk et al, 2016, Turkey [8]	6 years, M	R211X in exon 7	AIHA	Positive DCT, RF; negative ANA and ANCA	Group A Salmonella	None	Remained well on IFN-γ treatment
8	Sogkas et al, 2017, Germany [3]	50 year, M	Compound heterozygosity [c.1623_1624delGCinsTT (pGln542Stop) and c.1791 + 2T >C (donor splice site)	Sjogren syndrome	positive ANA and RF	None	Methotrexate and prednisolone	Responded to treatment
9	Index case	10 year, male	c.962C>A, p.S321X	AIHA, leukocytoclastic vasculitis (no immune deposit)	Positive DCT and ANA	Probable *Salmonella typhi*	Oral prednisolone for both vasculitis and AIHA	Responded to corticosteroid treatment

A: Adenine; AIHA: autoimmune hemolytic anemia; ANA: anti-nuclear antibody; ANCA: anti-neutrophil cytoplasmic antibody; C: cytidine; dsDNA: double stranded DNA;ENA: extractable nuclear antigen; F: female; G: guanine; M: male; NA: not available; NSAIDs: non-steroidal anti-inflammatory drugs; P: Proline; R: Arginine; RF: rheumatoid factor; SLE: systemic lupus erythematosus; T: thymidine; X: stop codon

*Both are cousin brothers

oral candidiasis, pyogenic skin and ear infections, and recurrent *Salmonella typhi* infection.

The rectal biopsy of the index case was performed in view of persistent diarrhea despite antimicrobial therapy. The biopsy was reported to be consistent with IBD. However, similar changes in the biopsy may also be seen with *S. typhi* infection [11, 12]. He responded later to prolonged intravenous therapy with ceftriaxone. Therefore, no immunosuppressive therapy was initiated for IBD.

He also developed leukocytoclastic vasculitis during the episode of a diarrheal illness. To date, four cases of IL-12Rβ1 deficiency associated with leukocytoclastic vasculitis have been reported [4–6, 13] (Table 1). In three of these cases, skin vasculitis was considered to be caused by *Salmonella* infection [4, 6], while in one case, a dual infection with *M. chelonae* and *Salmonella enteritidis* infection [5] was implicated. The skin biopsy direct immunofluorescence was reported to have immune deposits in two cases (C3 and IgM in one and C3, C1q, IgM, IgG, and IgA deposits in another patient) [5, 6] while immunofluorescence report was not mentioned in the remaining two case reports [4, 13]. In all cases, the manifestations of skin vasculitis subsided with the treatment of inter-current infection, and hence, these infections were considered to be a potential trigger. In the index case, the skin biopsy was consistent with leukocytoclastic vasculitis. However, direct immunofluorescence showed no immune deposits. The manifestations of skin vasculitis coincided with the onset of diarrheal illness but no organism could be isolated during this diarrheal episode. He continued to be symptomatic despite an adequate treatment for diarrhea and had to be given oral prednisolone. It may be speculated that the leukocytoclastic vasculitis in the index case may not entirely be because of infectious diarrheal illness and there may be likely contribution by the immune dysregulation due to underlying MSMD. He also had antinuclear antibody (ANA) positivity, while in three previously reported cases, ANA was found to be negative [4–6] and was not performed in remaining one case [13]. Other autoimmune manifestations that have been reported in these patients include systemic lupus erythematosus (SLE), Sjogren syndrome, photosensitive dermatosis, and autoimmune hemolytic anemia [3, 7, 8] (Table 1). Our case had ANA and DCT positivity with AIHA. Overall, 8 out of 237 total patients with IL12Rβ1 deficiency have been found to have autoimmune manifestations (approximate prevalence 3.4%). The prevalence of autoimmunity could be underestimated given the young age of reporting for most cases and early deaths.

To conclude, autoimmune manifestations associated with IL-12Rβ1 deficiency are rare. Underlying immune dysregulation due to a defect in IFN-γ axis associated with recurrent or persistent infection induced aberrant immune response may predispose these individuals for autoimmunity. It is unclear whether recently described patients with IL-12Rβ2 or IL-23R deficiency, and patients homozygous for P1104A TYK2 unresponsive to IL-23, are also prone to such autoimmune manifestations in the course of infection [14, 15].

Compliance with Ethical Standards

Conflict of Interests The authors declared that they have no conflict of interest.

References

1. Bustamante J, Boisson-Dupuis S, Abel L, Casanova J-L. Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-γ immunity. Semin Immunol. 2014;26(6):454–70.
2. Rosain J, Kong XF, Martinez-Barricarte R, Oleaga-Quintas C, Ramirez-Alejo N, Markle J, et al. Mendelian susceptibility to mycobacterial disease: 2014-2018 update. Immunol Cell Biol. 2018;97:360–7. https://doi.org/10.1111/imcb.12210.
3. Sogkas G, Atschekzei F, Schacht V, von Falck C, Jablonka A, Jacobs R, et al. First association of interleukin 12 receptor beta 1 deficiency with Sjögren's syndrome. Front Immunol. 2017;28:8.
4. Filiz S, Kocacik Uygun DF, Verhard EM, van Dissel JT, Uygun V, Bassorgun C, et al. Cutaneous leukocytoclastic vasculitis due to Salmonella enteritidis in a child with interleukin-12 receptor beta-1 deficiency. Pediatr Dermatol. 2014;31(2):236–40.
5. Kutukculer N, Genel F, Aksu G, Karapinar B, Ozturk C, Cavusoglu C, et al. Cutaneous leukocytoclastic vasculitis in a child with interleukin-12 receptor beta-1 deficiency. J Pediatr. 2006;148(3):407–9.
6. Khamassi I, Ben Ali M, Ben Mustapha I, Barbouche MR, Bejaoui M, Bouyahia O, et al. Salmonella enteriditis inducing cutaneous leucocytoclasic vasculitis: an unusual complication in a patient with an interleukine- 12 receptor beta-1 deficiency. Tunis Med. 2015;93(5):328–9.
7. Ling G, Ling E, Broides A, Poran Feldman H, Levy J, Garty B-Z, et al. IL-12 receptor 1β deficiency with features of autoimmunity and photosensitivity. Autoimmunity. 2016;49(3):143–6.
8. Göktürk B, Reisli İ, Çalışkan Ü, Oleaga-Quintas C, Deswarte C, Turul-Özgür T, et al. Infectious diseases, autoimmunity and midline defect in a patient with a novel bi-allelic mutation in IL12RB1 gene. Turk J Pediatr. 2016;58(3):331–6.
9. Nekooie-Marnany N, Deswarte C, Ostadi V, Bagherpour B, Taleby E, Ganjalikhani-Hakemi M, et al. Impaired IL-12- and IL-23-mediated immunity due to IL-12Rβ1 deficiency in Iranian patients with mendelian susceptibility to mycobacterial disease. J Clin Immunol. 2018;38(7):787–93.
10. de Beaucoudrey L, Samarina A, Bustamante J, Cobat A, Boisson-Dupuis S, Feinberg J, et al. Revisiting human IL-12Rβ1 deficiency. Medicine (Baltimore). 2010;89(6):381–402.
11. Dionisio D, Esperti F, Vivarelli A, Fabbri C, Apicella P, Meola N, et al. Acute terminal ileitis mimicking Crohn's disease caused by Salmonella veneziana. Int J Infect Dis. 2001;5(4):225–7.
12. Papanikolaou IS, Psilopoulos DI, Liatsos C, Lazaris AC, Petraki K, Mavrogiannis C. Salmonella colitis or inflammatory bowel disease? A case demonstrating overlapping of clinical, endoscopic and pathologic features. Ann Gastroenterol. 2001;14(1):65–9.

13. Sanal O, Turul T, De Boer T, Van de Vosse E, Yalcin I, Tezcan I, et al. Presentation of interleukin-12/23 receptor beta1 deficiency with various clinical symptoms of Salmonella infections. J Clin Immunol. 2006;26(1):1–6.
14. Boisson-Dupuis S, Ramerez-Alejo N, Li Z, Patin E, Rao G, Kerner G, et al. Tuberculosis and impaired IL-23–dependent IFN-γ immunity in humans homozygous for a common TYK2missense variant. Science Immunology. 2018. https://doi.org/10.1126/sciimmunol.aau8714.
15. Martínez-Barricarte R, Markle JG, Ma CS, Deenick EK, Ramírez-Alejo N, Mele F. Human IFN-γ immunity to mycobacteria is governed by by both IL-12 and IL-23. Science Immunology. 2018;3. https://doi.org/10.1126/sciimmunol.aau6759.