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CLINICAL CASE

# Waldenstrom hypergammaglobulinemic purpura as the initial manifestation of pediatric primary Sjogren's syndrome

## Púrpura hipergamaglobulinémico de Waldenstrom como manifestación inicial de Síndrome de Sjögren primario pediátrico

**Gabriela Romero[a], Camila Valdés[a,b], Natalie Alarcón[c], Katherine Aránguiz[a,b], Javiera Berho[a,b], Camila Downey[d], Claudio Arce[e], Alejandra King[a]**

[a]Departamento Inmunoreumatología, Hospital Dr. Luis Calvo Mackenna. Santiago, Chile.
[b]Departamento de Pediatría y Cirugía Infantil Oriente. Facultad de Medicina, Universidad de Chile. Santiago, Chile.
[c]Departamento Inmunoreumatología, Hospital Base Valdivia. Valdivia, Chile.
[d]Departamento Dermatología, Hospital Dr. Luis Calvo Mackenna. Santiago, Chile
[e]Departamento Anatomía Patológica, Hospital Dr. Luis Calvo Mackenna, Santiago, Chile

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**What do we know about the subject matter of this study?**

Hypergammaglobulinemic purpura of Waldenstrom (HGPW) is a clinical entity in adults that can be associated with systemic diseases such as systemic lupus erythematosus and Sjögren's syndrome. To date, it has been sporadically reported in the pediatric literature without details on its clinical presentation, evolution, associations, and prognosis.

**What does this study contribute to what is already known?**

This report describes a pediatric patient with HGPW as the initial manifestation of Sjögren's syndrome who required management with multiple immunosuppressants, with a favorable response to rituximab. This publication highlights the importance of considering HGPW within the differential diagnosis of cutaneous vasculitis in pediatrics and its association with systemic diseases.

## Abstract

Hypergammaglobulinemic Purpura of Waldenström (HGPW) is an uncommon benign condition that can be associated with rheumatic diseases. **Objective:** To report a clinical case of HGPW as the initial manifestation of primary pediatric Sjögren's syndrome (SS), an unknown condition in pediatrics, which makes its diagnosis and management challenging. **Clinical Case:** A 6-year-old female with symmetrical purpura on lower extremities, residual hyperpigmentation, ankle arthralgia, and recurrent leg edema without other manifestations. Laboratory tests showed eosinophilia, elevated erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA) titer 1/160 with speckled pattern, and rheumatoid factor (RF) as well as no cytopenia nor complement and urinalysis alterations. Skin biopsy showed leukocytoclastic vasculitis. Prednisone was started with a good response initially, but with recurrence of skin symptoms. After 4 months of treatment, a new analysis showed ANA titer

**Keywords:**
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Correspondence:
Gabriela Romero Morgado
gromero@calvomackenna.cl

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Luisa Schonhaut Berman

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1/1280 with speckled pattern, positive antibodies against extractable nuclear antigens (ENA) anti-Ro and anti-La, high serum immunoglobulin G (IgG) titers (2,900 mg/dL), hypergammaglobulinemia on serum protein electrophoresis, and normal Schirmer test. Recurrent parotitis was reported and salivary gland biopsy was compatible with SS. HGPW secondary to SS was suspected, therefore, she was treated with prednisone and hydroxychloroquine, then azathioprine and mycophenolate mofetil; she developed corticosteroid dependence and deterioration of her quality of life. She was treated with rituximab without recurrence at one year of follow-up. **Conclusions:** HGPW is a rare skin manifestation in pediatrics that can be associated with systemic diseases, thus it requires a comprehensive clinical and laboratory study, especially in diseases such as SS and systemic lupus erythematosus (SLE).

## Introduction

Hypergammaglobulinemic purpura of Waldenstrom (HGPW) was first described in 1943[1] and corresponds to a rare condition, characterized by episodes of recurrent, transient, nonthrombocytopenic purpura associated with edema. It mainly involves the lower extremities bilaterally and resolves with residual cutaneous hyperpigmentation. It may be accompanied by pruritus, burning sensation, and arthralgias. Triggering factors include increased sustained hydrostatic pressure, such as prolonged sitting, walking, wearing tight clothing, and exposure to heat. The duration of the lesions varies and can last up to 7 days, with recurring episodes at variable intervals, often up to once a week[2].

On the other hand, Sjögren's syndrome (SS) is a chronic systemic autoimmune disease characterized by the development of autoantibodies and inflammation of the exocrine glands, although other organs may also be affected[3]. It is the second most frequent rheumatologic disease in adults in the USA[4]. In children, its prevalence and incidence are unknown, with an increase in the number of reports in recent years, reaching more than 500 cases in 2020[5,6]. In a multinational cohort of primary SS, only 1.3% of 12,083 cases were diagnosed before the age of 19 years and, in this group, more than 80% of the patients were female with a mean age of symptom onset at 13.2 years old[6]. There are no Chilean epidemiological data on this pathology.

Pediatric SS has a wide spectrum of clinical presentations, and the classic manifestations of sicca syndrome (xerostomia and xerophthalmia) may be absent. Cutaneous involvement is reported in 6-29% of patients[3], with varied pictures including purpura, vasculitis, erythema annulare, erythema nodosum, cutaneous amyloidosis, and Raynaud's phenomenon[4]. In adults, HGPW is not uncommon as part of the cutaneous involvement of SS, however, in pediatrics, it is only described in case reports, with about 50 patients under 18 years of age published as of 2020 , with patients described as young as 2 years of age[2].

HGPW is classified as primary if it occurs in patients without comorbidities, or secondary when associated with systemic diseases. Initially, it was considered that, in childhood, most cases were primary, however, a recent publication by Theisen et al.[2] suggests that up to two-thirds of patients are diagnosed with a systemic disease in long-term follow-up. Reported pathologies include systemic lupus erythematosus (SLE), SS, cystic fibrosis, multiple sclerosis, immunodeficiency, primary sclerosing cholangitis, autoimmune hepatitis, mixed connective tissue disease, rheumatoid arthritis (RA), and Crohn's disease[7]. These data suggest that the diagnosis of HGPW in a patient younger than 18 years should include a thorough evaluation to rule out concomitant pathology.

The pathogenesis of HGPW is not fully elucidated. It is postulated that immune complexes, containing immunoglobulins (Ig) IgG, IgA, and/or rheumatoid factor (RF), would play a role in the development of the disease[8] by depositing in blood vessels. However, a series of 9 cases reported by Kimura et al. showed that serum IgG levels were not modified during episodes of purpura, suggesting that other mechanisms were involved in the appearance of HGPW[9]. It is worth mentioning that this entity has a benign course in adults and should not be confused with Waldenström's macroglobulinemia, a pathology of oncologic nature.

The objective of this work is to report the clinical case of a school patient with HGPW as the initial manifestation of a primary pediatric SS, a condition unknown in pediatrics, which poses a challenge in its diagnosis and management.

## Clinical Case

Female patient, eutrophic, with a history of asthma under treatment. At the age of 6 years, she presented purpuric macules and papules, some palpable, symmetrical, on lower extremities, from knee to distal, which resolved spontaneously with residual hyperpigmentation, associated with intense ankle arthralgia and

leg edema, of variable duration (from 24 to 72 hours), with no other symptoms (Figure 1). Initially, the purpura had a frequency of once a month, but after one year of evolution, it increased to once a week. The initial diagnosis of IgA vasculitis was proposed.

Two years later, at age 8, due to persistent symptoms, the patient was referred for evaluation by pediatric immuno-rheumatology. The initial study (Table 1) highlighted a complete blood count with eosinophilia, elevated HSV (70mm/hr), no cytopenias, ANA at 1:160 with speckled pattern, positive RF (202 IU/ml, normal value < 10 IU/ml), negative antistreptolysin O (ASO), negative anti-DNA, positive anti-neutrophil cytoplasmic antibodies (ANCAs) by direct immunofluorescence (DIF) at 1:160 with no availability of anti-MPO or PR3 antibodies at that time. C3-C4 complement levels and urinalysis were normal. A skin biopsy performed before referral was compatible with leukocytoclastic vasculitis.

Due to suspicion of eosinophilic granulomatosis with polyangiitis, a CT scan of the paranasal cavities was performed and showed multisinus inflammatory changes, without other findings and normal chest X-ray, with no respiratory symptoms. She did not meet the criteria for this pathology, therefore, 3 months after referral, small vessel vasculitis was postulated, and it was decided to start prednisone 1mg/kg/day for 2 weeks, with a progressive decrease.

She evolved with a good initial response to the use of corticosteroids, with absence of skin lesions for 2 months, but when the prednisone dose was reduced to 0.5mg/kg/day, she presented recurrence of cutaneous vasculitis with a frequency of once a month, with ankle arthralgia that hindered walking, so she consulted the emergency department for pain management with nonsteroidal anti-inflammatory drugs (NSAIDs). On one occasion she presented with distal purpura of the upper extremities. She also presented two episodes of parotitis, without xerostomia or xerophthalmia.

In a check-up 4 months after starting treatment, new tests were requested, highlighting ANA at 1:1280 with speckled pattern, negative ANCA by DIF with negative anti-MPO and PR3 antibodies, ENA with positive anti-Ro (> 200U) and positive anti-La (51 U), persistently elevated HSV (97 mm/hr), and IgG 2,900 mg/dL (normal range for age 858-1855 mg/dL). Parotid ultrasound showed signs of recurrent bilateral parotitis, and sialography showed normal results.

Due to recurrent parotitis and described serology, SS was suspected, thus hydroxychloroquine at 5mg/kg/day was indicated and she restarted prednisone at 1mg/kg/day which was progressively decreased to 0.5mg/day. She continued treatment for 3 months and then discontinued, referring to a lack of response, resuming check-ups at 11 years of age, where she reported recurrent purpura (2 episodes per month) and 3 parotitis episodes during that year, thus, the case was reevaluated. Table 1 describes the updated study. The persistence of hypergammaglobulinemia was highlighted, so protein electrophoresis was requested which showed polyclonal hypergammaglobulinemia. To complete the evaluation of SS and perform the differential diagnosis of vasculitis, serology tests for human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) were requested, all of which were negative. Negative VDRL, negative cryoglobulins, normal Schirmer's test, ankle ultrasound showed no signs of synovitis, and both chest X-ray and abdominal ultrasound were normal.

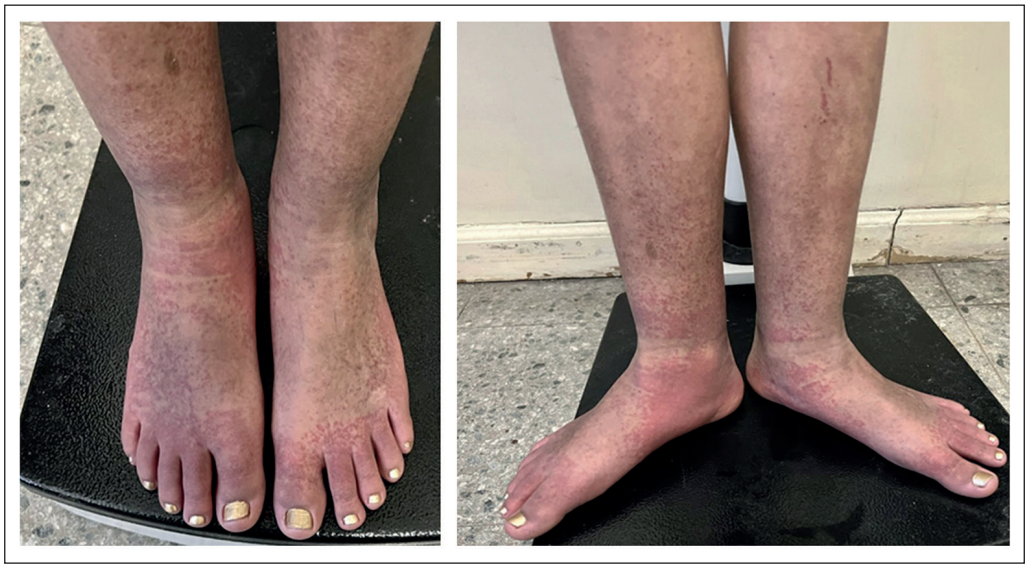

**Figure 1.** Patient images at the time of initial evaluation. Symmetrical purpuric macular and papular lesions are observed on the lower extremities, extending from the knees distally, associated with edema of the ankles and feet. Areas of hyperpigmentation are also visible, with no evidence of ulcers or crusting.

**Table 1. Summary of tests conducted since the initial evaluation in immunorheumatology**

| Evaluation | First (8 years old) | Second (9 years old) | Third (11 years old) |
|---|---|---|---|
| Laboratory | - ESR 70 mm/hr (N <20 mm/hr)<br>- ANA 1:160 speckled pattern (N: negative)<br>- ANCA by IIF positive, c-ANCA pattern 1:160 (N: negative)<br>- RF: 202 IU/mL (N <20 IU/mL)<br>- Anti-DNA: negative<br>- CBC: 10% eosinophils, no cytopenias<br>- Complement levels: C3 105 mg/dL, C4 12 mg/dL<br>- Urinalysis: normal | - ESR 97 mm/hr (N <20 mm/hr)<br>- ANA 1:1280 speckled pattern (N: negative)<br>- ANCA by IIF negative, anti-MPO and PR3 antibodies negative<br>- Anti-Ro antibodies (>200 U), Anti-La antibodies (51 U) | - Persistently elevated ESR<br>- IgG: 2,900 mg/dL (N: 858–1855 mg/dL)<br>- Serology for HIV, HCV, HBV negative<br>- Negative VDRL<br>- Negative cryoglobulins<br>- Protein electrophoresis: polyclonal hypergammaglobulinemia |
| Imaging | - Paranasal CT: multisinus inflammatory changes | - Parotid ultrasound: bilateral recurrent parotitis signs<br>- Salivary gland sialography: normal | - Ankle ultrasound: no synovitis signs<br>- Chest X-ray: unremarkable<br>- Abdominal ultrasound: normal |
| Biopsies | -Skin: leukocytoclastic vasculitis | | - Skin: superficial and deep perivascular dermatitis, focal purpuric with lymphoplasmacytic infiltrate containing eosinophils and occasional neutrophils, with focal nuclear dust. Immunofluorescence showed leukocytoclastic vasculitis with IgA deposits.<br>- Salivary glands: mild to moderate lymphoplasmacytic inflammation, mild fibrosis, and focal acinar atrophy, compatible with Sjögren's syndrome involvement. |
| Other Tests | | | - Schirmer test: normal |

Abbreviations: ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; Anti-DNA, anti-double stranded DNA antibodies; CBC, complete blood count; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; IIF, indirect immunofluorescence; MPO, myeloperoxidase; PR3, proteinase 3; RF, rheumatoid factor; VDRL, Venereal Disease Research Laboratory; N, normal.

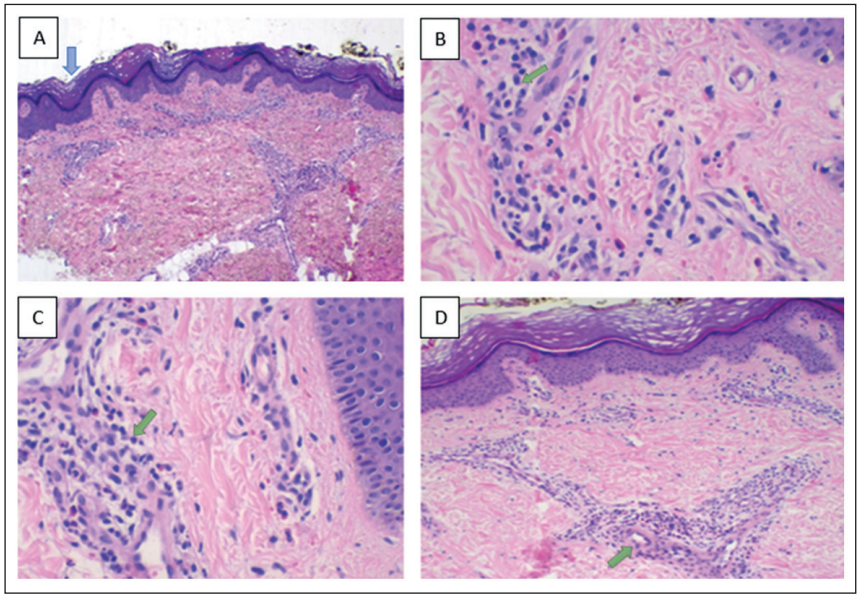


**Figure 2.** Skin biopsy from cutaneous lesions. Skin covered by squamous epithelium with a preserved appearance (Panel A, blue arrow). The superficial and deep dermis shows a perivascular inflammatory infiltrate composed of lymphocytes, plasma cells, eosinophils, and occasional interstitial neutrophils, with focal nuclear debris (Panels B, C, and D, green arrows). Scant extravasated red blood cells are noted. No microorganisms, mucin deposits, fibrinoid necrosis, or vascular wall degeneration are observed.

A new skin biopsy was collected (Figure 2) with immunofluorescence, reporting leukocytoclastic vasculitis with IgA, C3, and fibrin deposits in capillary vascular walls and immunoglobulin M (IgM) in subepidermal cytoid bodies. Salivary gland biopsy shows mild to moderate lymphoplasmacytic inflammation with mild fibrosis and focal acinar atrophy, compatible with SS involvement.

After multidisciplinary evaluation with rheumatology, immunology, and dermatology, a diagnosis of HGPW secondary to primary SS with glandular and cutaneous involvement was postulated. Prednisone at 1mg/kg/day was started with hydroxychloroquine at 5mg/kg/day and as a corticosteroid-sparing drug, azathioprine at 2mg/kg/day, showing isolated episodes of purpura in lower extremities (2 recurrences in 5 months, with no associated pain), without new episodes of parotitis or other symptoms, however, when reducing systemic corticosteroids doses to prednisone at 7.5 mg/day, the patient reported that purpuric lesions recurred (again with pain and 2 times per month) mainly when standing for long periods, performing physical activity, traveling by plane, or on hot days.

A change from azathioprine to mycophenolate mofetil at 690mg/m$^2$/day was indicated, with maintenance of hydroxychloroquine and suspension of prednisone, as well as measures to avoid physical triggers, with excellent clinical response for 6 months, then with recurrence of skin symptoms weekly, compromising her quality of life. It was decided to administer rituximab at 750 mg/m$^2$ in two doses (day 1 and 15), evolving asymptomatic at one year of follow-up, maintaining only the use of hydroxychloroquine.

## Discussion

The diagnosis of HGPW in pediatrics is challenging. The clinical picture of the patient described in this report is quite classic; however, the diagnosis was complex given the low frequency of the pathology in this age group and the low suspicion of this condition. Among the differential diagnoses in pediatrics, pigmented purpuric dermatoses, idiopathic leukocytoclastic vasculitis, essential mixed cryoglobulinemia, and hypocomplementemic vasculitis should be considered[10]. In the laboratory study of HGPW it is common to find polyclonal hypergammaglobulinemia, with increased levels of IgG and sometimes IgA or IgM; elevated HSV, positive RF, positive anti-Ro/La and ANA antibodies, mild anemia, and leukopenia[11]. Unlike other vasculitides, HGPW does not have renal or intestinal involvement, and compared to pigmented purpuras, the latter do not have edema and have a chronic course. Histopathology is a useful tool, however, biopsy in HGPW is nonspecific, usually finding erythrocyte extravasation with mild perivascular lymphocytic infiltrate or, occasionally, leukocytoclastic vasculitis.

It is worth mentioning that the patient was initially diagnosed as an IgA vasculitis since she fulfilled EULAR/PRINTO/PRES classification criteria due to the cutaneous involvement and the biopsy describing leukocytoclastic vasculitis with IgA deposits[12], however, these criteria have 93% of sensitivity and 89% of specificity[13]. After the multidisciplinary evaluation with rheumatology, immunology, and dermatology, the most likely diagnosis seems to be HGPW, as the condition was associated with persistent IgG hypergammaglobulinemia, without multisystem involvement (renal, gastrointestinal, others), and recurrences over 5 years. This was in association with SS, which is the pathology most frequently related to HGPW in adults [2]. In contrast, IgA vasculitis has not been described to date as being related to SS. Although there are exceptional cases, cutaneous recurrences of IgA vasculitis are mostly manifested during the first year after the onset[13], while HGPW has a prolonged course, as in this patient. Similar cases have been reported in the literature in pediatric patients with biopsies showing leukocytoclastic vasculitis. Additionally, two cases have described immunocomplexes composed of IgA in skin biopsy[14,15,16], as observed in this patient.

The treatment of HGPW secondary to autoimmune diseases is not standardized. A study published in 1995 reported that indomethacin and hydroxychloroquine could be useful in the treatment of mild HGPW, while corticosteroids would be useful in severe forms[17]. Cases of this condition with good response to colchicine have been published[18,19], whose mechanism of action in this context is unknown. In 2013, the use of rituximab with good results was reported in a patient previously treated with hydroxychloroquine and azathioprine[20,21]. Bortezomib has also been proposed as a therapeutic option[22].

In this case, the use of systemic corticosteroids was initially decided, despite the absence of involvement of other organs, due to the affectation in the quality of life by arthralgias and edema. Subsequently, treatment with hydroxychloroquine and azathioprine was initiated; however, the patient showed a corticosteroid-dependent course. Therefore, mycophenolate was started due to its effects on both cellular and humoral immunity, initially achieving a good response. However, the condition recurred, leading to the eventual decision to use rituximab, which resulted in complete symptom remission after one year of follow-up.

## Conclusions

HGPW is an infrequent cutaneous manifestation in pediatrics with a benign course but is associated in most cases with a systemic condition, mainly connective tissue diseases such as SLE and SS, so it requires a comprehensive clinical and laboratory evaluation, with emphasis on these pathologies. The reported case exemplifies the diagnostic and therapeutic challenge involved, in addition to the importance of incorporating this condition in the differential diagnosis of non-thrombocytopenic purpura.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

## Financial Disclosure

Authors state that no economic support has been associated with the present study.

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