Salmonella typhi infection causing prolonged chronic illness and cutaneous leucocytoclastic vasculitis in a patient with IL-12 receptor β 1 deficiency

Amarilla B. Mandola^{a,b}, Arnon Broides^b, and Amit Nahum^{a-c*}

ABSTRACT

Background: Interleukin-12 Receptor β 1 (IL-12R β 1) deficiency causes susceptibility to weakly virulent atypical mycobacteria and *Salmonella*. Genotype–phenotype correlations are weak and penetrance is not complete. Most of the culture-recovered *Salmonella* are with the non typhi types.

Case report: We describe an 11 year old male patient with IL-12R β 1 deficiency. He had an erythematous rash resembling Henoch Schonlein Purpura, and initially presented with slightly elevated CRP. Skin biopsy revealed leukocytoclastic vasculitis. Due to lack of evidence of an active infection, positive ANA, and positive direct Coombs test, an autoimmune lupus-like disease was suspected. In conjunction with rash flares, he showed progressively elevated inflammatory markers, chronic anemia, and hypoalbuminemia. Extensive investigations for an infectious etiology were negative, and without isolation of any pathogens. However, the last of a series of abdominal ultrasound examinations revealed enlarged peritoneal and retroperitoneal lymph-nodes, and biopsy yielded slow-growing bacteria, identified as *Salmonella typhi*. Prolonged treatment with 2 antimicrobial agents resulted in resolution of skin rash and normalization of laboratory results.

Conclusions: We describe an IL-12R β 1 deficient patient with a progressive inflammatory process with a unique immune dermatological manifestation which was probably triggered by an unexpected pathogen, *Salmonella typhi*. This patient's case demonstrates the need for invasive procedures to identify an infectious etiology when routine cultures and serology tests are negative.

Statement of novelty: In this case report, we describe a unique presentation of infection with *Salmonella typhi* in a patient with IL-12R β 1 deficiency, manifesting with bouts of leucocytoclastic vasculitis. We also report in the same patient, recurrent infection with an unusual pathogen, *Kocuria kristinae*. Both phenomena have not been reported in such constellation, and we believe this to be a useful and important description that could alert physicians, immunologists, and pediatricians alike to such manifestations. Further, it may help in a rapid and successful diagnosis, therefore benefiting such patients.

Introduction

Mendelian susceptibility to mycobacterial disease syndrome (MSMD) encompasses several genetic defects involving the interleukin-12/interferon (IFN) γ axis.

Nine different autosomal genes (*IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12RB1*, *IRF8*, *NEMO*, and *CYBB*) have been described. Interleukin-12 receptor beta 1 (IL-12R β 1) deficiency is the most common form of MSMD. This syndrome is characterized by susceptibility

^aPediatrics Department A, Saban Pediatric Medical Center, Soroka University Medical Center, and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel; ^bPediatric Immunology Clinic, Saban Pediatric Medical Center, Soroka University Medical Center, and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel; ^cThe Primary Immunodeficiency Research Laboratory, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

Submitted 27 October 2016
Accepted 29 November 2016
Available online 11 December 2016

*Corresponding author: Amit Nahum/amitna@clalit.org.il

LymphoSign Journal 4:25–29 (2017)
[dx.doi.org/10.14785/lymphosign-2016-0013](https://doi.org/10.14785/lymphosign-2016-0013)

to intracellular infections mainly with mycobacteria, some weakly virulent mycobacteria such as the bacille *Calmette-Guérin*, and *Salmonella* species. Salmonellosis occurs in more than half of affected patients, and while different species can be involved, most are non-typhoid type. Severe morbidity has been reported mainly with extra intestinal manifestations such as lymphadenopathy, septicemia, or recurrent infection with non-typhoid *Salmonellae* (De Jong et al. 1998; Dorman and Holland 2000). Endovascular involvement of blood vessels during the course of the disease is known but immune phenomena, such as leukocytoclastic skin vasculitis, without direct infection is extremely rare; such a case was previously described in 1 Tunisian and 3 Turkish patients (Kutukculer et al. 2006; Sanal et al. 2006; Filiz et al. 2014; Khamassi et al. 2015). We report here a patient with IL-12Rβ1 deficiency presenting with unusual infections and prolonged intermittent episodes of fever and cutaneous leukocytoclastic vasculitis, which were probably triggered by a *Salmonella typhi* lymphadenitis.

Patient description

Our patient is an 11 year old male, born to consanguineous parents of Bedouin origin. The patient has been studied and reported previously along with other family members with IL-12Rβ1 deficiency (Ling et al. 2016). He was diagnosed as part of family screening due to an index case. He has 3 family members who were diagnosed with the same mutation, 1 asymptomatic and 2 cousins who had severe infections. One succumbed to a fatal atypical mycobacteria infection, the second survived several *Salmonella* infections and is now an adult, with a long period of being free of infections. On his first hospitalization with fever, blood cultures were positive for *Kocuria kristinae*, an unusual pathogen; he was treated and recovered completely only to return a year later with fever without any other symptoms. Blood cultures yielded, again, *Kocuria kristinae* (Table 1). After a long period in which he was free of symptoms, he was admitted several times to our department with bouts of high fever and rash appearing on his lower extremities, resembling Henoch Schonlein Purpura. Extensive infectious, rheumatologic, and hematologic workup with numerous blood cultures, serologic tests as well as PCR studies of tissue and body fluids did not yield any evidence for infectious etiology. His blood work showed positive ANA with a low titer, and a positive Coombs test. Because of his

Table 1: Patient's infectious history during the past 10 y.

Year	Infectious agent	Location	Type of isolation
2006	<i>Staphylococcus aureus</i> , <i>Streptococcus</i> , and <i>Haemophilus influenzae</i>	Eye	Culture
2009	<i>Trichophyton violaceum</i>	Skin	Scraping
2011	<i>Giardia lamblia</i>	Stool	Culture
2012	<i>Streptococcus</i> Group C	Throat	Culture
2013	<i>Giardia lamblia</i> and <i>Trichomonas hominis</i>	Stool	Culture
2014	<i>Kocuria kristinae</i> (I.)	Blood	Culture
2014	<i>Haemophilus influenzae</i> , <i>Streptococcus viridans</i> , Adenovirus, and Cytalogemalovirus	BAL	Culture and PCR
2015	<i>Kocuria kristinae</i> (II.)	Blood	Culture
2015	<i>Trichophyton verrucosum</i>	Skin	Scraping
2016	<i>Salmonella typhi</i>	Lymph node	Biopsy

immunodeficiency, on each occasion, he was treated with broad spectrum antibiotics until cultures returned negative and he was discharged. He appeared well during these episodes and did not have any gastrointestinal or respiratory manifestations, and no other systemic manifestations such as malaise, pain, or other symptoms. On physical examination the only positive finding was progressive enlargement of his spleen. Biopsy of the skin lesions demonstrated a perivascular and interstitial mixed cell infiltrate in the upper and deep dermis, with nuclear dust and foci of extravasation, suggestive of leukocytoclastic vasculitis (Figure 1). Immunofluorescence stains were positive for IgM, C3, and fibrinogen in blood vessel walls. Due to lack of evidence of active infection, alongside positive ANA and positive direct Coombs test, an autoimmune lupus-like photosensitive disease was diagnosed (Ling et al. 2016).

During the last episode, an abdominal ultrasound study showed significant enlargement of abdominal lymph nodes. We proceeded to obtain a CT-guided lymph node biopsy (Figure 2). Culture from biopsy material yielded a slow-growing bacteria, which was identified as *Salmonella typhi*.

During this period, laboratory indices showed progressive microcytic anemia (hemoglobin 7.2 g/dL, mean corpuscular volume 68 fL), hyponatremia and hypoalbuminemia, elevated C-reactive protein (CRP), and normal white blood cell counts with normal differential (Table 1).

Figure 1: Laboratory indices results during treatment with antibiotics. The change in albumin (a), hemoglobin (b), and CRP (c) following initiation of long-course ceftriaxone therapy.

The patient received a combination of parenteral ceftriaxone with oral azithromycin for an initial period of 4 weeks. His laboratory test results improved dramatically, but upon cessation of treatment, inflammatory markers and rash re-emerged. We therefore resumed the same treatment. The patient's inflammatory indices improved and skin manifestations resolved. However, following a short cessation of therapy due to non compliance by the family, the child again experienced a flare of the vasculitis rash and a rise of CRP. We decided to continue his antibiotic therapy for another 4 weeks which resulted in a remarkable improvement; his spleen size receded significantly, he started to gain weight and all laboratory indices improved (Figure 3).

Discussion

Vasculitis may be associated with infection, autoimmune diseases, immunization as well as medications. Conversely, patients with an inflammatory disease involving vasculitis may develop infection, which

Figure 2: CT scan showing enlarged periportal, intra- and retroperitoneal lymph nodes (arrows).

Figure 3: The histopathological picture of skin biopsy, showing leukocytoclastic vasculitis: (a) perivascular neutrophil infiltrate, (b) extravasation, (c) nuclear "dust", and (d) intraluminal fibrin deposit.

sometimes mimics relapse of the disease. Therefore, such events pose a challenge to the physician caring for an immune deficient patient. Some pathogens are associated with several types of vasculitis (e.g., HIV), whereas others induce a typical vasculitis syndrome (Belizna et al. 2009). The association of enteric pathogen infection with immune phenomenon has led to the suggestion that the adaptive immune response to infection has an auto-immune component (Toivanen et al. 1987; Soloski and Metcalf 2007). In the case presented here, a patient with IL-12Rβ1 deficiency showed a

presumed autoimmune phenomenon, which after a considerable period of time, proved to be infectious related. The culprit agent, *Salmonella typhi*, did not present in any of the common presentations involving the gastrointestinal tract, but rather as recurrent, self-limited, bouts of fever and vasculitic rash. We reviewed the literature describing infections and other manifestations in patients with MSMD and IL-12R β 1 deficiency in particular, and found that the vast majority of *Salmonellae* infections are of the non-typhi species. *Salmonella typhi* was found in 3 of 88 patients (de Beaucoudrey et al. 2010). The very few reports describing vasculitic rash with infections, were associated with mycobacteria, and *Salmonella enteritidis* (Kutukculer et al. 2006; Sanal et al. 2006; Filiz et al. 2014; Khamassi et al. 2015). This may suggest that in IL-12R β 1 deficient patients this is a rare but pathognomonic presentation. The mechanism responsible for such a phenomenon is not entirely understood, since secretion of IL-12 resulting in IFN γ release would promote the activity of T cells, and in some autoimmunity models, this is a necessary part of the auto-inflammatory response (Zundler and Neurath 2015). It is possible that the constant inflammatory state in these patients due to an inability to clear infections is, by itself, a promoting factor for autoimmune phenomenon.

Due to the nature of the immune defect involving impaired immune clearance mechanisms, the pathogen being an intracellular bacteria and its propensity to dwell in the reticuloendothelial system, treatment of such patients is often challenging. Our case shows that therapy should probably include at least 2 antimicrobial agents, with one of them having an intracellular effect and for a prolonged period, much longer than any standard therapy protocol, in an effort to prevent persistent or relapsing infection. In our patient, any interruption in therapy resulted in recurrence of the disease. Although clinical symptoms resolved fairly quickly, it took as long as 3 months of treatment to reach normal levels of inflammatory makers and blood counts.

It is of interest that this patient had bacteremia with *Kocuria kristinae* on 2 different occasions. This is an unusual pathogen which is not common in healthy children, but rather found in secondary immunocompromised patients (e.g., patients with cancer or those with complicated diabetes prone to infections) or patients with long standing indwelling catheters (e.g., intensive care unit), where it is known to cause endocarditis

(Ahmed et al. 2014). A recent article described a series of cases with the pathogen, where most of the patients were premature newborns and 1 child with leukemia (Chen et al. 2015). However, it has not been described in patients with MSMD to date.

Our report suggests a role for *Salmonella typhi* as a trigger for vasculitis in patients with immunodeficiency. We also report infections with *Kocuria kristinae*, an unusual and, to our knowledge, a pathogen not reported yet in this group of patients. It appears that in immunodeficient patients with vasculitic rash, failure to retrieve pathogens by routine tests should prompt a more invasive approach to identify an infectious cause.

REFERENCES

- Ahmed, N.H., Biswal, I., Roy, P., and Grover, R.K. 2014. *Kocuria kristinae*, an unusual pathogen causing opportunistic infections in patients with malignancy. Indian J. Med. Microbiol. 32(4):456–458. PMID: 25297040. doi: 10.4103/0255-0857.142232.
- Belizna, C.C., Hamidou, M.A., Levesque, H., Guillemin, L., and Shoenfeld, Y. 2009. Infection and vasculitis. Rheumatology. 48(5):475–482. PMID: 19258377. doi: 10.1093/rheumatology/kep026.
- Chen, H.M., Chi, H., Chiu, N.C., and Huang, F.Y. 2015. *Kocuria kristinae*: A true pathogen in pediatric patients. J. Microbiol. Immunol. Infect. 48(1):80–84. PMID: 23968754. doi: 10.1016/j.jmii.2013.07.001.
- de Beaucoudrey, L., Samarina, A., Bustamante, J., Cobat, A., Boisson-Dupuis, S., Feinberg, J., Al-Muhsen, S., Jannire, L., Rose, Y., de Suremain, M., Kong, X.F., Filipe-Santos, O., Chapgier, A., Picard, C., Fischer, A., Dogu, F., Ikinciogullari, A., Tanir, G., Al-Hajjar, S., Al-Jumaah, S., Frayha, H.H., AlSum, Z., Al-Ajaji, S., Alangari, A., Al-Ghoniaum, A., Adimi, P., Mansouri, D., Ben-Mustapha, I., Yancoski, J., Garty, B.Z., Rodriguez-Gallego, C., Caragol, I., Kutukculer, N., Kumararatne, D.S., Patel, S., Doffinger, R., Exley, A., Jeppsson, O., Reichenbach, J., Nadal, D., Boyko, Y., Pietrucha, B., Anderson, S., Levin, M., Schanden, L., Schepers, K., Efira, A., Mascart, F., Matsuoka, M., Sakai, T., Siegrist, C.A., Freceirova, K., Bletters-Sawatzki, R., Bernhft, J., Freiherst, J., Baumann, U., Richter, D., Haerynck, F., De Baets, F., Novelli, V., Lammas, D., Vermylen, C., Tuerlinckx, D., Nieuwhof, C., Pac, M., Haas, W.H., Mller-Fleckenstein, I., Fleckenstein, B., Levy, J., Raj, R., Cohen, A.C., Lewis, D.B., Holland, S.M., Yang, K.D., Wang, X., Wang, X., Jiang, L.,

- Yang, X., Zhu, C., Xie, Y., Lee, P.P., Chan, K.W., Chen, T.X., Castro, G., Natera, I., Codoceo, A., King, A., Bezrodnik, L., Di Giovanni, D., Gaillard, M.I., de Moraes-Vasconcelos, D., Grumach, A.S., da Silva Duarte, A.J., Aldana, R., Espinosa-Rosales, F.J., Bejaoui, M., Bousfiha, A.A., Baghdadi, J.E., Ozbek, N., Aksu, G., Keser, M., Somer, A., Hatipoglu, N., Aydogmus, C., Asilsoy, S., Camcioglu, Y., Gölle, S., Ozgur, T.T., Ozen, M., Oleastro, M., Bernasconi, A., Mamishi, S., Parvaneh, N., Rosenzweig, S., Barbouche, R., Pedraza, S., Lau, Y.L., Ehlayel, M.S., Fieschi, C., Abel, L., Sanal, O., and Casanova, J.L. 2010. Revisiting human IL12 R β 1 deficiency: A survey of 141 patients from 30 countries. *Medicine (Baltimore)*. **89**:381–402. PMID: [21057261](#). doi: [10.1097/MD.0b013e3181fdd832](#).
- De Jong, R., Altare, F., Haagen, I.-A., Elferink, D.G., de Boer, T., van Breda Vriesman, P.J.C., Kabel, P.J., Draaisma, J.M.T., van Dissel, J.T., and Kroon, F.P. 1998. Severe mycobacterial and *Salmonella* infections in interleukin-12 receptor-deficient patients. *Science*. **280**:1435–1438. PMID: [9603733](#). doi: [10.1126/science.280.5368.1435](#).
- Dorman, S.E., and Holland, S.M. 2000. Interferon-gamma and interleukin-12 pathway defects and human disease. *Cytokine Growth Factor Rev.* **11**:321–333. PMID: [10959079](#). doi: [10.1016/S1359-6101\(00\)00010-1](#).
- Filiz, S., Kocacik Uygun, D.F., Verhard, E.M., van Dissel, J.T., Uygun, V., Bassorgun, C., Bingol, A., Yegin, O., and van de Vosse, E. 2014. Cutaneous leukocytoclastic vasculitis due to *Salmonella enteritidis* in a child with interleukin-12 receptor beta-1 deficiency. *Pediatr. Dermatol.* **31**(2):236–240. PMID: [23004925](#). doi: [10.1111/j.1525-1470.2012.01856.x](#).
- Khamassi, I., Ben Ali, M., Ben Mustapha, I., Barbouche, M.R., Bejaoui, M., Bouyahia, O., and Gandoura, N. 2015. *Salmonella enteritidis* inducing cutaneous leukocytoclastic vasculitis: An unusual complication in a patient with an interleukine-12 receptor beta-1 deficiency. *Tunis Med.* **93**(5): 328–329. PMID: [26578053](#).
- Kutukculer, N., Genel, F., Aksu, G., Karapinar, B., Ozturk, C., Cavusoglu, C., Casanova, J.L., and Fieschi, C. 2006. Cutaneous leukocytoclastic vasculitis in a child with interleukin-12 receptor beta-1 deficiency. *J. Pediatr.* **148**(3):407–409. PMID: [16615980](#). doi: [10.1016/j.jpeds.2005.10.003](#).
- Ling, G., Ling, E., Broides, A., Poran Feldman, H., Levy, J., Garty, B.Z., and Nahum, A. 2016. IL-12 receptor β 1 deficiency with features of autoimmunity and photosensitivity. *Autoimmunity*. **49**(3):143–146.
- Sanal, O., Turul, T., De Boer, T., Van de Vosse, E., Yalcin, I., Tezcan, I., Sun, C., Memis, L., Ottenhoff, T.H., and Ersoy, F. 2006. Presentation of interleukine-12/-23 receptor β 1 deficiency with various clinical symptoms of *Salmonella* infections. *J. Clin. Immunol.* **26**(1):1–6. PMID: [16418797](#). doi: [10.1007/s10875-006-7830-3](#).
- Soloski, M.J., and Metcalf, E.S. 2007. *Salmonella* as an inducer of autoimmunity. *EcoSal Plus.* **2**(2). doi: [10.1128/ecosalplus.8.8.13](#).
- Toivanen, A., Lahesmaa-Rantala, R., Meurman, O., Sappinen, O., Kosunen, T., Yazici, H., Yurdakul, S., Ozbakir, F., and Müftüoglu, A. 1987. Antibodies against *Yersinia*, *Campylobacter*, *Salmonella*, and *Chlamydia* in patients with Behçet's disease. *Arthritis Rheum.* **30**(11):1315–1317. PMID: [3689469](#). doi: [10.1002/art.1780301119](#).
- Zundler, S., and Neurath, M.F. 2015. Interleukin-12: Functional activities and implications for disease. *Cytokine Growth Factor Rev.* **26**(5):559–568. PMID: [26182974](#). doi: [10.1016/j.cytogfr.2015.07.003](#).