



## Leukocytoclastic vasculitis due to reactivation of virus varicella zoster. Case report

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### ABSTRACT

Vasculitis is an inflammatory process of blood vessels, which can affect vessels of different calibers causing necrosis of tissues and organs. The type of vasculitis with the highest incidence is the cutaneous one called leukocytoclastic vasculitis (LCV) through mainly by a hypersensitivity process or formation of immune complexes to different known and unknown factors. The diagnosis of LCV includes a large number of laboratory and imaging parameters aimed at ruling out systemic disease, which causes delay in starting treatment, prolongation of ischemia and increased tissue damage. The fundamental contribution of the present report case is to show the importance of timely diagnosis of skin limited small vessel LCV to apply an early therapeutic scheme that produces the least possible damage to the affected tissue. A case of a 54-year-old female patient is presented with mucosal and cutaneous manifestations of reactivation of the varicella-zoster virus as a triggering factor for LCV. An adequate protocol was proposed to diagnose through anamnesis and exhaustive physical examination that would allow guiding the paraclinical evaluation to rule out a systemic disease and to obtain a comprehensive and timely therapeutic approach with short-term resolution of the pathology.

**Keywords:** Leukocytoclastic vasculitis, cutaneous vasculitis, varicella zoster virus.

### Vasculitis leucocitoclástica originada por reactivación de virus varicela zóster. Reporte de caso

#### RESUMEN

La vasculitis es un proceso inflamatorio de vasos sanguíneos que puede afectar vasos de diferentes calibres, produciendo necrosis

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de tejidos y órganos; el tipo de vasculitis con mayor incidencia es la cutánea denominada vasculitis leucocitoclástica (LCV) mediada principalmente por un proceso de hipersensibilidad o formación de inmunocomplejos a diferentes factores conocidos y desconocidos. El diagnóstico de LCV incluye gran cantidad de parámetros de laboratorio e imagenológicos para descartar enfermedad sistémica, lo que ocasiona retardo en la instauración del tratamiento, prolongando la isquemia y aumentando el daño tisular. El aporte fundamental del presente reporte de caso es evidenciar la importancia del diagnóstico oportuno de LCV de pequeños vasos limitada a piel con la finalidad de aplicar un esquema terapéutico precoz que produzca el menor daño posible del tejido afectado. Se presenta el caso de paciente femenino de 54 años de edad con manifestación mucosa y cutánea de reactivación del virus varicela zóster como factor desencadenante de LCV, proponiendo un adecuado protocolo para diagnóstico, mediante una anamnesis y exploración física exhaustiva que permitió la orientación de la evaluación paraclínica guiada al descarte de enfermedad sistémica, obteniendo un abordaje terapéutico integral y oportuno con resolución de la patología a corto plazo.

**Palabras clave:** Vasculitis leucocitoclástica, vasculitis cutánea, virus varicela zóster.

### INTRODUCTION

Vasculitis is defined as inflammation of the blood vessel wall, characterized by white blood cell invasion causing reactive damage to the wall structures and loss of tissue integrity,<sup>1</sup> causing deterioration and rupture with bleeding or obstruction of the flow of blood originating ischemia and distal necrosis.<sup>2</sup> This pathology encompasses a group of diseases, which have been classified based on clinical and histological data,<sup>3</sup> being the most accepted classification the proposal at the Chapell-Hill International Council Conference in 1994, revised in 2012,<sup>4</sup> mainly taking into account the size of the affected vessels<sup>5</sup> (Table 1). Considering the heterogeneous nature of vasculitis and the limited knowledge of its causes, it is difficult to establish adequate subgroups, since the diagnosis does not depend on a single pathognomonic test, various criteria must be considered for its categorization.<sup>6</sup> The etiological factors of vasculitis are diverse

and include infectious agents (15-20% of cases), inflammatory diseases (15-20%), medications (10-15%), malignancies (5%), and the highest percentage of cases (45-55%) without an etiological diagnosis.<sup>7</sup>

Skin lesions in different types of vasculitis are very common and can be the only manifestation of the disease (skin limited vasculitis) or they can form part of a systemic condition (systemic vasculitis), affecting one or more organs.<sup>8</sup> According to the clinical evolution, three patterns can be observed in cutaneous vasculitis:<sup>9</sup>

- 1) Acute episode of spontaneous relief, which is generally associated with infectious processes or administration of medications.
- 2) Recurrent episodes of vasculitis with disease-free periods, which can be observed in patients with Henoch-Schönlein purpura and cryoglobulinemia.

- 3) Chronic course without remission of the clinical presentation of vasculitis, which occurs mainly in systemic primary vasculitis.<sup>9</sup>

The timing of the episode of cutaneous vasculitis is highly variable, it can take from one week to 318 months, with an average duration of 28 months, only suffering from a systemic condition. Only 20% of patients suffer from systemic affection and less than 7% experience fatal condition.<sup>8</sup>

Leukocytoclastic vasculitis (LCV) is the most frequent type of cutaneous vasculitis in clinical practice,<sup>10</sup> also known as leukocytoclastic angitis or hypersensitivity vasculitis or necrotizing cutaneous venulitis.<sup>11</sup> It affects the small vessels (capillaries, arterioles, and venules less than 50 microns), it is seen in women and men, and can occur at any age.

**Table 1: Skin involvement status by category of vasculitis and disease.**

CHCC2012 vasculitis category, name	Skin involvement status	
	Cutaneous component of systemic vasculitis	Limited or dominant skin variant
<b>Large vessel vasculitis</b>		
Takayasu arteritis	No	No
Giant cell arteritis	Rare	No
<b>Medium vessel vasculitis</b>	Yes	Yes
Polyarteritis nodosa	Yes	Yes
Kawasaki disease	No	No
<b>Small vessel vasculitis</b>		
Microscopic polyangiitis	Yes	Yes
Granulomatosis with polyangiitis	Yes	Yes
Eosinophilic granulomatosis with polyangiitis	Yes	Yes
Anti-glomerular basement membrane disease	No	No
Cryoglobulinemic vasculitis	Yes	Yes
IgA vasculitis (Henoch-Schönlein)	Yes	Yes
Urticarial hypocomplementemic vasculitis (anti-C1q vasculitis)	Yes	Yes
<b>Variable vessel vasculitis</b>		
Behçet's disease	Yes	Yes
Cogan's syndrome	Rare	No
<b>Vasculitis associated with systemic disease</b>		
SLE, rheumatoid vasculitis, sarcoid vasculitis, etc.	Yes	Yes
<b>Vasculitis associated with probable etiology</b>		
Drugs, infections, sepsis, autoimmune diseases, etc.	Yes	Yes
<b>Cutaneous SOV (not included in CHCC2012)</b>		
IgM/IgG vasculitis	No (not observed yet)	Yes (as SOV)
Nodular vasculitis (erythema induratum of Bazin)	No	Yes (as SOV)
Nodular vasculitis (Bazin's indurated erythema)		
Erythema elevatum et diutinum	No	Yes (as SOV)
Hypergammaglobulinemic macular vasculitis	No	Yes (as SOV)
Normocomplementemic urticarial vasculitis	No	Yes (as SOV)

CHCC2012 = 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides; SLE = systemic lupus erythematosus; SOV = single-organ vasculitis.

The etiopathogenesis is complex because multiple causes have been reported and pathophysiological mechanisms are involved,<sup>12</sup> being the most known, but not the only one, the hypersensitivity type III or mediated by immunocomplex.<sup>13</sup> In the latter, the endogenous or exogenous antigen deposits on the endothelium are recognized by the antibodies, activating the complement cascade (C3, C4 and C5a), chemokine deposits cause chemotaxis mainly of neutrophils, phagocytose the antigen-antibody complex and cause vascular damage from lysosome enzyme release.<sup>5</sup> Furthermore, the release of IL1 and TNF- $\alpha$  favors the expression of P-selectin, E-selectin, ICAM-1, and VCAM-1 that bind to the Sialil Lewis, LFA-1, MAC1, and VLA4 proteins allowing the cellular passage of intravascular to extravascular or diapedesis.<sup>14</sup> LCV is clinically manifested as livedo reticularis and purpuric lesions<sup>15</sup> that generally measure from 0.3 to 0.6 cm in diameter can fuse and form extensive areas of skin involvement with devitalized tissue and risk of superinfection. Sometimes erythematous papules, vesicles, bullae, pustules, ulcers, accompany these purpuric lesions or ring-shaped plaques found on the lower extremities or in declining areas.<sup>8</sup> The subclassification of the pathology proposed in 2014 (Table 2) allows a greater approximation of the diagnosis, according to its histopathology.<sup>12</sup>

Related to the diagnosis of LCV, it is usually late, the response to treatment is variable, obtaining in most cases resolution in weeks or months, and in very few cases (10%), the patients experience recurrent or chronic disease.<sup>16</sup> For this reason, the evaluation requires a complete anamnesis focused on the background of chronic inflammatory diseases, administration of new drugs or recent infections,<sup>5</sup> excluding clinically obvious causes of vasculitis of other organs or systemic vasculitis, such as respiratory distress, cough, hemoptysis, hypertension, edema, weakness, paraesthesia, abdominal pain, diarrhea, bloody stools, arthralgia, fever.<sup>17</sup> Laboratory data include a complete blood count, erythrocyte sedimentation rate, renal function tests, cryoglobulins, antineutrophil cytoplasmic antibodies (ANCA), C3 and C4 complement level, rheumatoid factor, blood culture, antibodies to hepatitis B and C viruses, protein electrophoresis.<sup>15</sup> Also imaging tests such as chest X-ray, paranasal sinus radiography, abdominal echo-sonogram, computed tomography, magnetic resonance imaging, angiography, etc., should be performed when the indications of some affected organs require it.<sup>17</sup> The microscopic study or biopsy of the tissue is essential, characterized by fibrinoid-like necrosis, endothelial damage, invasion of

**Table 2: Summary of subtypes and etiologies of leukocytoclastic vasculitis.<sup>12</sup>**

Subtype	n (%)
Palpable purpura (predominant) CSVV (N = 38)	
Idiopathic	29 (76.0)
ACTD <sup>a</sup>	2 (5.0)
Infection <sup>b</sup>	6 (16.0)
Drug reaction <sup>c</sup>	1 (3.0)
IgA vasculitis (N = 25)	
Idiopathic	24 (96.0)
Infection <sup>d</sup>	1 (4.0)
ANCA-associated vasculitis (N = 8)	
Microscopic polyangiitis	1 (12.5)
Granulomatosis with polyangiitis	2 (25.0)
Eosinophilic granulomatosis with polyangiitis	2 (25.0)
p-ANCA, NOS	2 (25.0)
c-ANCA, NOS	1 (12.5)
Cryoglobulinemic vasculitis (N = 3)	
ACTD <sup>e</sup>	1 (33.0)
Infection <sup>f</sup>	2 (67.0)
Urticaria like infection	
Urticarial vasculitis (N = 10)	
Normocomplementemic	8 (80.0) <sup>g</sup>
Idiopathic	6 (75.0)
Infection <sup>h</sup>	1 (12.5)
Drug reaction <sup>i</sup>	1 (12.5)
Hypocomplementemic	2 (20.0)
ACTD <sup>j</sup>	2 (100.0)

ACTD = autoimmune connective tissue disease; ANCA = antineutrophil cytoplasmic antibody; c-ANCA = cytoplasmic ANCA; CSVV = cutaneous small-vessel vasculitis; NOS = not otherwise specified; p-ANCA = perinuclear ANCA. <sup>a</sup>Sjögren syndrome and systemic lupus erythematosus in one patient each. <sup>b</sup>Hepatitis C in two patients and hepatitis B and C, parvovirus, pneumonia, and streptococcal infection in one patient each. <sup>c</sup>Amoxicillin. <sup>d</sup>Streptococcal infection. <sup>e</sup>Rheumatoid arthritis. <sup>f</sup>Hepatitis C. <sup>g</sup>Complements were not checked in two patients. <sup>h</sup>Hepatitis C. <sup>i</sup>Epoetin alfa. <sup>j</sup>Systemic lupus erythematosus and mixed connective tissue disease in one patient.

neutrophils in the vascular walls, nuclear fragments of neutrophils (leukocytoclasia), extravasation of erythrocytes, and monoclonal inflammatory infiltrate with a predominance of neutrophils and eosinophils in acute processes.<sup>5</sup> There is no specific therapeutic scheme, it includes elimination or treatment of the triggering factor (if present), rest with elevation of the lower limbs, cold compresses, antihistamines (in mild VCL), NSAIDs, hemorrhagic agents, antimalarial agents, sulfones, colchicine, glucocorticoids, cyclophosphamide, chlorambucil, azathioprine, methotrexate, cyclosporine, monoclonal antibodies, immunoglobulins, plasmapheresis, depending on the type of vasculitis.<sup>5,17</sup>

LCV triggered by the varicella-zoster virus (VZV) has been reported in low frequency. This virus is

establishes itself in the cranial, spinal, and autonomic ganglia. It and replicates almost exclusively in human cells and tissues due to superficial receptors on cells for the anchorage of viral proteins,<sup>18</sup> causing, either by primary infection or by reactivation, a wide range of diseases such as herpes zoster, postherpetic neuralgia, vasculopathy, myelopathy, retinal necrosis, cerebellitis and non-herpes zoster.<sup>19</sup> Its reactivation and complications are frequently associated with immunosuppression situations, within them in the inflammatory action that compromises small and medium vessels through immune-mediated pathophysiological mechanisms with inflammatory lesions.<sup>18</sup>

### CASE REPORT

A 54-year-old female patient was referred to the Oral Pathology Clinic for consultation. She had severe pain in the lateral zone of the right palate for five days, pruritic lesions on the skin of the lower limbs and abdomen dated 10 days, some of them beginning as small macular lesions which evolve in size and number, transforming into ulceration, she presented a concomitant episode of anxiety, without medication. The patient signed the corresponding informed consent.

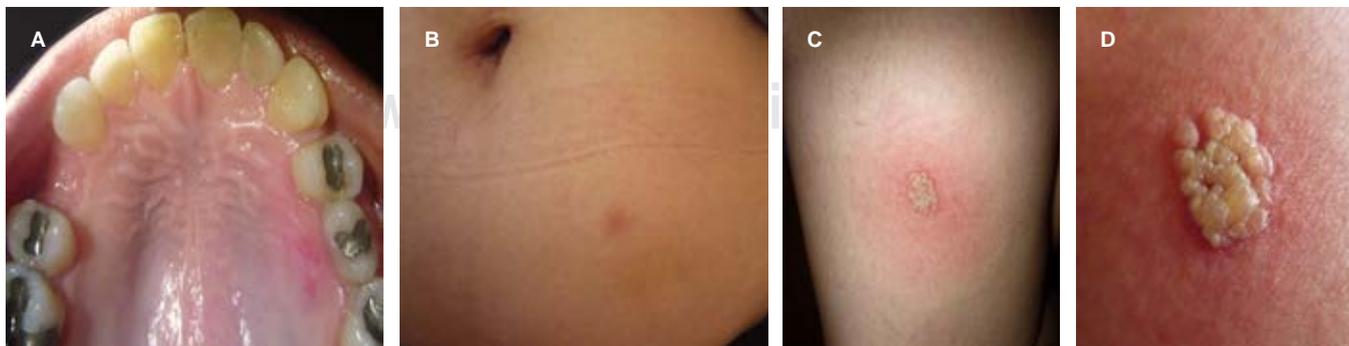
Background: lesions due to reactivation of the varicella-zoster virus three years ago, hypothyroidism for five years complying with the scheme with levothyroxine 50 mg/day. Standard vital signs. On intraoral physical examination, she presented punctate ulceration on an erythematous base in the right lateral palatal mucosa adjacent to the teeth 24 (*Figure 1A*). Extraoral observation showed, multiple erythematous lesions (dermatomes) were evident, located in the lower-left hypogastric region (*Figure 1B*), and the rest disseminated in the lower limbs, one of them

accompanied by centrally distributed vesicles, located in the right anterior femoral region (*Figure 1C and 1D*).

A presumptive diagnosis of skin-limited leukocytoclastic vasculitis was made due to reactivation of the varicella-zoster virus to detect signs or symptoms that suggested the involvement of other organs. The modified laboratory protocol<sup>20</sup> was indicated, obtaining standard values in complete hematology, blood chemistry (glycemia, cholesterol, triglycerides, urea, creatinine, ALT/AST, bilirubin). PT, PTT, urinalysis, coprology (fecal occult blood), serum IgA, antinuclear antibodies (ANA), and anti-neutrophil cytoplasmic antibodies (ANCA). An incisional skin punch biopsy was performed, hematoxylin and eosin staining, confirming the clinical diagnosis by reporting polymorph nuclear perivascular inflammatory infiltrate with a predominance of neutrophils, nuclear debris, fibrinoid necrosis, extravasated red blood cells, and focal epidermal necrosis. The therapeutic approach consisted of oral prednisolone (20 mg/day for 15 days; 10 mg/day for 10 days; 5 mg/day for 5 days). In addition, long-acting acyclovir (Acyclovir AP 1 g/12 hours for 30 days), ibuprofen (400 mg/every 8 hours for three days), alprazolam (0.5 mg tablets/inter-daily × 30 days), chlorhexidine gluconate (Peridont®) 0.12% + benzylamine 15% (mouthwash three times a day for seven days), iodopovidone spray. Favorable evolution was observed when all the lesions were resolved in the short term (*Figure 2A-2C*). After 10 months, post-inflammatory hyperpigmentation is observed (*Figure 2D*).

### DISCUSSION

Among small vessel vasculitis, leukocytoclastic vasculitis is the one reported with the highest incidence. Occasionally, its diagnosis has become a challenge for the clinician, considering that in most



**Figure 1:** **A)** Herpes zoster virus reactivation erythema palatal mucosa. **B)** Reactivation of herpes zoster, dermatome in the abdominal region. **C)** Reactivation of herpes zoster, dermatome in femoral region. **D)** Dermatome and vesicles in femoral region.



**Figure 2:** **A)** LCV (purples) posterior region of the right lower limb. **B)** LCV (ulcers) posterior region of the left lower limb. **C)** Resolution after treatment in the region of the left lower limb. **D)** Post-inflammatory hyperpigmentation of the left lower extremity.

cases no associated factor (idiopathic) is known. The parameters used to categorize the LCV may overlap according to different authors, so its treatment must be individualized according to the type of injury, cause, local or systemic condition, and the severity of the episode.<sup>21</sup> Suspicious symptoms of systemic vasculitis include fever, sweating, asthenia, weight loss, arthralgia, and myalgia; although these symptoms may be nonspecific, their absence does not rule out systemic vasculitis,<sup>22</sup> which requires their inclusion as a diagnostic possibility.

Pharmacological etiology of LCV is performed by exclusion, since it is presumed that some drugs act as haptens, among many drugs, the famciclovir is one of them.<sup>13</sup> When ruling out the drug cause, viral infections should be considered as a trigger, especially if there is no other apparent factor,<sup>23</sup> even when the infection is not clinically tangible. The spread of the varicella-zoster virus is a complication of variable frequency with high morbidity that requires rapid management based on high clinical suspicion.<sup>18</sup> Treatment must anticipate complications by starting a specific and early program. Acyclovir in full dose seems to be the most effective agent,<sup>19</sup> so in LCV caused by this virus (as is the case presented), the therapeutic approach involves acyclovir as an essential element since by attenuating the triggering factor, it inhibits replication and minimizes the potentiation capacity of the viral microorganism, due to steroid therapy.

Most of the authors indicate mild antihistamines and NSAIDs as pharmacological treatment of LCV.<sup>5</sup> However, it is extremely important to ensure the cessation of the very short-term vascular damage provided by steroids. In vasculitis processes, due to its multiple etiological factors, a long time is consumed

between the onset of the disease and establishing the therapeutic scheme due to the variety of complementary parameters that must be obtained on many occasions, which can affect more blood vessels aggravating the manifestation of pathology. For this reason, it is considered of utmost importance to carry out an accelerated diagnostic protocol and establish the therapeutic scheme as soon as possible.

In the exposed case, despite the clinical reactivation by the varicella-zoster virus, which allowed a diagnostic guide, an interdisciplinary approach was performed, ruling out systemic factors throughout the clinic and laboratory, applying a simplified protocol, and establishing therapeutics as soon as possible to avoid the appearance of more lesions than the existing ones. Taking into consideration that the manifestations of cutaneous vasculitis can be the first sign of a generalized disease, it should not be considered as limited without evaluating its evolution for at least six months, since other signs that suggest systemic pathology could develop.<sup>1</sup> In the evaluation of the case 10 months after treatment, no other signs were found, maintaining a diagnosis of leukocytoclastic vasculitis due to infection.

A palate biopsy was not performed because herpes lesions in this area are characteristic, as are herpes zoster virus lesions, which have their clinical manifestations and a clinical diagnosis is made. A professional with clinical experience can quickly diagnose them. Along with the erythematous lesions by herpes zoster virus and with the patient's history, spots or macules are seen in contrast, which indicates that there was spontaneous blood extravasation, without associated factors. These macules turned into ulcerated lesions, which is characteristic of vasculitis

processes, where blood extravasation occurs first when there is a rupture of the vessels, then there is necrosis, and then the ulcer is seen. Finally, it is important for the diagnosis, to establish the relationship with the initial pathology due to the herpes zoster virus that triggered the vasculitis process.

## CONCLUSION

Leukocytoclastic vasculitis is the most common cutaneous vasculitis. Its causes can be multiple, and it can be idiopathic, so diagnosis can become a challenge for the clinician and treatment must be individualized according to the patient. The time that elapses between diagnosis and the establishment of the therapeutic scheme should be as short as possible, to avoid further damage to affected tissues. In the case of skin-limited small vessel LCV in which the etiological factor can be quickly identified, initiating adequate therapy early, the prognosis is quite favorable with short-term resolution. It is extremely important to take into account the medicinal and infectious factors through a correct anamnesis and a thorough physical examination, accompanied by an adequate laboratory protocol that can guide the diagnosis of the type of vasculitis for the timely initiation of treatment.

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