Recurrent Salmonella Infections and Nephritis Complicating IgA Vasculitis in a Patient with IL12-RB1 Deficiency

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Mendelian susceptibility to mycobacteria (MSMD) is a group of inborn errors of immunity (IEI) due to 32 defects in the (IL)-12/IL-23/ISG15/interferon-gamma (IFN-γ) axis mediated immunity, predisposing to infections by intracellular bacteria of the genera *Mycobacterium* spp., *Salmonella* spp. and others [1]. IL-12Rβ1 deficiency is the most common genetic etiology of MSMD with a frequency of 60% [1]. It is characterized by the total loss of IL-12Rβ1 function, eliminating the cellular response to IL-12 and IL-23 [1]. Some cases can be complicated by sepsis caused by *Salmonella* spp. associated with leukocytoclastic vasculitis [1-5]. We present the case of a Mexican patient with IL12Rβ1 deficiency and nephritis secondary to IgA vasculitis associated with *Salmonella* infections. Informed consent was obtained from the patient´s family.

A 10-year-old female from a non-endogamous community and no history of consanguinity presented with disseminated BCG infection at 8 months of age. At 2 years-of-age she presented the first event of sepsis due to *Salmonella* group D associated with arthritis and palpable purpura of the lower extremities. The skin biopsy of the lesions reported leukocytoclastic vasculitis. At 3 years-old a generalized lymphadenopathy was observed; the axillary lymph node biopsy showed necrotizing granulomatous

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lymphadenitis and positive PCR for *Mycobacterium tuberculosis* complex, and antifimic treatment was administered with improvement. No IFN-□ induction in response to IL-12 was detected in whole blood, PHA activated T-cells from healthy control expressed IL-12R□1, whereas PHA-activated T-cells had no detectable IL-12R□1 expression. The diagnosis was confirmed by the presence of the heterozygous c.1561C>T (p.R521*) mutation by Sanger and also identified a heterozygous 991 bp deletion encompassing exon 8 (Δ8) by Copy Number Variation [5]; each parent carrying each one of the pathogenic variants. During her follow-up over the years, she had required more than 30 hospitalizations for recurrent episodes of fever, generalized adenitis, reactive arthritis, extrinsic hemolytic anemia, and leukocytoclastic vasculitis characterized by palpable purpura, despite treatment with antibiotic prophylaxis (ciprofloxacin or trimethoprim-sulfamethoxazole) and elective cholecystectomy (removal of a possible *Salmonella* reservoir). Recombinant IFN-□ was administered for more than a year but recurrent episodes of purpura associated with *Salmonella* continued to occur. The following etiological agents' *Salmonella enterica* serotypes *typhi, choleraesius, enteritidis*, have been isolated in all events in blood cultures. At 7 years of age, persistent glomerular hematuria was evident, and a renal biopsy was performed, which revealed segmental mesangial hyperplasia, positive IgA with a granular pattern, positive IgM and C3, negative C1q compatible with nephritis secondary to IgA vasculitis (Figure 1). Laboratory studies showed C3: 113 mg/dl (88-201), C4: 13.2 mg/dl (15-45), IgG: 2230 mg/dl (700-1600), IgA: 222 mg/dl (50-170), IgM: 227 mg/dl (40-230) and negative antinuclear antibodies. One year later, proteinuria raised to 4.8 g in 24 hours, for which she has received the following medications in different times: methotrexate, rituximab, and cyclosporine. She is currently on an immunomodulatory dose of intravenous

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immunoglobulin (IVIG), prophylactic antibiotics, enalapril, and low-dose oral corticosteroids. She continues to present relapses of *Salmonella* spp. bacteremia, at least twice a year, which are associated with palpable purpura, hematuria, and proteinuria.

AR complete IL-12Rβ1 deficiency has been occasionally associated with the presence of autoimmune complications, including systemic lupus erythematosus and Sjögren syndrome [1]. Additionally, several cases describing the relationship between active *Salmonella* infection and the presence of leukocytoclastic vasculitis affecting small vessels of the skin have been published [2-5]. Notably, when the infection is eradicated in our patient, the skin lesions disappear. IgA-vasculitis affecting only the skin have been repeatedly described in this disease which responds to antibiotics [1, 3-5]. In the present case, compared to others, IgA-vasculitis presented with nephritis. Autoimmune manifestations in IL-12Rβ1 deficiency as a group are rare, thus a correlation between the different pathogenic variants and the presence of autoimmunity has not been done. It is thought that recurrent or persistent infections induce an aberrant immune response predisposing these patients to autoimmunity [1, 3-5]. Intriguingly, spontaneous development of autoimmunity with immune complex glomerulonephritis was observed in *il2rb2* deficient mice [6]. IgA-nephritis has also been described as a complication of other immunodeficiencies, including chronic granulomatous disease, Wiskott-Aldrich syndrome, HIV infection, and IgA deficiency [7].

Patients with AR complete IL12Rβ1 deficiency require perpetual prophylactic antibiotics to avoid recurrent infections and, in some cases, recombinant IFN-γ therapy [1]. Our

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patient received this therapy with no improvement. A clear etiological link has been established between *Salmonella* and IgA nephritis, as in this case [8]. Every bout of clinical associated vasculitic skin lesions has been associated invariably with Salmonella's positive blood culture, giving proof to the concept that *Salmonella* is vital in the development of this autoimmune complication. Patients who present with infection susceptibility and autoimmunity pose a particular challenge to treat. In the described patient, systemic steroids, immunosuppressive therapy, and regular infusion of IVIG have been administered with improvement. The rationale behind the use of IVIG lies in the anti-infectious and immunomodulatory properties it possesses. Extracellular *Salmonella* in the blood can be target by IVIG, enhancing their uptake and killing by phagocytes in the spleen and liver. In addition, IVIG provides several mechanisms of action in vasculitis, including downregulation of antibody synthesis, facilitation of autoantibody clearance and inhibition of complement damage, and has been used with positive results in IgA nephritis [9]. However, when she presents a new episode of *Salmonella* infection, renal symptoms reappear. Strong IL-6 up-regulation has been detected in lymphoid infiltrates in the *il12rb2* knockout mice, which opens the theoretical therapeutic approach of anti-IL-6 biologics, which have been used successfully in isolated case reports of IgA-vasculitis [10]. Occasionally, hematopoietic stem cell transplantation has been performed [1]. There is varying clinical presentation with substantial genetic heterogeneity in this condition, hence treatment risk-benefit ratio must be assessed on a case-by-case basis.

To our knowledge, this is the first case report of a patient with IL12Rβ1 deficiency and IgA nephritis associated with *Salmonella* infection. It should be considered in all those

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cases with IL12Rβ1 deficiency that, in addition to purpura and infection, presents persistent hematuria and proteinuria.

Conflict of Interests

T*he authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article".*

Availability of the data

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