Journal of Inflammation Research

Dovepress
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CASE REPORT

Baricitinib Successfully Treated a Teenager with Refractory Livedoid Vasculopathy: A Case Report and Literature Review

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Background: The pathogenesis is of livedoid vasculopathy (LV)—a rare, chronic, and recurrent cutaneous vascular obstructive disease—is not fully understood. Conventional anticoagulant therapy sometimes exhibits limited efficacy, and although JAK inhibitors have demonstrated some efficacy in the treatment of refractory LV, the evidence remains insufficient.

Case Presentation: This study reports a case of a 14-year-old girl who were failed to maintain remission following treatment with oral rivaroxaban combined with external use of heparin sodium cream. However, the symptoms improved significantly 2 weeks after treatment with baricitinib, and remission was maintained during its gradual reduction.

Conclusion: Successful treatment of this refractory patient with baricitinib provides another evidence for the potential therapeutic effect of JAK1/JAK2 inhibitors in LV, and also offers a reference for the dosage tapering regime of baricitinib in LV.

Keywords: livedoid vasculopathy, refractory, baricitinib

Background

Livedoid vasculopathy (LV) is a rare, chronic, and recurrent cutaneous vascular obstructive disease, with clinical manifestations broadly classified into three stages. The first stage presents as purplish-red maculae and papules, often symmetrically distributed in the lower limbs, ankles, and back of the foot. The second stage progress into painful ulcers. The third stage involves ulcer healing resulting in a porcelain white atrophic scar, which may be accompanied by telangiectasia and pigment-like changes.[1] Notably, peripheral neuropathy may occur in some patients.[2] LV primarily affects middle-aged women and tends to worsen in summer while being less severe in winter.[3]

The pathogenesis of LV remains insufficiently understood and may involve vascular embolism and a potential inflammatory response due to hypercoagulability.[4] Although drugs such as anticoagulants, antiplatelet agents, vasodilators, and steroid exhibit favorable results in certain cases, some patients still respond poorly to conventional treatment. The present case provides new evidence regarding the efficacy of JAK inhibitors in the treatment of refractory LV.

Case Presentation

In June 2023, a 14-year-old girl presented to our hospital with a history of painful recurrent ulcers on the lateral ankles and back of both feet for over 1 year. Physical examination revealed multiple necrotic ulcers on the feet and ankles surrounded by erythema, porcelain white atrophic scars, and pigmentation (Figure 1). The composite clinical score was 7, with 2, 2, and 3 points for moderate pain, skin ulcer, and severe erythema, respectively. The patient previously received oral rivaroxaban combined with external use of heparin sodium cream for 3 months. However, she failed to achieve sustained remission following drug discontinuation. Notably, no recurrent oral ulcers, genital ulcer, fever, Raynaud phenomenon, frostbite rash, butterfly erythema, purpura rash, finger numbness, arthralgia, alopecia, celialgia, polydipsia,

Received: 10 September 2024
Accepted: 20 January 2025
Published: 1 February 2025

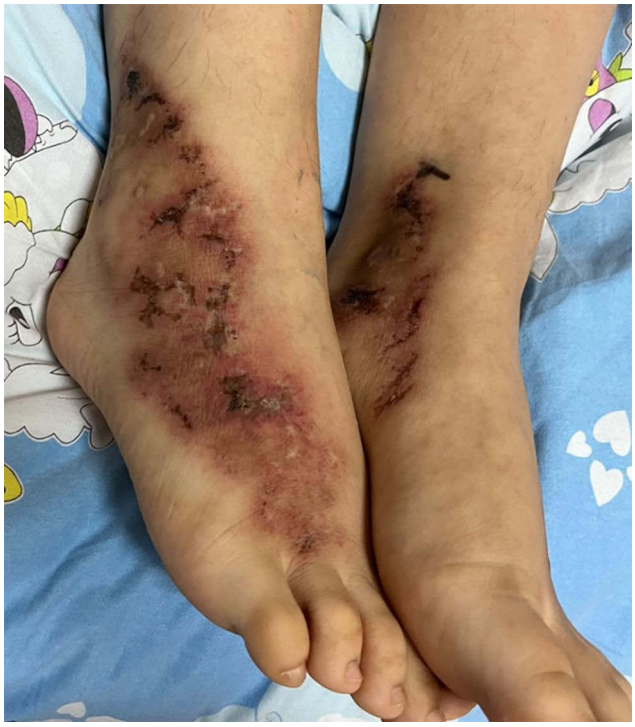

Figure 1 Initial skin appearance Painful recurrent ulcers on the lateral ankles and back of both feet when LV before baricitinib used.

polyuria, dyspnea, fatigue, hypertension, lymphadenopathy, or weight loss were complained. Laboratory and imaging examinations revealed normal or negative results for complete blood cell count, hemoglobin, platelet count, urinalysis, renal function, antineutrophil cytoplasmic antibodies, cold agglutinin test, protein electrophoresis, erythrocyte sedimentation rate, antinuclear antibody, anti-ribosome antibody, anti-Smith antibody, anti-SSA/Ro52 antibody, anti-SSA/Ro60 antibody, anti-SSB antibody, anti-double-stranded DNA antibody, anti-nucleosome antibody, anti-histone antibody, anti-ribosomal antibody, anti-cardiolipin antibody, rheumatoid factor, complement, prothrombin time, bleeding time, blood glucose, tuberculosis interferon-gamma release assay, serology for Epstein-Barr virus and cytomegalovirus, lower extremity vascular ultrasound, chest CT, and cardiac ultrasound. The patient denied any significant travel history, medical history, or family history of deep vein thrombosis, autoimmune diseases, or other diseases affecting the coagulation status. A skin biopsy revealed focal epidermal ulceration, superficial dermal edema, vascular proliferation and dilation, partial vascular endothelial cell proliferation, partial vascular wall destruction, partial vascular wall thickening and occlusion, and partial deposition of cellulose in the vascular wall. Furthermore, erythrocyte exosmosis and the infiltration of interstitial inflammatory cells were also observed. All these pathological manifestations were consistent with a diagnosis of LV (Figure 2).

As the patient was a school-aged girl with growth and development needs and the convenience of oral preparations, a treatment regimen of baricitinib (4 mg daily) in combination with amlodipine (5m g daily) were developed. Following 2 weeks of treatment, the erythema became notably lighter in color and significantly smaller, with a part of the scab falling off and replaced with new skin (Figure 3A). The ulcers healed completely following treatment for 3 months, without any new lesions (Figure 3B). The composite clinical score was 1, including 0, 0, and 1 point for pain, intact skin, and mild erythema, respectively. At the most recent follow-up in March 2024, the patient only had pigmentation on feet and ankles (Figure 3C). Amlodipine was continued until its withdrawal in February 2024. Baricitinib was reduced to 3, 2, and 1mg daily in September 2023, November 2023, and January 2024, respectively, and finally discontinued in March 2024. During the course of treatment, the patient did not experience any drug-related adverse reactions, including infection, liver function injury, or gastrointestinal symptoms.

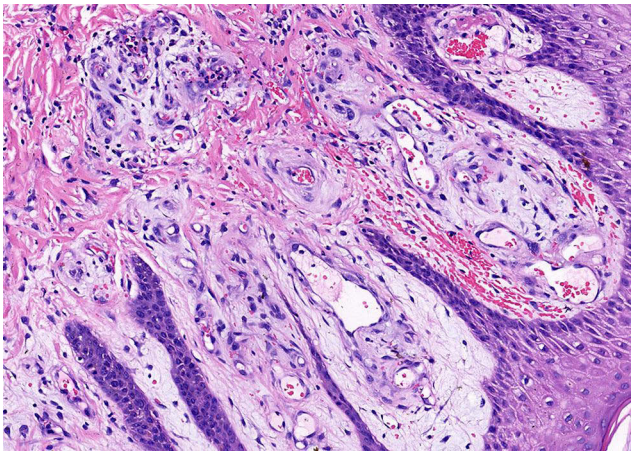

Figure 2 The histological features Histopathological examination showed focal epidermal ulceration, superficial dermal edema, vascular proliferation and dilation, partial vascular endothelial cell proliferation, partial vascular wall destruction, partial vascular wall thickening and occlusion, and partial deposition of cellulose in the vascular wall. Furthermore, erythrocyte exosmosis and the infiltration of interstitial inflammatory cells were observed. (hematoxylin–eosin, ×200).

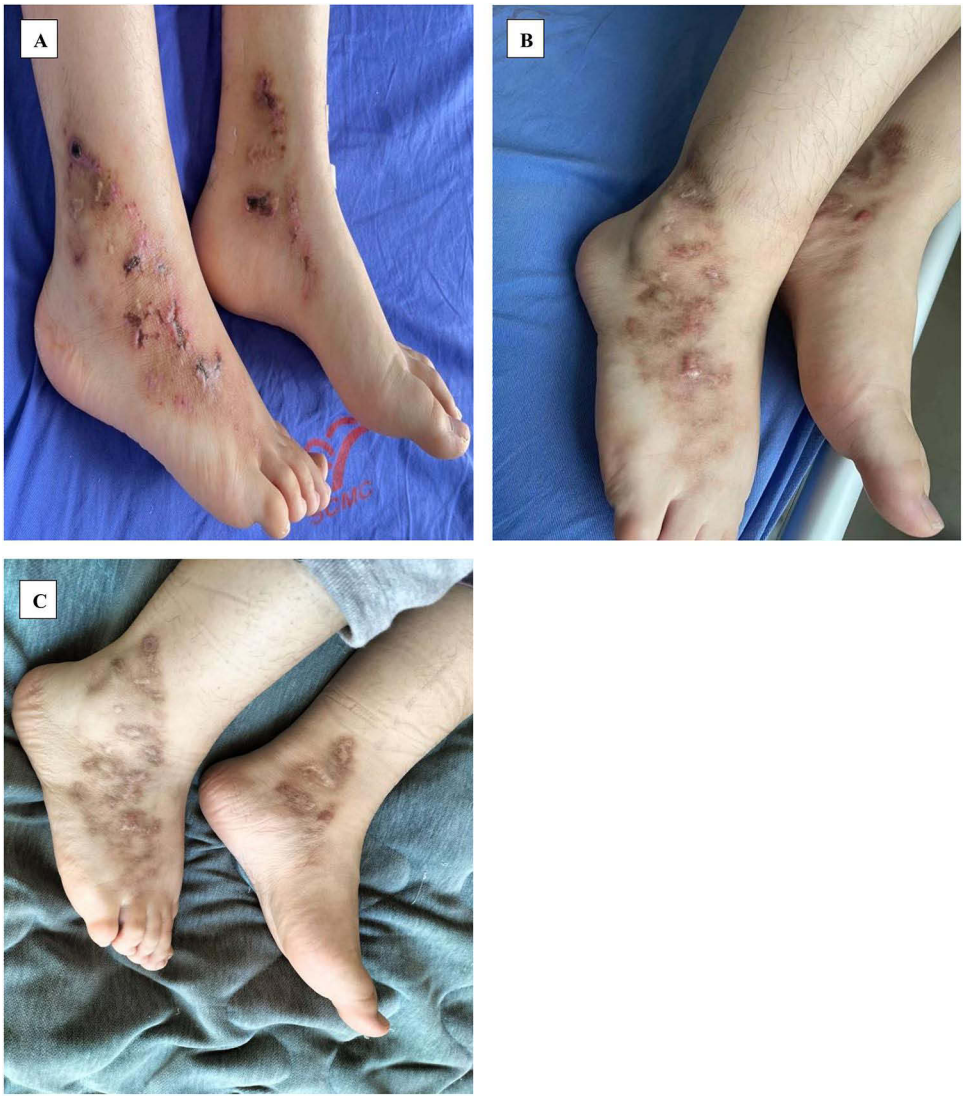

Figure 3 Clinical Response of Livedoid Vasculopathy to Baricitinib Therapy. (**A**) After 2 weeks of treatment, the rash was obviously lighter in color and significantly smaller in scope, and part of the scab fell off and was covered by new skin. (**B**) After 3 months of treatment, the ulcers healed completely, and there was no new lesion presented. (**C**) the patient had only pigmentation on feet and ankle in March 2024.

https://doi.org/10.2147/JIR.S495481

Discussion and Conclusions

The pathogenesis of LV is complex, with no consensus regarding its treatment plan. Furthermore, evaluation of its clinical efficacy is challenging because of its rare and recurrent occurrence. Specifically, the current mature treatment of LV is mainly limited to anticoagulants, platelet inhibitors, fibrinolytic solvents, and vasodilators, as the mechanism underlying LV may mainly involve vascular embolism and the potential inflammatory response due to hypercoagulability. Immunosuppressants, including glucocorticoids, cyclophosphamide, and azathioprine, are also candidate drugs for its treatment as immune mechanisms may also play a role in its development. Moreover, anti-inflammatory drugs such as colchicine, which inhibit neutrophils, can also be used for treating the acute stage of LV. Additionally, some physical therapies, including hyperbaric oxygen therapy and 8-methoxypsoralen combined with A-band ultraviolet therapy, may be effective.[5–7] However, not all patients benefit from these treatments.

In patients with refractory LV, JAK inhibitors, particularly baricitinib, have demonstrated some efficacy, which was confirmed in 14 patients, including children, adolescents, and adults, in 5 studies (Table 1).[8–12] Baricitinib can be administered alone or in combination with other drugs at a starting dose of 2 mg/ day or 4 mg/ day. Skin improvement can be observed after 2–12 weeks and it is safe without side effects.[8–12] In the present case, the initial dose of baricitinib was 4 mg/ day, corresponding to the 60.4 kg body weight of the patient. The drug was discontinued at approximately 9 months. The skin symptoms, including pain, ulceration, and erythema, were relieved at approximately 2 weeks, the ulcer healed completely at approximately 3 months, and no recurrence or drug-related adverse reactions during baricitinib reduction were observed.

Table 1 Patient Characteristics and Response to Baricitinib Therapy

Study	Age(years)/ Sex	Previous Therapies	Current Therapies	Follow-Up
Zhang H, et al[12]	14/F	Chinese medicine decoction, oral and topical corticosteroids.	Baricitinib 4 mg/day and stopped at 3rd month.	2 weeks later, ulcerations, erythema, swelling and pain started to remission. By 7 weeks, there was a remarkable improvement of lesions. At 3rd month, all the lesions disappeared, baricitinib was stopped. After 6-month follow-up, no reoccurrence happened, with no adverse events.
Xiao Y, et al[10]	26/F	Systematic steroids and anti-ulcer treatment.	Baricitinib 4mg/day as initial dosage, and it was reduced to 2mg/qod since week 24.	At week 12, the erythema was gradually diminished, and the ulcers were healed. The patient maintained stable conditions for over 42 weeks without adverse events.
Song X, et al[8]	8/M	Prednisone, Chinese medicine, and topical mucopolysaccharide polysulfate cream.	Baricitinib 2 mg/day and aspirin 100 mg/day for 1 month followed by monotherapy with baricitinib.	Darkening and reduced erythema by month 6.
	26/M	Thalidomide, compound glycyrrhizin tablets, cetirizine, prednisone, tripterygium glycosides, and regular debridement twice a week.	Baricitinib 2 mg/day, and topical fusidic acid cream.	Complete healing of ulcers and residual scars by month 1.
	26/F	Prednisone, rivaroxaban, thalidomide, and aspirin.	Baricitinib 2 mg/day, and topical fusidic acid cream.	Darkening livedo reticularis, healed ulcers, and residual hyperpigmentation by month 2.
Peñuelas Leal R, et al[11]	48/F	Pentoxifylline, nifedipine, aspirin, systemic corticosteroids and etanercept 50 mg weekly.	Baricitinib 4 mg by mouth daily in combination with aspirin alone.	Four weeks into therapy, the patient's ulcers had healed completely, and she remained asymptomatic. After 16 weeks of follow-up, the patient had not developed adverse events while maintaining complete control of the disease including resolution of livedo racemosa.

(*Continued*)

Table 1 (Continued).

Study	Age(years)/ Sex	Previous Therapies	Current Therapies	Follow-Up
Han Y, et al[9]	36/F	Corticosteroid, thalidomide, tripterygium glycosides, aspirin, rivaroxaban, and enoxaparin.	Baricitinib 2 mg/day.	Composite clinical scores reduced from 8 to 3, scores of erythema reduced from 3 to 1, and scores of ulceration reduced from 2 to 1 after follow-up for 16 weeks. No adverse events were happened during the process of treatment.
	17/M	Corticosteroid, thalidomide, tripterygium glycosides, aspirin, rivaroxaban, and enoxaparin.	Baricitinib 2 mg/day.	Composite clinical scores reduced from 8 to 0, scores of erythema reduced from 3 to 0, and scores of ulceration reduced from 2 to 0 after follow-up for 10 weeks. No adverse events were happened during the process of treatment.
	26/F	Compound glycyrrhizin and thalidomide.	Baricitinib 2 mg/day.	Composite clinical scores reduced from 7 to 0, scores of erythema reduced from 3 to 0, and scores of ulceration reduced from 1 to 0 after follow-up for 28 weeks. No adverse events were happened during the process of treatment.
	26/M	Corticosteroid, compound glycyrrhizin, and Chinese traditional anti-inflammatory drugs.	Baricitinib 2 mg/day.	Composite clinical scores reduced from 8 to 1, scores of erythema reduced from 3 to 1, and scores of ulceration reduced from 2 to 0 after follow-up for 16 weeks. No adverse events were happened during the process of treatment.
	8/M	Corticosteroid and Chinese traditional anti-inflammatory drugs.	Baricitinib 2 mg/day.	Composite clinical scores reduced from 5 to 1, scores of erythema reduced from 2 to 1, and scores of ulceration reduced from 1 to 0 after follow-up for 11 weeks. No adverse events were happened during the process of treatment.
	26/F	Compound glycyrrhizin and thalidomide.	Baricitinib 2 mg/day.	Composite clinical scores reduced from 8 to 2, scores of erythema reduced from 3 to 2, and scores of ulceration reduced from 2 to 0 after follow-up for 14 weeks. No adverse events were happened during the process of treatment.
	18/F	Corticosteroid and Chinese traditional anti-inflammatory drugs.	Baricitinib 2 mg/day.	Composite clinical scores reduced from 8 to 3, scores of erythema reduced from 3 to 1, and scores of ulceration reduced from 2 to 1 after follow-up for 16 weeks. No adverse events were happened during the process of treatment.
	12/F	Corticosteroid and Chinese traditional anti-inflammatory drugs.	Baricitinib 2 mg/day.	Composite clinical scores reduced from 4 to 1, scores of erythema reduced from 2 to 1, and scores of ulceration reduced from 2 to 0 after follow-up for 16 weeks. No adverse events were happened during the process of treatment.
Our study	14/F	Oral rivaroxaban combined with external use of heparin sodium cream	Baricitinib 4 mg/day in combination with amlodipine 5 mg/day.	2 weeks later, ulcerations, erythema, and pain started to remission.

https://doi.org/10.2147/JIR.S495481

Nevertheless, the mechanism of JAK action remains unclear from the perspective of thrombosis. Meanwhile, JAK is increasingly used in rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, MDA5+ dermatomyositis, and other immune-mediated inflammatory diseases. The occurrence of thromboembolic events, as a drug-related adverse reaction should be considered when using JAK inhibitors.[13] In contrast, a study also reported that JAK inhibitors can reduce the upregulation of critical prothrombotic pathways and prevent increased leukocyte-endothelial adhesion.[14] From an inflammatory perspective, a pathological study involving 137 patients with LV reported that the occlusion of small vessels may represent a phenomenon secondary to lymphocytic vasculitis, explaining the effectiveness of anti-inflammatory agents, including intravenous immunoglobulin, tumor necrosis factor-α inhibitors, and JAK inhibitors, in LV.[15]

In addition to baricitinib, other biologics, including rituximab, adalimumab, and etanercept, can also be used to treat LV, although the underlying therapeutic mechanism remains unclear and limited to case reports.[16–19] Vieira et al reported a case of a 58-year-old female patient with sensory disorders in the back of the foot and recurrent episodes for many years, exhibiting poor response to conventional drugs. Rituximab was administered to the patient as a 1.0 g infusion, followed by another 1.0 g infusion 14 days later. The ulcer healed completely, and sensory disorders in the back of the foot improved after 1 year.[19] In another study on the efficacy of etanercept for LV, five patients with LV were administered subcutaneous injections of etanercept 25–50 mg once a week for 12 consecutive weeks. Notably, pain, erythema, and ulcer improved at average times of 2, 8.8, and 10.6 weeks, respectively, and the LV severity score, numerical rating scale, and dermatology life quality index decreased by 26.1%, 32.0%, and 34.3%, respectively, after 12 weeks of treatment without any adverse reactions.[18]

In conclusion, biologics for LV treatment are still being explored. The successful treatment of our patient with baricitinib provides additional evidence for the potential therapeutic effect of JAK1/JAK2 inhibitors in the LV, providing a reference for the dosage tapering regime of baricitinib in LV.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The collection and usage of the clinical information for research purpose were approved by Shanghai Children's Medical Center Ethical Committee. All procedures in this study were in accordance with the ethical standards specified in the World Medical Association Declaration of Helsinki. Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent was obtained from all participants or if participants are under 16, from a parent and/or legal guardian.

Consent for Publication

The authors certify that they have obtained the consent of the patient's parents for publication.

Acknowledgments

The authors would like to thank the patients and their family for their consent to publish this report and also would like to thank Editage (www.editage.cn) for English language editing.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All authors declare that they have no competing interests.

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