## Recurrent *Salmonella* Infections and Nephritis Complicating IgA Vasculitis in a Patient with IL-12Rβ1 Deficiency

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**Palabras clave:** Deficiencia de la cadena beta receptor IL-12. *Salmonella* spp. Vasculitis leucocitoclástica. Infecciones recurrentes. Nefritis por IgA.

Mendelian susceptibility to mycobacterial disease (MSMD) is a group of inborn errors of immunity (IEI) due to 32 defects in the interleukin (IL) 12/IL-23/ISG15/interferon-gamma (IFN-γ) axis. It predisposes to infections by intracellular bacteria of *Mycobacterium* species, *Salmonella* species, and other species [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, which leads to elimination of the cellular response to IL-12 and IL-23 [1]. Some cases can be complicated by sepsis caused by *Salmonella* species associated with leukocytoclastic vasculitis [1-5]. We present the case of a Mexican patient with IL-12Rβ1 deficiency and nephritis secondary to IgA vasculitis associated with *Salmonella* infection. Informed consent was obtained from the patient's family.

A 10-year-old girl from a nonendogamous community with no history of consanguinity presented with disseminated bacille Calmette-Guérin infection at 8 months of age. At 2 years of age, she presented the first septic event due to *Salmonella* group D associated with arthritis and palpable purpura of the lower extremities. Skin biopsy of the lesions confirmed leukocytoclastic vasculitis. At age 3 years, she developed generalized lymphadenopathy; the axillary lymph node biopsy revealed necrotizing granulomatous lymphadenitis and a positive PCR result for *Mycobacterium*

 

*tuberculosis* complex. Antituberculosis treatment was administered, and the patient's condition improved. Analysis of whole blood revealed no induction of IFN-γ in response to IL-12. Phytohemagglutinin-activated T cells from healthy controls expressed IL-12Rß1, whereas phytohemagglutinin-activated T cells had no detectable IL-12Rß1 expression. The diagnosis was confirmed by the presence of the heterozygous c.1561C>T (p.R521*) mutation after Sanger sequencing and by a heterozygous 991-bp deletion encompassing exon 8 (Δ8) after copy number variation analysis [5]; each parent carried each of the pathogenic variants. During the following years, the patient was admitted to hospital on more than 30 occasions 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 and trimethoprim-sulfamethoxazole) and elective cholecystectomy (removal of a possible *Salmonella* reservoir). Recombinant IFN-γ was administered for more than a year, but recurrent episodes of purpura associated with *Salmonella* continued to occur. The *Salmonella enterica* serotypes *typhi*, *choleraesuis*, and *enteritidis* were isolated in all events in blood culture. At 7 years of age, persistent glomerular hematuria was evident, and a renal biopsy was performed. This revealed segmental mesangial hyperplasia, positive IgA with a granular pattern, positive IgM and C3, and negative C1q compatible with nephritis secondary to IgA vasculitis (Figure). The laboratory work-up revealed the following: 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 increased to 4.8 g in 24 hours, and the patient received methotrexate, rituximab, and cyclosporine at different times. She is currently receiving an immunomodulatory dose of intravenous immunoglobulin (IVIG), prophylactic antibiotics, enalapril, and low-dose oral corticosteroids. At least twice a year, she continues to present relapses of *Salmonella* species bacteremia, which are associated with palpable purpura, hematuria, and proteinuria.

Complete autosomal recessive IL-12Rβ1 deficiency has occasionally been associated with the presence of autoimmune complications, including systemic lupus erythematosus and Sjögren syndrome [1]. Additionally, several published reports describe the relationship between active *Salmonella* infection and the presence of leukocytoclastic vasculitis affecting small vessels of the skin [2-5]. It is striking that in the present case, the skin lesions disappeared when the infection was eradicated. IgA vasculitis affecting only the skin has been repeatedly described in this disease and responds to antibiotics [1,3-5]. Compared with other reports, in the present case, IgA vasculitis presented with nephritis. Since autoimmune manifestations in IL-12Rβ1 deficiency as a group are rare, no correlation has been established between the different pathogenic variants and the presence of autoimmunity. It is thought that recurrent or persistent infections induce an aberrant immune response predisposing affected 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].

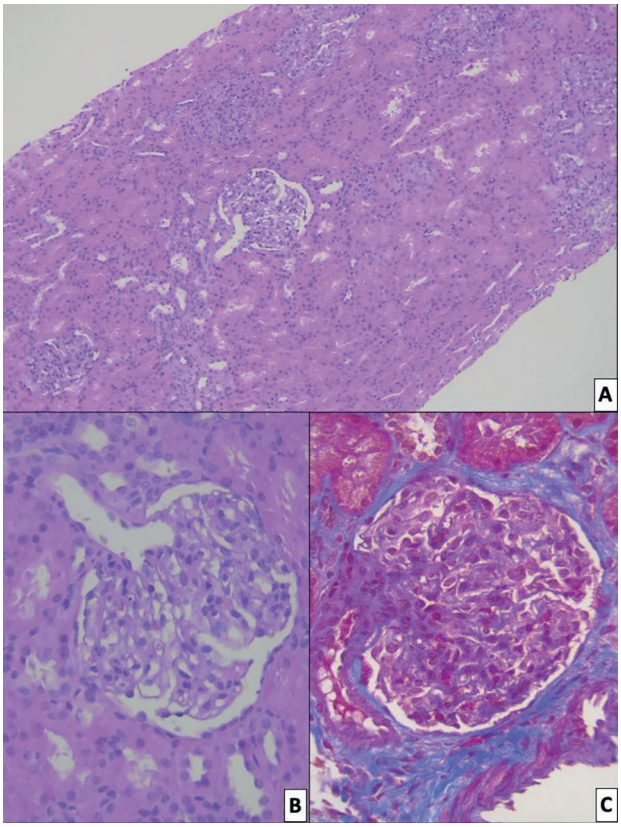


**Figure.** Histological sections of the kidney. A, Photomicrograph (×4) showing the presence of glomeruli with mesangial hyperplasia. B, Photomicrograph (×40) showing mesangial hyperplasia, which becomes evident with Masson trichrome stain (C).

Patients with autosomal recessive complete IL-12Rβ1 deficiency require lifetime prophylactic antibiotics to avoid recurrent infections and, in some cases, recombinant IFN-γ therapy [1]. In the case we report, the patient did not improve with this therapy. A clear etiological link has been established between *Salmonella* and IgA nephritis, as in the present case [8]. Every episode of vasculitic skin lesions was invariably associated with a positive *Salmonella* blood culture, giving proof to the concept that *Salmonella* is vital in the development of this autoimmune complication. Patients who present with susceptibility to infection and autoimmunity are particularly challenging. In the present case, systemic corticosteroids, immunosuppressive therapy, and regular infusion of IVIG were administered and led to 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 targeted by IVIG, enhancing uptake and killing by phagocytes in the spleen and liver. In addition, IVIG has several mechanisms of action in vasculitis, including downregulation of antibody synthesis, improved autoantibody clearance, and inhibition of complement damage, and has been administered with positive results in IgA

nephritis [9]. However, when the patient we report presents a new episode of *Salmonella* infection, renal symptoms reappear. Strong upregulation of IL-6 has been detected in lymphoid infiltrates in *il12rb2* knockout mice, thus suggesting a theoretical role for anti–IL-6 biologics, which were used successfully in a case of IgA vasculitis [10]. Hematopoietic stem cell transplantation has been performed [1]. Given that the condition is characterized by a varying clinical presentation with substantial genetic heterogeneity, the risk-benefit ratio of treatment must be assessed on a case-by-case basis.

To our knowledge, this is the first case of IL-12Rβ1 deficiency and IgA nephritis associated with *Salmonella* infection. IgA nephritis should be considered in all cases of IL-12Rβ1 deficiency that, in addition to purpura and infection, present with persistent hematuria and proteinuria.

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*Conflicts of Interest*

The authors declare that they have no conflicts of interest.

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