JRMI
Journal of Rehman Medical Institute

Volume 10, No. 1
January - March 2024
www.jrmi.pk

CASE REPORT

Leucocytoclastic Vasculitis: a perplexing diagnosis with a simple cure

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Submitted
January 08, 2024

Accepted
February 09, 2024

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Citation: Asif Islam A, Haider S, Khan A, Khurshid F. Leucocytoclastic Vasculitis: a perplexing diagnosis with a simple cure. [Case Report]. J Rehman Med Inst. 2024 Jan-Mar;10(1):38-41.

ABSTRACT

For such a puzzling diagnosis, Leukocytoclastic Vasculitis (LCV) has a relatively simple and effective cure. We present a case report of a male patient in his thirties with a rash on his left leg for around a year without a definite diagnosis. The eruption of the rash was likely related to his Covid-19 immunization. After an extensive workup, it was diagnosed as a case of Leukocytoclastic Vasculitis. It was then successfully treated with immunosuppressive therapy.

Physicians need to consider the possibility of leukocytoclastic vasculitis in patients presenting with a skin rash especially after starting a medication or getting immunized. The recent surge in Covid-19 vaccinations could mean an increased incidence of LCV, therefore physicians need to be more mindful of this possibility when evaluating a skin rash. A thorough history needs to be undertaken to identify the trigger responsible and a skin biopsy should be done as soon as possible to confirm the diagnosis and start treatment.

Keywords: Leukocytoclastic Vasculitis; Vaccine; Covid-19 Vaccination; Small Vessel Vasculitis.

The authors declared no conflict of interest. All authors contributed substantially to the planning of research, data collection, data analysis, and write-up of the article, and agreed to be accountable for all aspects of the work.

INTRODUCTION

Leukocytoclastic vasculitis (LCV) is the immune mediated damage and inflammation of small blood vessel walls.[1,2] In most cases, the condition is idiopathic and diagnosed by exclusion but at other times it can occur secondary to triggers such as drugs, vaccination, infections, malignancy, and autoimmune disorders.[3]

Leukocytoclastic vasculitis usually presents as a rash on the lower extremities. In about 30% of patients, there can be involvement of the systemic blood vessels causing symptoms such as fever, malaise, weight loss, arthralgias and myalgias.[3,4]

The variability in its aetiology and clinical presentation makes LCV likely to be confused with many systemic and autoimmune disorders.[5] This warrants an extensive workup to rule out differentials, which is both expensive and burdensome for low resource health care systems. Furthermore, a thorough patient history needs to be recorded to identify the possible triggers for the said condition. The eventual gold standard investigation for diagnosis is a punch biopsy of the skin which confirms the specific histopathological pattern of vascular and perivascular damage seen with LCV.[6]

In majority of patients, an episode of LCV is mild and self-resolving.[7] In a few cases a course of immunosuppressive therapy may be considered.[5] We present a case report where we review the task of diagnosing a patient with Leukocytoclastic vasculitis and finding a plausible cause. The patient was not diagnosed for one year and was successfully cured after confirming this diagnosis.

CASE PRESENTATION

A 30 year old male patient, normotensive and normoglycemic, presented to us in the outpatient department of Mayo Hospital, Lahore, on November 18, 2021, with the complaint of a skin rash on the inner and lower aspect of his left leg for the past one year. He had a history of multiple visits to the primary healthcare centre in his village which had limited resources to carry out the required investigations and resulted in a delay of his correct diagnosis. The rash became a cause of much discomfort recently as it was associated with pain, itching, and a yellowish coloured discharge for the last two months. He denied having any fever, chills, weight loss, or joint pains. There was no history of genitourinary, gastrointestinal, respiratory, or neurological symptoms. He had not been taking any medications and there was no family history of autoimmune disease.

On examination, a non-healing ulcer was observable on the medial aspect of the lower left leg (Figure 1).

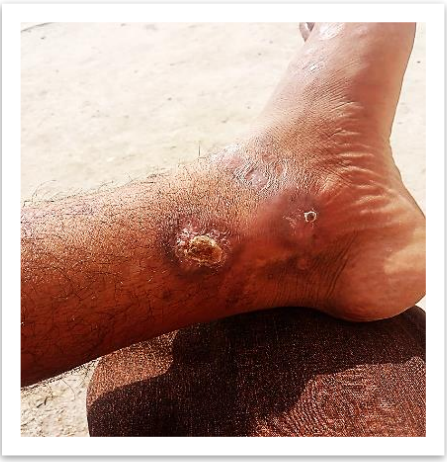

Figure 1: Skin on medial and lower aspect of left leg before treatment.

It was 4cm by 5cm in size with areas of erythema, exudation, yellow brown crusting and extensive desquamation. The lesion was tender, and the surrounding skin showed some hypopigmentation. Patient was vitally stable, and the rest of the general physical and systemic examination was nonsignificant.

Baseline investigations were ordered. Complete blood count (CBC), liver function tests (LFTs) and renal function tests (RFTs) showed no anomaly. A Doppler Ultrasound of both legs showed normal arteries and veins. In the next step, a range of laboratory investigations were ordered to rule out probable differentials. These investigations included an autoimmune panel including antinuclear antibody (ANA), anti-mitochondrial antibody (AMA), anti-smooth muscle (ASMA) antibodies, an Anti-phospholipid antibodies (APLA) profile, a vasculitis screen including ANCA and CRP and Plasma levels of Factor V and proteins C & S. Results of all these tests were normal. A normal beta-2 microglobulin level was also recorded.

The final step was to consult the dermatology department for a punch biopsy of the ulcer margins. The histopathology report read as follows: *"A field of damaged blood vessels with leukocytoclastic neutrophils, not seen to be penetrating the vessel walls. Nuclear dust scattered in very edematous dermis. Some vessels show histiocyte penetration of their walls indicating a chronic vasculitic process. Many plasma cells and pigment granules seen. Collagen bundles in reticular dermis show some homogenization suggesting fibrosis. Epidermal flaking. Ulcer shows regions of focal orthokeratosis and hyperkeratosis. Subjacent area shows prominent spongiosis and acanthosis. Basement membrane is intact. Underlying dermis shows hemorrhage, vascular dilation, edema and mixed infiltrate abundant with neutrophils. Features suggestive of Leukocytoclastic vasculitis"*.

Based on the biopsy report, a diagnosis of Leukocytoclastic vasculitis was finalized. After obtaining informed consent, the patient was started on pulse therapy with Cyclophosphamide for six months. A revised and thorough history was taken once again to probe for a plausible secondary cause/trigger for his rash to counsel the patient to avoid exposure. Upon being asked about receiving any vaccination, the patient recalled that the rash had first started appearing around the time he was vaccinated for Covid-19. He mentioned that he had experienced only a mild fever and malaise after receiving the first dose of covid 19 vaccination last year without any other symptoms. When he was vaccinated with a second dose after about 28 days, there were no symptoms immediately but about two weeks later a small red and itchy rash appeared on the medial side of his left lower leg. The lesion did not resolve over the course of the year. It was also revealed that he had received a Covid-19 booster shot about two and a half months ago, around which time his rash had become more painful and a discharge had started appearing.

After about three months of immunosuppressive therapy, the rash started improving and at six months it had mostly cleared up. After completion of pulse therapy, patient was shifted to oral steroids which were eventually tapered off. Figure 2 shows the medial aspect of his left leg on his last follow up visit.

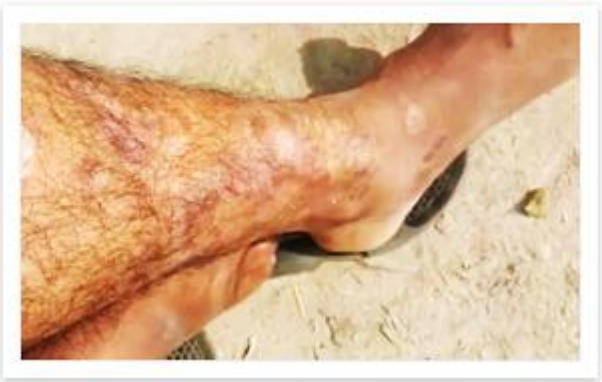

Figure 2: Skin on medial and lower aspect of left leg showing clearing of rash after treatment

DISCUSSION

The pathogenesis of Leukocytoclastic Vasculitis is thought to start with the deposition of IgM and IgG antibody-antigen complexes into the wall of small blood vessels, most commonly in the capillaries and venules of the skin.[5,8] The immune complexes cause activation of the complement cascade. This is followed by the recruitment of immune cells, especially neutrophils, into the tissue containing the affected vessels and the inflammatory onslaught damages the vessel walls. Loss of vascular integrity causes extravasation of fluid and RBCs into the surrounding tissue and loss of parenchymal cell functions.[9]

While 50% of the cases are idiopathic and intrinsic, the remaining involve a secondary trigger that predisposes to this hypersensitivity reaction. Many drugs have been reported to act as triggers such as NSAIDS, ceftriaxone, fluoroquinolones, vancomycin, methimazole, metformin and thiazide diuretics to name a few.[7,10-12] Infections with HCV, HBV and HIV can also act as culprits.[13] Malignant states, especially leukaemia and lymphomas, and chronic inflammatory states such as systemic lupus, rheumatoid arthritis, inflammatory bowel disease, and Henoch-Schönlein purpura have also been known to be associated with cutaneous eruptions of LCV. [3,14] The history recorded from our patient did not reveal any of these to be a likely cause.

Patients with LCV usually present to outpatient settings with complaints of a skin rash on the legs. Cutaneous manifestations of this rash are variable and can involve erythematous macules, crusts, desquamation and palpable violaceous nodules or purpura.[5,15] Our patient presented with what appeared to be a non-healing ulcer with erythema and an exudative discharge, which is not a very common presentation and likely indicates chronic and repetitive skin injury. In the majority of cases the rash disappears a few weeks after it erupts.[7] In a few cases, it can recur and sometimes becomes chronic. Persistence of the rash for months in our patient likely resulted from a severe and uncontrolled immune response. Sometimes the rash can also be painful and itchy like we observed in our patient. Some patients can also present with constitutional symptoms, most notably fever and arthralgias,[4] but our patient did not experience any such symptoms.

The rationale we adopted for ordering various investigations in this case was to rule out differentials, check for systemic involvement of LCV and to find a possible secondary cause or association with LCV all the while viewing this data in the light of patient history and taking a holistic approach in making judgements.[5] Our patient was mostly healthy with no significant medical history and normal results for almost all investigations. The final step was to go for a confirmatory biopsy.

The pathogenesis of LCV explains the basis of the histological findings seen in the skin punch biopsy of patients. Vascular wall destruction with fibrinoid necrosis and infiltration of neutrophils into the vessel wall and perivascular spaces is pathognomonic of LCV.[6] The neutrophils exhibit nuclear degeneration and their break down releases nuclear dust, pigments and cellular debris in the dermis. The dermis shows extensive inflammation with vascular dilation, edema and hemorrhage. As mentioned above, our patient's biopsy report showed all the typical features of LCV and served as the final say in formulating this diagnosis and starting treatment. In the majority of cases, it always comes down to the skin biopsy in confirming a diagnosis of LCV.[7,10,20] The sooner a biopsy of the suspected lesion is done, the sooner can the appropriate treatment be started.

When a detailed history was taken the second time in one of the follow up visits, our patient recalled that the rash had first appeared about two weeks following the second dose of his Covid-19 vaccination and did not resolve afterwards. As per our understanding, there could be a correlation of his cutaneous LCV to his exposure to the Covid-19 vaccine. Cases have been reported previously to document immunization as a trigger for leukocytoclastic vasculitis.[16] The influenza vaccine has been reported multiple times to cause cutaneous flare ups of LVC.[17,18] One such case report was by Stella X Chen and Philip R Cohen that mentioned the eruption of an extensive purpuric rash on both the upper and lower limbs of an old patient two weeks after receiving his annual flu shot.[19] Recently a few cases of Leukocytoclastic Vasculitis in association to Covid-19 vaccines have been reported. One report has described the appearance of a rash in a 38-year-old male just 4 days after receiving the Covid-19 vaccine, which was confirmed by biopsy to be Cutaneous Leukocytoclastic Vasculitis and improved on treatment with prednisone.[20] Another report has mentioned the occurrence of Leukocytoclastic Vasculitis in an a 71-year-old woman after she received the second dose of her SARS-COV-2 Vaccine.[21] A few other cases have also come forward and tried to explain the underlying mechanism that causes this dysregulated immune response to vaccines.[21,22] In the light of available studies, we attempt to explain our patient's case. After receiving the first dose of Covid-19 vaccine, our patient's immune system most likely entered a sensitization phase to the components in the vaccine and on repeat exposure, an immune response was elicited that led to the eruption of the skin rash. Furthermore, receiving a booster of the same Covid-19 vaccine several months later could have caused worsening of his rash. Following the Covid-19 pandemic, the world has now entered a phase of *en masse* immunization for Covid-19 and the potential side effects are being reported and studied.[23] We believe that more studies need to be conducted to establish a correlation between Covid-19 vaccines and Leukocytoclastic Vasculitis.

Leukocytoclastic Vasculitis mostly resolves on its own in a few weeks. Treatment can be as simple as stopping exposure to triggering drugs.[10,11] For more severe flares, immunosuppressive therapy with cyclophosphamide and steroids can be offered which yields favorable results.[5] Our patient took six months of pulse therapy with a single monthly dose of cyclophosphamide followed by oral Deltacortril therapy. An antihistamine was also prescribed to control itching and skin hygiene was advised to prevent any superadded infection. There was an excellent response and his rash showed remarkable regression.

CONCLUSION

Leukocytoclastic Vasculitis (LCV) might be a puzzling diagnosis due to its diverse appearance and probable relationship with medicine or vaccination. Despite its complexities, LCV has a rather easy solution. This case study emphasizes the need of addressing LCV in patients who have a skin rash, especially after taking a drug or having an immunization such as the Covid-19 vaccination. When diagnosing a skin rash, doctors should keep LCV in mind and take a detailed history to identify probable causes. A confirmed skin biopsy is required for diagnosis, and the immediate beginning of suitable treatment, such as immunosuppressive medicine, can lead to successful outcomes.

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