

Leukocytoclastic vasculitis and acute allergic interstitial nephritis following ceftriaxone exposure

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ABSTRACT

Leukocytoclastic vasculitis (LCV), also known as hypersensitivity vasculitis is a small vessel inflammatory disease which mainly involves the postcapillary venules. A 17-year-old girl developed palpable purpura over lower limbs and acute allergic interstitial nephritis 5 days after exposure to ceftriaxone. Skin biopsy from the lesion over lower limbs confirmed the diagnosis of LCV. Discontinuation of drug and treatment with steroid resulted in resolution of skin lesions and normalization of kidney functions. Beta-lactams are commonly used antibiotics in various types of infection in day-to-day practice. LCV, a rare complication of ceftriaxone should be kept in mind while using this drug.

Key words: Acute allergic interstitial nephritis, ceftriaxone, leukocytoclastic vasculitis

INTRODUCTION

Leukocytoclastic vasculitis (LCV), also known as hypersensitivity vasculitis is a small vessel inflammatory disease, which mainly involves the postcapillary venules. Most common organ involved in LCV is the skin which mainly present as palpable purpura predominantly on dependent area such as lower limbs and buttock region. Various factors which can lead to the development of LCV include drugs, infections, especially upper respiratory tract infections, intravenous drug abuse, malignancy, and connective tissue disorders. Among the drugs, antibiotics especially beta-lactams has been the most common drugs known to precipitate LCV. Here, we present a

case of LCV proven on skin biopsy developed after exposure to ceftriaxone.

CASE REPORT

A 17-year-old young girl reported to hospital with complaints of pain in right iliac fossa since 2 days associated with mild grade fever and nausea. On examination, her pulse was 110/min, blood pressure of 110/70 mmHg, and temperature of 99°F. Abdominal examination revealed the presence of mild diffuse tenderness, rest of the clinical examination was within normal limit. Hematological investigations revealed hemoglobin of 10 g/dL, total leukocyte count of 14,000/uL with differential count of 60% granulocyte, 24% lymphocyte, and 16% monocyte. Her platelet count was 334,000/uL. Erythrocyte sedimentation rate was 40 mm/1st h. Biochemical investigations showed serum creatinine of 0.6 mg/dL with urea of 24 mg/dL. Urine examination was within normal limit. Ultrasound examination of the abdomen and chest radiograph did not reveal any positive finding. A probable diagnosis of acute colitis was kept. She was started on injection ceftriaxone 1 g 12 hourly along with intravenous fluid supplementation.

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Five days after starting on intravenous ceftriaxone, she developed facial puffiness, anasarca, decrease urine output and reddish palpable purpuric nonblanching rash over both the legs [Figure 1] which spread to the both upper limbs in next 24 h [Figure 2]. There was no evidence of gastrointestinal bleed or hematuria. Her urine examination showed the presence of albumin in the range of 30 mg/dL, urine microscopic examination showed the presence of eosinophils and granular cast. Serum creatinine jumped to 2.1 mg/dL with urea of 55 mg/dL. Urine output over next 24 h was 400 ml with total intake of 2 L. Patient was evaluated for the probable cause of acute renal failure and palpable rash. Laboratory tests for hepatitis B, hepatitis C antigens and antibodies, retrovirus test, antinuclear antibodies, antineutrophil cytoplasmic antibodies, C3, rheumatoid factor, and cryoglobulins were negative. Repeat chest radiograph did not show any evidence of tuberculosis. Echocardiography did not reveal any evidence of infective endocarditis. Repeat complete blood count showed the presence of eosinophilia (4%) with an absolute eosinophil count of 620/mm³. Skin biopsy was performed from the palpable purpura over lower limbs [Figure 3] which revealed the presence of LCV. Immunofluorescence microscopy of skin biopsy did not show any IgA deposits. Suspecting a possibility of drug induced LCV, ceftriaxone was stopped immediately. In view of renal involvement, she was started on oral prednisolone 40 mg once a day. Investigations to search for the alternative cause for the LCV did not reveal any positive finding. Over next 48 h, patient improved clinically with a significant decrease in skin rash. Renal parameters came down to normal (serum creatinine 1.2 mg/dL, urea 20 mg/dL) 5 days after stopping ceftriaxone with adequate urine output. Patient was discharged after 1-week with a significant reduction in skin rash and normal renal parameters.

DISCUSSION

Here, we present a case of LCV proven on skin biopsy developed 5 days after exposure to ceftriaxone. However, it is difficult

to prove cause and effect relationship between LCV and ceftriaxone, but this was the only medication, which patient was receiving in the hospital stay and other potential causes for the development of LCV were ruled out by the various laboratory investigations. Improvement in the skin lesions, normalization of renal parameters after discontinuation of the offending drug and presence of urinary eosinophilia also support a diagnosis of LCV and transient allergic interstitial nephritis due to ceftriaxone.

Leukocytoclastic vasculitis, also known as hypersensitivity vasculitis is a small vessel inflammatory disease, which mainly involves the postcapillary venules. LCV is defined histologically as a predominantly neutrophilic perivascular infiltrate effecting cutaneous postcapillary venules with fibrinoid deposits in and around the vessel wall, endothelial swelling, leukocytoclasia (destruction of polymorphonuclear leukocytes with the formation of nuclear dust) and extravasations of red blood cells.^[1]

In 1990, American college of rheumatology have developed criteria for the diagnosis LCV, which includes age >16 years at onset; history of taking medication at the onset; the presence of palpable purpura, the presence of maculopapular rash and biopsy showing the presence of granulocyte around arteriole or venules. Presence of three or more criteria out of five were found to have sensitivity of 71% and specificity of 83.9%.^[2] In the present case, patient had all the five criteria required for diagnosis of LCV. However, it was found difficult to distinguish LCV from Henoch–Schonlein purpura, a disease that shares many clinicopathological features with LCV. Therefore, new differential criteria were developed to distinguish these two disease entity which includes palpable purpura, bowel angina, gastrointestinal bleed, hematuria, age at onset fewer than 20 years and no medications. Presence of equal or fewer than two criteria gives a correct diagnosis of LCV in 74% patients.^[3] In the present case, patient has only two criteria out of six which supports a diagnosis of LCV.



Figure 1: Palpable purpuric rashes over lower limbs



Figure 2: Palpable purpuric rashes over upper limbs

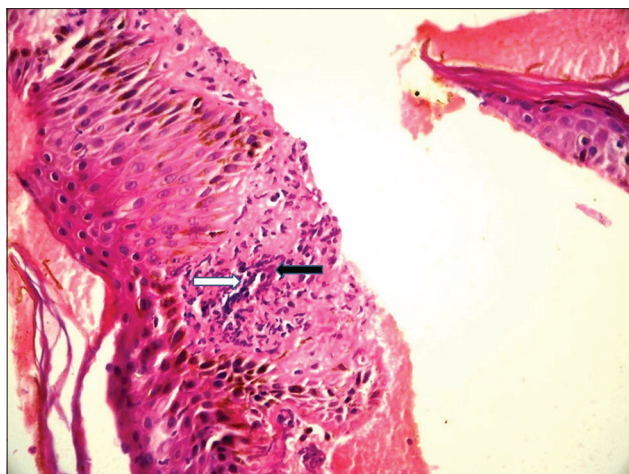


Figure 3: Skin biopsy showing leukocytoclastic vasculitis. White arrow showing neutrophilic perivascular infiltration around the vessel. Black arrow showing fibrinoid deposit around the vessel

Most common organ involved in LCV is the skin, which mainly present as palpable purpura mainly on dependent areas such as lower limbs and buttock region; however, other dermatological lesions such as maculopapular rash, urticaria, nodule and ulceration can be the presenting complaints.^[4,5] In 50% of cases of LCV, other system such as renal, gastrointestinal, pulmonary, cardiovascular, and central nervous may be involved. Vasculitis involving the kidneys associated with hematuria and proteinuria carries the most serious threat to the patient.^[6] In the present case, patient developed acute kidney injury and cutaneous LCV following use of ceftriaxone. The most likely etiology of acute kidney injury in this patient is allergic interstitial nephritis, which was supported by the presence of eosinophils in urine. Since patient improved clinically and acute kidney injury resolved after stopping the ceftriaxone and with steroid therapy, we did not perform kidney biopsy which would have confirmed the diagnosis of allergic interstitial nephritis.

Various factors which can lead to the development of LCV include drugs, infections especially upper respiratory tract infections, intravenous drug abuse, malignancy, and connective tissue disorder. However, in around one-third of the patients, it is not possible to find out the precipitating factors.^[4] There is a long list of drugs, which can precipitate LCV. Among them, the important one are antibiotics, nonsteroidal antiinflammatory drugs, methotrexate, antithyroid drug especially propylthiouracil, cyclosporine, azathioprine, allopurinol, diuretics, sulfasalazine, and tumor necrosis factor- α blocker.^[4,7] One-fourth cases develops LCV within 1-week of exposure to drug as happened in our case.^[5,7] Among the drugs, antibiotics especially beta-lactam groups has been most common culprit drugs known to precipitate LCV.^[4,5] Various beta-lactam antibiotics such as oxacillin, vancomycin have been reported to cause LCV;^[8,9] however, a search of PubMed over last 30 years did not reveal any case report on ceftriaxone-precipitating

LCV. Of the 6472 patients who reported side-effects of this drug on eHealthMe website, which continuously monitors drug adverse effects reported to US Food and Drug Administration, 20 (0.31%) reported LCV after receiving ceftriaxone. All of these patients developed LCV within a month after receiving ceftriaxone and 60% of patients were above the age of 50 years.^[10]

Most of the mild cases of LCV can be managed conservatively and by removal of the offending agent. Various therapeutic agents used to manage purpura without any ulceration includes dapsone and colchicine. Systemic steroid can be used during an acute episode of LCV, especially if there is renal involvement in the form of interstitial nephritis.^[6] However, long-term use of steroid should be avoided in case of chronic or recurrent LCV due to its serious side-effects.

CONCLUSION

To conclude, this is an original case report on LCV, a rare side-effect of ceftriaxone, highlighting its presentation, diagnostic criteria, and etiology. We could not find any published case report in the literature on ceftriaxone as a precipitating factor for LCV.

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