Leucocytoclastic Vasculitis Presenting as Bilateral Ulcerative Keratitis: A Case Report

Clinical Medicine Insights: Case Reports
Volume 16: 1–4

DOI: 10.1177/11795476231204358

Hui Feng*, Shang Li* and Ying Jie

Beijing Ophthalmology and Visual Sciences Key Laboratory, Beijing Tongren Eye Center, Beijing Institute of Ophthalmology, Beijing Tongren Hospital, Capital Medical University, Beijing, China.

ABSTRACT

INTRODUCTION: Small artery disease caused by neutrophils and immune-mediated is known as leucocytoclastic vasculitis (LCV). Clinically, it manifests as palpable, asymptomatic purpuric papules on the limbs. Ocular manifestation is rare. Here, we describe a case of peripheral ulcerative keratitis (PUK) associated with LCV.

CASE PRESENTATION: A 59-year-old man was referred to the hospital with blurred vision due to corneal perforation in his left eye. He complained of itchy nodules on his hands and lower legs for 15 years and the skin biopsy of the back of his hand revealed LCV 6 years ago, which suggested erythema elevatum diutinum. The patient was under treatment with anti-inflammatory and immunosuppressive drugs and physical features of LCV seen in him included erythema on his hands and legs. After receiving conjunctival flap covering surgery, the corneal perforation was resolved. Conjunctival flaps covered cornea that limited his vision to hand motion. Six months later, he was referred to our clinic again because of pain, redness, photophobia, and tearing in the right eye, presenting with PUK. Necrotic tissue was removed during surgery, which also included a conjunctival flap covering procedure. Following surgery, the symptoms were reduced, and the postoperative eye condition remained stable.

CONCLUSION: To our knowledge, it is the first case of PUK secondary to LCV which was diagnosed 6 years ago. This case demonstrates that PUK associated with LCV can be successfully treated by surgical interventions.

KEYWORDS: Leukocytoclastic vasculitis, peripheral ulcerative keratitis, erythema elevatum diutinum, conjunctival flap covering surgery

RECEIVED: March 8, 2023. **ACCEPTED:** September 8, 2023.

*These authors contributed equally to this work and share first authorship.

TYPE: Case Report

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Ying Jie, Beijing Ophthalmology and Visual Sciences Key Laboratory, Beijing Tongren Eye Center, Beijing Institute of Ophthalmology, Beijing Tongren Hospital, Capital Medical University, 1 Dongjiaominxiang Street, Dongcheng District, Beijing, China. Email: jie_yingcn@aliyun.com

Introduction

Leukocytoclastic vasculitis (LCV) is a term used in histopathology to describe a common kind of small vessel vasculitis (SVV), which can affect the skin and internal organs.[1] Palpable purpura is the most prevalent clinical manifestation of LCV, and histological analysis is applied to confirm the diagnosis. A chronic skin condition known as erythema elevatum diutinum (EED) is characterized by persistent red or purple pimples and nodules.[2] Histopathologically, EED characteristically presents as LCV. As the condition worsens, the inflammatory cells are replaced by granulation tissue, fibrosis, and lipid deposits.[3] Only 4 biopsy-validated cases of EED presenting as peripheral ulcerative keratitis (PUK) have been reported in the previous literature.[4-6]

We describe a patient with LCV that was diagnosed 6 years ago, who presented with PUK of the right eye and corneal perforation of the left eye. To our knowledge, this is the first case of PUK secondary to cutaneous LCV that was diagnosed 6 years ago, and he had been successfully treated with conjunctival flap covering surgery.

Case Presentation

A 59-year-old man suffering from blurred vision in his left eye came to our clinic. He complained of itching nodules on his hands and legs for 15 years. Six years ago, the patient was admitted to the department of dermatology and a physical examination revealed petechiae on the trunk and extremities. The lesions of the lower legs were confluent purpura, with deep-skin ulcers and blood effusion. The skin biopsy of the back of his hand revealed LCV, and the clinical indication was EED. He was on treatment with Tripterygium Glycosides Tablets, 20 mg, 3 times daily, and Sulfasalazine Enteric-coated Tablets, 50 mg, 3 times daily. He underwent cataract surgery in the right eye 6 years ago and had a history of pterygium in the left eye for 6 years.

Clinical examination revealed multiple well-demarcated nodules and plaques, red and firm, on the knuckle and dorsum of the hand. Some of the lesions were superficially eroded and partially crusted (Figure 1). The best-corrected visual acuity of the right eye was 1.0 and visual acuity in the left eye was restricted to movement of the hand. Slit-lamp examination showed nasal conjunctival thickening with stroma infiltration of ~3 mm (pterygium), central corneal thinning associated with perforation, corneal edema, anterior chamber disappearance in the left eye, and senile nuclear cataract. The right eye anterior segment was normal. The patient received the conjunctival flap covering. He received topical gatifloxacin ophthalmic gel 3 times daily, recombinant bovine basic fibroblast growth factor

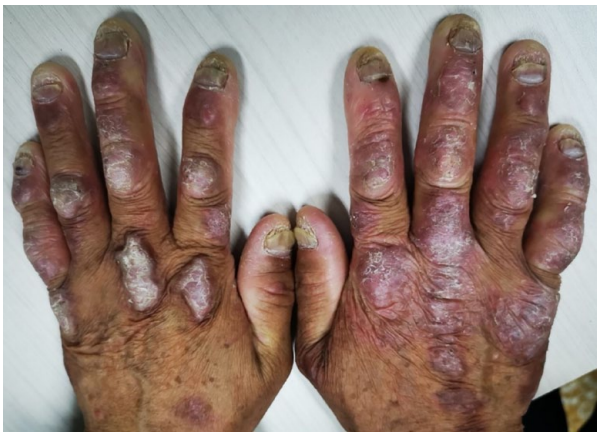

Figure 1. Clinical appearance of the cutaneous lesions characterized by erythematous palpable purpura and joint nodules on the dorsum of the patient's hands.

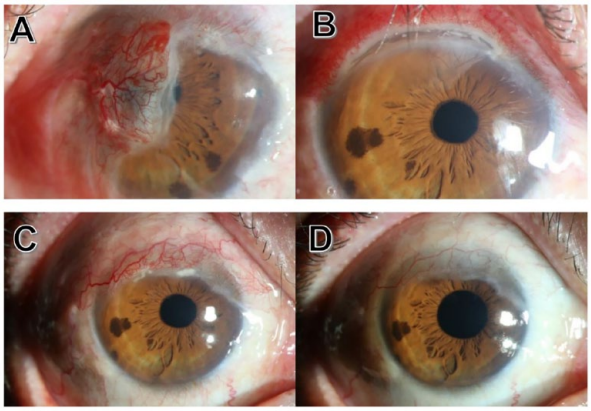

Figure 2. Slit-lamp photograph showing nasal conjunctival tissue were growing well in the left eye (A) and conjunctival hyperemia, marginal corneal guttering from 11 o'clock to 1 o'clock with corneal ulceration in the right eye (B). Two-month after surgery, the edges of the ulcer showed dense stromal inflammatory cell infiltrations (C). Three-month after surgery, the patient's ocular condition remained stable (D).

3 times daily, fluorometholone 0.1% eye drops twice daily, and cyclosporine 0.05% eye drop 3 times daily after surgery. On follow-up examination 1 week later, the corneal perforation resolved, leaving a central scar with vascularized pseudopterygium that limited his vision to hand motion (Figure 2A).

After 6 months, this patient was referred to our clinic again because of pain, redness, photophobia, and tearing in the right eye. Visual acuity was 0.6 in the right eye, and vision was restricted to counting fingers in the left eye. Examination of the anterior segment in the right eye showed conjunctival hyperemia, and marginal corneal guttering from 11 to 1 o'clock position, with corneal ulceration (Figure 2B). The posterior segment of the right eye was normal. He received a conjunctival flap covering in the right eye. In the right cornea, a perilimbal strip of affected conjunctiva, 3 mm in width, was resected between the 11 and 1 o'clock meridians adjacent to the stromal fusion. The center and edge within 4 mm of the ulcer were removed with a scalpel to expose the ulcer stroma and healthy tissue. The corneal lesions were covered with a conjunctival flap and stitched with 10-0 nylon sutures. He received topical gatifloxacin ophthalmic gel 3 times daily, recombinant bovine basic fibroblast growth factor 3 times daily, fluorometholone 0.1% eye drops twice daily, and cyclosporine 0.05% eye drop 3 times daily after surgery. After 2 months of follow-up, the margins of the ulcer showed a dense infiltration of stromal inflammatory cells. (Figure 2C) Treatment with tobramycin and dexamethasone ointment once daily was added to the ocular medications. After 1 week, a slit-lamp examination of the cornea in the right eye revealed a clear cornea without infiltrates. After 3 months of follow-up, visual acuity was 0.6 and conjunctival tissue was growing well and the corneal ulcer healed well in the right eye (Figure 2D).

A laboratory workup was performed to further assess his autoimmune disease, which included routine blood and urine tests, liver and kidney function analysis, infectious disease inspections (including hepatitis serology, syphilis antibody, HIV antibodies), cryoglobulins, immunological parameters (including IgA, IgG, IgM, complement component 3, and complement component 4), erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibody, antineutrophilic cytoplasmic antibody (ANCA), as well as serum protein electrophoresis. Only his C-reactive protein, IgA, and D-dimer was elevated. The erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibody, and ANCA were unremarkable.

Skin samples of his hand were analyzed by histopathological methods. Histopathological analysis verified the diagnosis of LCV and the clinical indication was EED. A massive neutrophilic infiltrate in soft tissue mainly consisted of polymorphonuclear leukocytes, leukocytoclasis, nuclear dust around the blood vessels, and perivascular fibroblastic proliferation was discovered by histopathology (Figure 3).

Discussion

LCV is a histopathological description of a form of SVV, involving small arterioles, capillaries, and postcapillary venules, in which the inflammatory infiltrate consists of neutrophils and nuclear fragments (leukocytoclasia).[1]Approximately 50% of the patients with LCV have one organ involved except the skin lesions.[7] Affected organs may include the kidneys, lungs, and brain, but ophthalmic manifestations of LCV are rare.

EED is a rare, distinctive form of cutaneous LCV. The main clinical manifestation of EED is palpable purpura on the lower limbs, although lesions can occur anywhere on the surface of the skin. Frequently the lesions tend to merge with confluent aspects that may cover a wide range of skin areas.[3,8] In this case, we also observed palpable purpura across the lower limbs, hands, knees, and elbows, suggesting a cutaneous LCV syndrome called EED (Figure 1).

Ocular involvement has been described in some patients with EED, including PUK with or without progressive keratolysis,[4-6] PUK with corneal perforation, nodular scleritis, panuveitis,[9] inflammatory sclerokeratitis,[10] Terrien's marginal

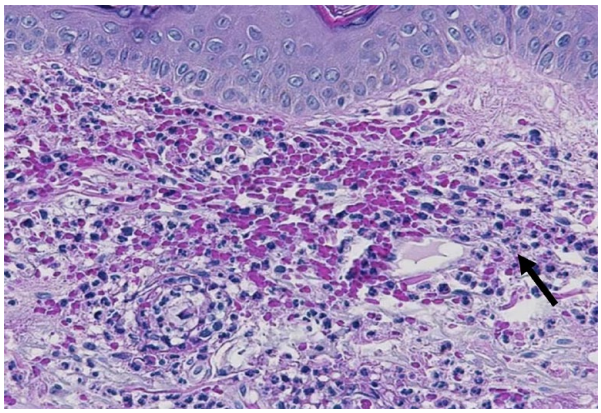

Figure 3. Skin biopsy showed massive neutrophilic infiltrate in soft tissue mainly consisted of polymorphonuclear leukocytes, leukocytoclasis, nuclear dust around the blood vessels, and perivascular fibroblastic proliferation.

degeneration with adjacent episcleritis.[11] PUK seems to be the most prevalent ocular involvement. Casanova et al[6] identified a patient with EED associated with autoimmune keratolysis. Ocular examination showed conjunctiva thickening in both eyes and bilateral superior corneal melting with perforation in the left eye. Lekhanont et al[4] reported a 64-year-old female patient presenting with pseudopterygium and progressive keratolysis associated with EED. A fatal case of LCV was described by Li Yim et al.[12] The patient initially presented with bilateral marginal keratitis without any cutaneous lesions.

LCV, as an immune-mediated disease of systemic vasculitis, targets specific vessels in the body.[1] Antigen-antibody immune complexes at the end of the limb vessels cause a subsequent multicellular immunological cascade and activation of adaptive immunity.[13] Although LCV was diagnosed 6 years ago, we still observed palpable purpuric lesions in the hands, as well as abnormalities in laboratory tests and pathological examinations. For this reason, PUK in this case was the ocular complication of LCV. To our knowledge, this case represents the longest interval of corneal complications after being diagnosed with LCV. The differential diagnosis of PUK is broad. It includes other inflammatory conditions such as rheumatoid arthritis, polyarteritis nodosa, inflammatory bowel disease, collagen vascular diseases and ANCA vasculitides. This reminds us that a comprehensive history, assessment of systems, laboratory testing, and imaging and biopsies are important to evaluate the systemic disease in patient with PUK. It is vital to identify potential disease and treat it with other professionals who are knowledgeable in diagnosis and management of systemic diseases.

Laboratory workup should include infection serology, antinuclear antibody panel, serum protein electrophoresis, rheumatoid factor, immunoglobulins, serum complement C3 and C4 levels, ANCAs, and cryoglobulins.[1] However, leukocytosis, increased C-reactive protein level, or joint pain is not sufficient evidence of systemic vasculitis. Skin biopsy is of paramount importance and should be performed whenever possible to confirm the diagnosis of LCV. LCV describes a histopathological entity characterized by: (1) evidence of neutrophilic infiltration within and around the vessel wall with signs of leukocytoclasia; (2) fibrinoid necrosis; and (3) signs of damage of the vessel wall and surrounding tissue.[1,7] This case also showed that only C-reactive protein, IgA, and D-dimer were increased, while rheumatoid factor, erythrocyte sedimentation rate, antinuclear antibody, and ANCA were unremarkable. The diagnosis of this case also relies on histopathological examination, in which the inflammatory infiltrate is composed of neutrophils with fibrinoid necrosis and disintegration of nuclei into fragments.

Sulfasalazine and Tripterygium Glycosides Tablets are the common immunosuppressive agents which have anti-inflammatory and suppressing effects on cellular and humoral immunity used for treatment in the most case of LCV,[14,15] and can quickly resolve both cutaneous and ocular inflammations after treatment.[16] The combination of the 2 drugs is common and effective in the clinic for control of LCV progression.[17] This patient adhered to the treatment with Tripterygium Glycosides Tablets, 20 mg, 3 times daily, and Sulfasalazine Enteric-coated Tablets, 50 mg, 3 times daily for these 6 years. Liver and renal function abnormalities were not observed. However, LCV is a long-term chronic disease with frequent recurrent attacks, it is possible that patients in risk of relapse.[7] Although the specific pathogenesis of recurrent has not been elucidated, some study found it might be associated with vascular thrombosis or peripheral neuropathy.[7] The condition of this patient remains unstable and ocular manifestations developed undergoing systemic immunosuppressive therapy. We thought that the patient's ulcerative keratitis may be due to a recurrence of LCV. Based on systemic immunosuppressive therapy, we found that conjunctival flap covering and topical immunosuppressive agent was effective for the treatment of PUK secondary to LCV. The mechanism of this therapy can be explained as follows: (a) elimination of necrotic tissue is aimed at reducing the number of inflammatory cells producing antibodies near the ulcer, absorbing anti-inflammatory and immunomodulatory agents[18]; (b) the conjunctival flap is beneficial by increasing blood vessels to the infected site and providing a stable ocular surface[19]; and (c) topical immunomodulatory agents act directly on cornea ulcer and reduce autoimmune-reactions.

In conclusion, PUK may be associated with LCV. It seems important to look for corneal lesions in patients with LCV, especially if they have ocular symptoms. Comprehensive medical history and physical examination are necessary to identify the specific etiology. Our case was successfully treated for PUK associated with LCV. Timely surgical intervention is essential to avoid severe vision impairment.

Author Contributions

LS and JY collected the data. HF contributed to the creation of the report and writing the manuscript. LS and JY contributed to the selection of images and all authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was approved by Ethics Committee of Beijing Tongren Hospital. The patients/participants provided their written informed consent to participate in this study. No potentially identifiable human images or data is presented in this study.

ORCID iD

Hui Feng https://orcid.org/0000-0002-1982-1357

REFERENCES

1. Fraticelli P, Benfaremo D, Gabrielli A. Diagnosis and management of leukocytoclastic vasculitis. *Intern Emerg Med*. 2021;16:831-841.
2. Gibson LE, el-Azhary RA. Erythema elevatum diutinum. *Clin Dermatol*. 2000;18:295-299.
3. Wahl CE, Bouldin MB, Gibson LE. Erythema elevatum diutinum: clinical, histopathologic, and immunohistochemical characteristics of six patients. *Am J Dermatopathol*. 2005;27:397-400.
4. Lekhanont K, Patarakittam T, Mantachote K, Waiyawatjamai P, Vongthongsri A. Progressive keratolysis with pseudopterygium associated with erythema elevatum diutinum. *Ophthalmology*. 2011;118:927-933.
5. Takiwaki H, Kubo Y, Tsuda H, Arase S, Shiota H. Peripheral ulcerative keratitis associated with erythema elevatum diutinum and a positive rheumatoid factor: a report of three cases. *Br J Dermatol*. 1998;138:893-897.
6. Casanova FHC, Meirelles RL, Tojar M, Martins MC, Rigueiro MP, de Freitas D. Autoimmune keratolysis in a patient with leukocytoclastic vasculitis: unusual erythema elevatum diutinum with granulomatous pattern. *Cornea*. 2001;20:329-332.
7. Bouiller K, Audia S, Devilliers H, et al. Etiologies and prognostic factors of leukocytoclastic vasculitis with skin involvement: a retrospective study in 112 patients. *Medicine*. 2016;95:e4238.
8. Fort SL, Rodman OG. Erythema elevatum diutinum. Response to dapsone. *Arch Dermatol*. 1977;113:819-822.
9. Mitamura Y, Fujiwara O, Miyanishi K, Sato H, Saga K, Ohtsuka K. Nodular scleritis and panuveitis with erythema elevatum diutinum. *Am J Ophthalmol*. 2004;137:368-370.
10. Aldave AJ, Shih JL, Jovkar S, McLeod SD. Peripheral keratitis associated with erythema elevatum diutinum. *Am J Ophthalmol*. 2003;135:389-390.
11. Shimazaki J, Yang HY, Shimmura S, Tsubota K. Terrien's marginal degeneration associated with erythema elevatum diutinum. *Cornea*. 1998;17:342-344.
12. Li Yim JF, Agarwal PK, Fern A. Leucocytoclastic vasculitis presenting as bilateral marginal keratitis. *Clin Exp Ophthalmol*. 2007;35:288-290.
13. Sura AA, McCallum RM. Peripheral ulcerative keratitis due to systemic diseases. *Curr Opin Ophthalmol*. 2022;33:543-550.
14. Li M, Li Y, Xiang L. Efficacy and safety of tripterygium glycosides as an add-on treatment in adults with chronic urticaria: a systematic review and meta-analysis. *Pharm Biol*. 2023;61:324-336.
15. Feng Z, Fu L, Wang J, et al. Efficacy of tripterygium glycosides (TG) in rheumatoid arthritis as a disease-modifying anti-rheumatic drug (DMARD) in combination with conventional DMARDs: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*. 2022;184:106405.
16. Fredenberg MF, Malkinson FD. Sulfone therapy in the treatment of leukocytoclastic vasculitis. *J Am Acad Dermatol*. 1987;16:772-778.
17. Papachristodoulou E, Kakoullis L, Tiniakou E, Parperis K. Therapeutic options for cutaneous polyarteritis nodosa: a systematic review. *Rheumatology*. 2021;60:4039-4047.
18. Kato T, Yamaguchi T, Hamanaka T, Kanai A. Corneal marginal ulcer in relapsing polychondritis: treatment with keratoepithelioplasty. *Ophthalmic Surg Lasers*. 1998;29:767-769.
19. Sun GH, Li SX, Gao H, Zhang WB, Zhang MA, Shi WY. Clinical observation of removal of the necrotic corneal tissue combined with conjunctival flap covering surgery under the guidance of the AS-OCT in treatment of fungal keratitis. *Int J Ophthalmol*. 2012;5:88-91.