

Leukocytoclastic Vasculitis Secondary to Methotrexate: Case Presentation and Literature Revision

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Abstract

Leukocytoclastic vasculitis (LV) is one of the most common types of vasculitis. The pathology can be caused by infection, systemic autoimmune conditions, malignancies or medication. Leukocytoclastic vasculitis caused by medication represents 20% of the total cases. Several drugs can produce this pathology such as: antibiotics, antihypertensive, NSAIDs, antifungals, antivirals, immunosuppressive, and blood-thinning medications, among others. Methotrexate, anti-mitotic and immunosuppressive medication, is used for the treatment of illnesses such as vasculitis, malignancies, psoriasis and rheumatoid arthritis as a disease-modifying treatment. Until now, there are rare cases reported in the literature of LV secondary to the trial of methotrexate. The case of a 57 year old male patient is presented. The patient presented biopsy confirmed LV after daily administration of methotrexate as psoriasis disease treatment.

Keywords: Methotrexate; Vasculitis; Leukocytoclastic; Psoriasis

Abbreviations: LV: Leukocytoclastic Vasculitis; MTX: Methotrexate; DNA: Deoxyribonucleic Acid; RNA: Ribonucleic Acid

Introduction

Leukocytoclastic vasculitis (LV) is the most common vasculitis condition observed in the dermatological

practice. The condition was described as a differentiated entity in 1948 by Zeek who stated that the disease was caused by hypersensitivity mechanisms. The illness is also known as hypersensitivity vasculitis and it can be identified as a group of small and light cutaneous skin vasculitis that affects skin predominantly. Skin vasculitis is present in 15.4 people a year in a million of inhabitants

[1-2]. Leukocytoclastic vasculitis shows a varied etiology, in a third of patients, it is idiopathic.

Infectious diseases represent the 22% of the cases, being the most frequently found those that affect the upper respiratory tract (as beta-hemolytic streptococcus), Human Immunodeficiency Virus (HIV). Hepatitis A, B and C as well as parvovirus B19, among others. Systemic Autoimmune diseases represent 10-15% of skin vasculitis, from where the most frequent are rheumatoid arthritis, systemic lupus erythematosus, Sjögren, dermatomyositis, antiphospholipid syndrome, systemic vasculitis associated with ANCA, Behcet disease and polyarteritis nodosa. There are some cases of inflammatory bowel disease, autoimmune hepatitis, primary biliary cirrhosis, sarcoidosis, cystic fibrosis associated with LV. Equally, neoplasms are an extremely rare cause of this type of vasculitis, it presents in less than 1% of the cases. Close to 20% of LV cases are associated with the intake of several drugs, as in the case herein studied [2-5].

Case Presentation

This document presents the case of a 57 year old patient with a year history of type 2 diabetes mellitus precedent treated with metformin 850 mg every 12 hours, psoriasis in x-ray from 37 years now, treated with weekly methotrexate (MTX) 7.5 mg, dose that patient took by mistake every day during a year. One month previous to medical visit, patient presented unquantified fever, general unrest, several melanic evacuations and vomit of gastric content 6 times. The patient is diagnosed with food poisoning due to the referral of a recent ingestion of sea food, for he was treated with metronidazole and levofloxacin for 3 days.

The patient didn't show any improvement and related that 3 days after initiated the treatment, a bilateral swelling was presented as well as multiple blisters in his lower limbs; reason why the patient decided to get to the hospital. The patient was admitted when several symptoms were observed such as algal facies and jaundice as well as the presence of a clean erythematous substrate oval ulcer of well-defined uneven edges of 2 cm diameter located in the inferior lip (Figure 1), a black spot in the tongue (Figure 2) and bilateral parotid hypertrophy. The inferior limbs presented symmetric bilateral disseminated dermatosis at the pre-tibia region constituted by petechial, tense blisters of hematic content (Figure 3) and several circular lesions. The rest of the physical exam presented no other alterations.



Figure 1: Uneven edges of 2 cm diameter located in the inferior lip.



Figure 2: A black spot in the tongue.



Figure 3: Tense blisters of hematic content and several circular lesions.

The initial clinical diagnoses were secondary mucositis to methotrexate, hairy black tongue for viral or fungal etiology to be discarded as well as probable secondary to drugs vasculitis. Diagnosis approach was initiated by obtaining a biopsy of the lesions which resulted into a compatibility of leukocytoclastic vasculitis (Figure 4).

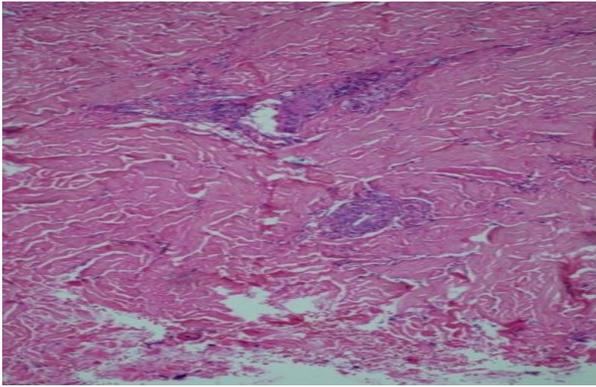


Figure 4: Compatibility of leukocytoclastic vasculitis.

Furthermore, a cytological exam of the blister content was performed from which abundant lymphocytes were reported. A lesion culture was also performed deriving into the development of *S.Epidermidis*. Subsequently, the search for systemic complications was initiated. Laboratory tests were performed with results of glucose 146 mg/dl, urea 15.6 mg/dl, creatinine 1.1 mg/dl, total protein 6.1 mg/dl, total bilirubin 8.10 mg/dl, direct bilirubin 3.7 mg/dl, indirect bilirubin 4.4, AST 95 UI/L, ALT 53 UI/L, LDH 307 UI/L, Hb 14.5 mg/dl, Hto 40.7%, mean corpuscular volume of 113.7 fl, leukocytes $13 \times 10^9/L$, neutrophils $80.6 \times 10^9/L$, lymphocytes $5.4 \times 10^9/L$, blood platelets $88 \times 10^9/L$, PT 30.2 seconds, PTPP

54.7 seconds, INR 2.38 and negative viral load test for HIV.

Once altered hepatic function values were obtained, an abdominal ultrasound was required. The study delivered diffuse liver disease, splenomegaly and the presence of liquid consistent with ascites. Treatment with enoxaparin, albumin, furosemide and spironolactone. As for psoriasis, there were no visible plaque for treatment start. Blisters and inferior limp ulcer gave in to the application of sulphate fomentas as well as a 20 day treatment with high strength steroids as fluocinolone. The remaining trace was a residual spot. The culture taking resulted into a diagnosis of *Candida albicans* treated with a 20 day nystatin suspension 100 000 UI presenting an improvement of the injury. The patient showed improvement so hospital discharge was mandated along with a continuous care in an outpatient basis.

Discussion

The etiology for LV drugs is rare and reaches the 20%. The classification of vasculitis can be complicated, they are classified into primary or secondary according to the size of the vessels they impair. Currently, there are 2 different ways of classifying LV, the first one suggested by de American College of Rheumatology (ACR) and the second one proposed by the Conference of Chapel Hill Consensus (CHCC). The most notorious difference among them is that the first classification names this type of vasculitis as hypersensitivity whereas the second one defines it as skin leukocytoclastic vasculitis. The nomenclature of CHCC was released for the first time in 1994. Afterwards, in the year 2012, new terms were added such as dermal vasculitis and some of the pre-existing terms were also modified. The general accepted terminology in CHCC is shown in (Table 1) [6-11].

Group	Nomenclature
High vessel vasculitis	• Takayasu arteritis Giant cell arteritis (5) (7) (10)
Midsize vessel vasculitis	• Kawasaki disease • Polyarteritis nodosa (5) (7) (10)
Midsize vessel vasculitis	• Kawasaki disease Polyarteritis nodosa (5) (7) (10)
Small vessel vasculitis	• Vasculitis associated with ANCA's • Microscopic polyangitis • Wegener granulomatosis Churg-Strauss (5) (7) (10)
	• Vasculitis due to immune-complexes • Anti-glomerular basement membrane antibody disease • Cryoglobulinemic vasculitis • Schönlein-Henoch vasculitis Urticarial hypocomplementemic vasculitis (5) (7) (10)
Variable vessel vasculitis	• Cogan syndrome Behcet disease (5) (7)

Single organ vasculitis	<ul style="list-style-type: none"> • Skin leukocytoclastic vasculitis • Dermal arteritis • Primary vasculitis of the central nervous system • Isolated aortitis Etc. (7) (10)
Vasculitis associated with a systemic disease	<ul style="list-style-type: none"> • Lupus vasculitis • Rheumatoid vasculitis • Sarcoid vasculitis Etc. (5) (7)
Vasculitis associated with a probable etiology	<ul style="list-style-type: none"> • Vasculitis due to immune-complexes associated with medication • Vasculitis associated with ANCA by drugs • Cryoglobulinemic vasculitis associated with hepatitis C virus • Vasculitis associated with hepatitis B virus • Aortitis associated with syphilis
	Vasculitis associated with neoplasms (5) (7) (10)

Table 1: Accepted terminology in CHCC.

The disease occurs when a type III hypersensitivity reaction develops, which explains the presence of immune-complexes, immunoglobulins and complements. It also occurs the formation of antigen-antibody complexes as well of immuno-complexes deposits in the walls of the blood vessels. All of this causes the release of inflammatory mediators, adhesion molecules, free radicals, and some enzymes that produce damage in the vascular walls, extravasation of red blood cells and

fragmentation of neutrophils [2,4]. In the specific case of LV caused by medication, there are several factors influencing the condition such as the antibodies formation to confront medication hapten, the vascular lesion that can be caused by medication itself and the antibodies, formed to confront endothelial cells generated by the chemo taxis produced by the damage to vascular walls. In (Table 2), main medication involved in this pathology is listed [4, 5].

Group of medication	Examples
Antibiotics	Beta-lactamic, macrolides, cefaclor, minocycline, tuberculostatic, etc. (2)
Antihypertensive	Beta-blockers, captopril, diltiazem, nifedipine, hydralazine, diuretics(furosemide, hydrochlorothiazide, spironolactone, chlorthalidone) etc. (2)
Immunosuppressive	Methotrexate, azathioprine, sirolimus, cyclophosphamide, tacrolimus, interferon, D-penicillamine, sulfasalazine, TNF inhibitor, etc. (2)
NSAIDs	Ketoprofen, piroxicam, Ibuprofen, diclofenac, acetylsalicylic acid etc. (2)
Anti-thyroid agents	Propylthiouracil. (2)
Anticonvulsants/antiarrhythmic	Amiodarone, carbamazepine, phenytoin (2)
Anticoagulants	Heparin, warfarin. (2)
Antidepressants	Amitriptyline, diazepam, fluoxetine. (2)
Others	Allopurinol, colchicine, tamoxifen, isotretinoin, granulocytic and macrophage colony stimulating factors, inhibidores de los leukotriene blockers, metformin, sympathomimetic, opioids, antivirals, antifungals, etc. (2)

Table 2: Medication involved in this pathology is listed.

Methotrexate is a widely used medication for treating diseases such as vasculitis, neoplasms, psoriasis and

rheumatoid arthritis. The medication acts as a folate antagonist. The usage of this drug has been associated

with hematological, lung and liver toxicity. Skin manifestations have been reported as a few while urticaria and photo sensibility are more commonly reported manifestations. In the vast majority of cases, adverse effects occur at the moment of intake or application of the drug. Until recent days, there are a few reported cases of LV associated with methotrexate. In the literature search performed in this article, only 5 reported cases were found [12-16]. In this type of vasculitis, symptoms usually appear within 7 to 10 days after exposure to the triggering antigen. Generally, the disease only harms skin, however, in rare cases it can affect other organs. Patients usually present palpable purpura (though it could not be purpura at the start), abdominal pain, edema and arthralgia. Systemic symptoms occur in the acute phase most of the times. After several days, blisters can be found, as well as bloody blisters, lumps and ulcers. Those injuries are normally small though they vary in size and can even merge [4,3,17,18].

Most of the times, the disease affects inferior limbs, nevertheless, in bedridden people, injuries can occur in pressure areas. The disease is usually asymptomatic in a 30% of the cases, yet, predominant symptoms are pain, edema and itching [4,9]. The approach towards a vasculitis patient always starts with a clinical suspicion [5]. In (Figure 5) an algorithm of the steps to follow in the diagnosis of LV is shown. Once the clinical suspicion is established, it is necessary to obtain a biopsy in order to confirm the diagnosis. Different authors suggest that the best moment to obtain it is 24 hours after the occurrence of the injuries since after 48 hours, the findings could be nonspecific [1,3,5,6,18].

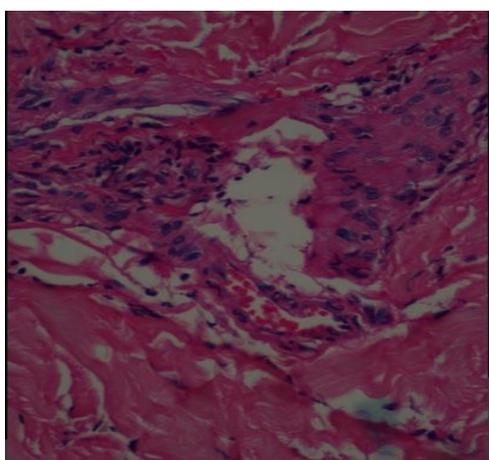


Figure 5: The diagnosis of LV is shown.

The histopathological examination shows signs of inflammation in small blood vessels, mainly in post

capillary venules with deposits of fibrin, though it can also be observed a disorder in arterioles and capillaries. It is commonly observed nuclear fragmentation of neutrophils in the wall of blood vessels, known as leukocytoclasia. Necrosis of low size caliber and skin can be observed. A systemic disorder diagnosis depend on the depth of the condition of the skin, for the sample is of greater importance to include subcutaneous cell tissue [1,2,11,17]. There are histological variants that may conduct towards a possible cause. Generally, lymphocytic vasculitis is related to autoimmune processes such as a reaction to medications, connective tissue disorders or infections. Likewise, if eosinophilia is observed in the tissue, the first disorder to be discarded must be LV derived from drugs [6].

After diagnosis is made, it is of outstanding importance to look for the causal agent and the possible systemic complications, mainly renal, gastrointestinal, lung and cardiac conditions [4,6,9]. Most of the LV restrict in an approximate time of 3 weeks, so support treatment is administered. Contact with the triggering factor must be avoided. The treatment starts by hydrating the patient, resting and providing relief from symptoms either by administering pain killers or anti-inflammatories. In acute cases the use of corticosteroids as prednisone, a dose of 1 mg/kg a day is a well-accepted and effective treatment for almost all cases. Several adverse effects may appear in recurring cases due to the use of prednisone which is not recommended.

In these cases, it is useful to treat the disease with azathioprine or methotrexate though this solution is controversial. Precaution is required with the last drug for it can induce LV. Some authors state that in moderate or severe cases colchicine can be useful only when combined with dapson. In recent years, drugs as infliximab, that block tumor necrosis factor Alpha-receptor, have been introduced showing promising results in different clinical trials [2,5,19]. There is no worldwide accepted therapy for systemic disorder vasculitis that may threaten life, still, there are cases in which satisfying results are obtained by administering bolus of methylprednisolone. The prognosis of the disease will depend on the acuteness and affectation on other organs. The prognosis is favorable in the specific case in which vasculitis is caused by medication hence identifying the cause and eliminating it is the mainstay of the treatment, avoiding recurring of the disease [4]. Methotrexate is an antimetabolite that acts inhibiting competitively the dihydrofolate reductase. The enzyme participates in tetrahydrofolate formation, necessary for the thymidine nucleoside required for DNA, RNA, thymidylates and protein synthesis.

It also partially inhibits immune system and, though its mechanism is not widely known, it reduces the autoimmune inflammation in the long run. The oral uptake of MTX is dose-dependent and significantly varies according to intestinal transit. Meals, diarrhea and non-absorbable antibiotics diminish uptake whereas constipation increases it. Oral bioavailability is of 33% and parenteral of 77%. When in serum, 50% circulates bound to proteins, with an average life between 3 and 10 hours. Excretion is carried out in a 90% by the kidneys and in a 10% by gastrointestinal tract Figure 6.

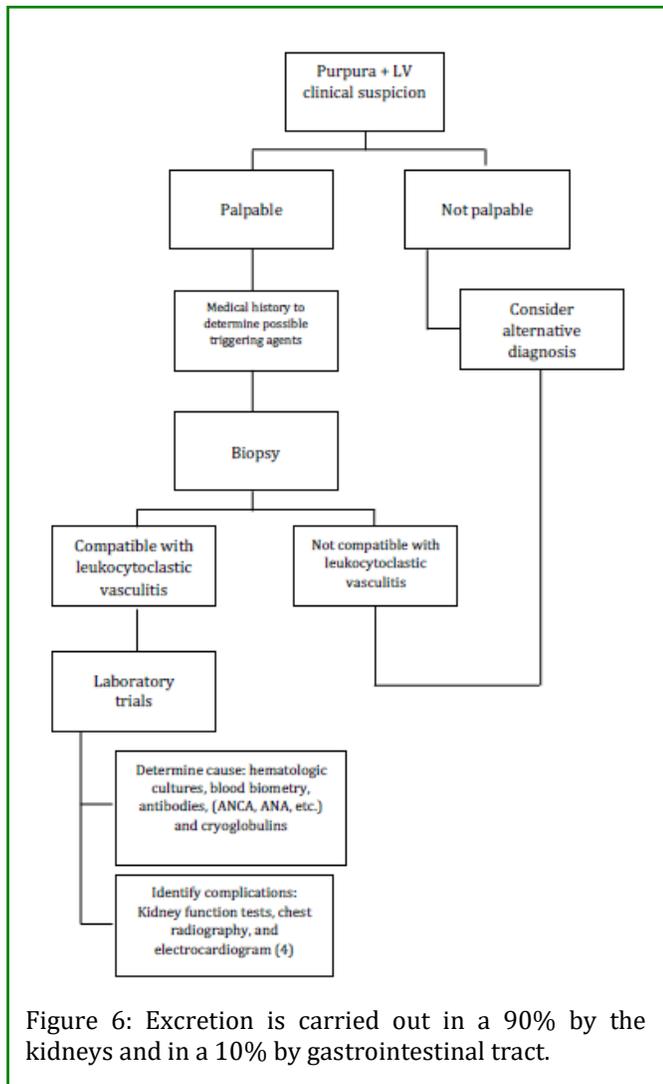


Figure 6: Excretion is carried out in a 90% by the kidneys and in a 10% by gastrointestinal tract.

These are the factors to be taken into consideration when assessing the risk of adverse conditions and secondary effects of the drug given that its frequency grows in proportion to its plasma levels [20]. Diverse groups of rheumatologists have recommended to start with a weekly 7.5- 10 mg. dose within a day during 4 weeks associated with folic acid in a daily 5-10 mg dose after the

administration of MTX. Subsequently, they recommend to gradually increase the dose among 2.5-5 mg each 2-4 weeks until reaching a 25 mg dose in the 3rd and 6th month of treatment, since high doses of weekly 25-30 mg are more effective as a disease-modifying drug than the ones of 10-15 mg [20].

References

1. Aounallah A, Arouss A, Ghariani N, Saidi W, Sriha B et al. (2017) [Cutaneous leukocytoclastic vasculitis: about 85 cases Amina]. *Pan African Med J* 26: 138.
2. Jovani V, Fernández C, Ibero I, Contreras A (1990) Vasculitis Leucocitoclásticas. In: *Enfermedades reumáticas: Actualización SVR* Pp: 289-99.
3. Bhattacharyya A, Yeddula K, Nwankwo N, Senussi MH (2018) Leucocytoclastic vasculitis. *Rheumatology* Pp:1-2.
4. Koutkia P, Mylonakis E, Rounds S, Erickson A (2001) Leucocytoclastic vasculitis: an update for the clinician. *Scand J Rheumatol* 30(6): 315-22.
5. Carlson JA, Cavaliere LF, Grant-kels JM (2006) Cutaneous vasculitis: diagnosis and management. *Clin Dermatol* 24(5): 414-29.
6. Goeser MR, Laniosz V, Wetter DA (2014) A Practical Approach to the Diagnosis, Evaluation, and Management of Cutaneous Small-Vessel Vasculitis. *Am J Clin Dermatol* 15(4): 299-306.
7. Bielsa I (2015) Actualización en la nomenclatura de las vasculitis. Conferencia de Consenso Internacional de Chapel Hill, 2012. *Actas Dermosifiliogr* 106(8): 605-608.
8. Sunderkötter C, Zelge B, Chen K, Requena L, Piette W, et al. (2014) Nomenclature of Cutaneous Vasculitis: Dermatologic Addendum to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheumatol* 70(2): 171-184.
9. Rawlings CR, Fremlin GA, Nash J, Harding K (2015) A rheumatology perspective on cutaneous vasculitis: assessment and investigation for the non-rheumatologist. *Int Wound J* 13(1): 17-21.
10. Markham R, Whittam L, Armstrong J, Wilkinson N, Williamson L (2017) Methotrexate-induced vasculitis in a child with systemic onset juvenile idiopathic Arthritis. *Rheumatology* 56(2): kex062.045.

11. Pastuszczak M, Celinska-Löwenhoff M, Sułowicz J, Wojas-Pelc A (2017) Clinical study on single-organ cutaneous small vessels vasculitis (SoCSVV). *Medicine (Baltimore)* 96(12): e6376.
12. Somonart T, Durez P, Margaux J, Van Geertruyden J, Goldschmidt D, Parent D (1997) Cutaneous Necrotizing Vasculitis after Low Dose Methotrexate Therapy for Rheumatoid Arthritis A Possible Manifestation of Methotrexate. *Clin Rheumatology* 16(6): 623-625.
13. Yoruk A, Cizmecioglu F, Yukselgungor H, Timur C, Baydilli H, et al. (2002) Methotrexate-Induces Systemic Vasculitis. *Med Pediatr Oncol* 38(2): 139-140.
14. Fondevilla C, Milone G, Pavlovsky S (1989) Cutaneous vasculitis after intermediate dose of methotrexate (IDMTX). *Br J Hematol* 72(4): 591-592.
15. Halevy S, Giryes H, Avinoach I, Livni E, Sukenik S (1998) Leukocytoclastic vasculitis induced by low-dose methotrexate: in vitro evidence for an immunologic mechanism. *J Eur Acad Dermatol Venereol* 10(1): 81-85.
16. Moreno JC, Vélez A, Medina I, Valverde F, Fernández-roldán JC, et al. (2003) Psoriasis, vasculitis and methotrexate. *J Eue Acad Dermatol Venereol* 17(4): 466-468.
17. Johnson E, Wetter D, Lehman J, Hand J, Davis D, et al. (2017) Leukocytoclastic vasculitis in children: clinical characteristics, subtypes, causes and direct immunofluorescence findings of 56 biopsy-confirmed cases. *J Eur Acad Dermatol Venereol* 31(3): 544-549.
18. Demirkesen C (2017) Approach to cutaneous vasculitides with special emphasis on small vessel vasculitis: histopathology and direct immunofluorescence. *Curr Opin Rheumatol* 29(1): 39-44.
19. Baigrie D, Crane J (2018) Leukocytoclastic Vasculitis (Hypersensitivity Vasculitis). *StatPearls [Internet]*.
20. Visser K, Katchamart W, Loza E, Salliot C, Trudeau J, et al. (2009) Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3. *Ann Rheum Dis* 68(7): 1086-1093.