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CASE REPORT

Refractory Segmental Hyaline Vasculitis Treated with Janus Kinase Inhibitor Tofacitinib: A Case Report

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Abstract: This article reports a 59-year-old female patient who was diagnosed with segmental hyaline vasculitis and treated with tofacitinib for 2 months. In this case, multiple dark purplish-red spots were seen on both lower limbs, which did not fade with pressure. Flaky dark red spots, petechiae, ulcers, and necrosis were seen on the ankles. Histopathological manifestations were consistent with segmental hyaline vasculitis. The lesions subsided after the patient was treated with oral tofacitinib 5 mg twice daily for 1 month.

Keywords: cutaneous vasculitis, segmental hyaline vasculitis, tofacitinib

Introduction

Segmental hyaline vasculitis is a rare skin disease. It is characterized by thrombosis of small dermal vessels and local hypoxia leading to skin ulceration. It is often accompanied by significant pain, which severely impairs patients' quality of life. Treatment of segmental hyaline vasculitis aims to improve the skin lesions, reduce pain, and prevent the recurrence of the disease. There are various treatments have been reported. Treatments include anticoagulants, antiplatelet agents, thrombolytics, vasodilators, anabolic steroids, immunosuppressants, anti-inflammatory drugs, intravenous immunoglobulins, physiotherapy, and so on.[1] However, a clear consensus on treating this disease has not been reached. In addition, treatments with biologics, Janus kinase (JAK) inhibitors, and platelet-rich plasma (PRP) in combination with nonsteroidal anti-inflammatory drugs have been reported to be potentially effective.[2–4] Recently, a patient with segmental hyaline vasculitis was treated in our outpatient clinic. The patient was treated with tofacitinib, and achieved a good therapeutic effect. This case is reported as follows.

Case Report

A 59-year-old female patient went to our hospital on 10 July 2024 because of a rash on both lower limbs with itching for 1 day. One day ago, the patient found flaky, purpura-like erythema and papules on both lower limbs, accompanied by obvious itching. She was considered to have an "allergic purpura". She was given intravenous dexamethasone sodium phosphate, 10 mg daily for one day, and then 8 mg daily for 2 days. Then, the dose was reduced to 7 mg daily for 1 day, finally 5 mg daily for 3 days. At the same time, oral emetine fumarate at a dose of 2 mg daily and oral bispyrimethamine tablets at 75 mg daily were given. Topical dieldrin cream was also included. However, the treatment was not effective. The rash worsened, with patches of erythema and ecchymosis on the ankles, some crusted with central erosions. Allergic purpura with infection was considered. She was again given intravenous dexamethasone sodium phosphate, 8 mg daily, and oral cefdinir at a dose of 300 mg daily. However, the rash remained uncontrolled, with ecchymosis, local necrosis, and ankle pain (Figure 1a and b).

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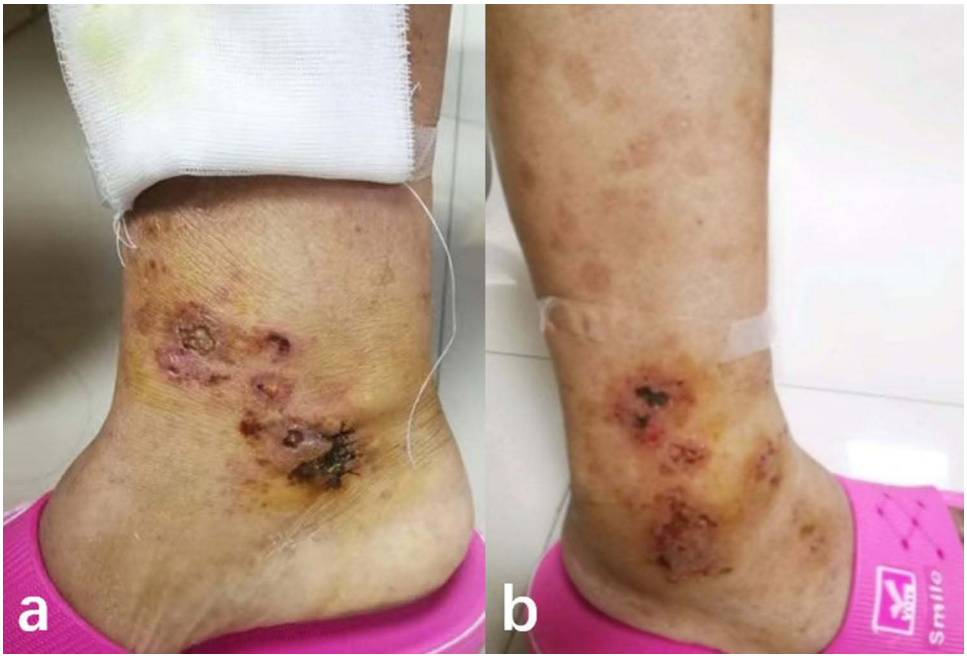

Figure 1 Before the patient was prescribed tofacitinib, there was erythema and ulcers covered with black scabs on the bilateral ankles and feet (**a** and **b**).

The patient has a history of hypertension and diabetes mellitus. She denied other systemic diseases and a family history of similar diseases. Physical examination revealed no obvious abnormality in each system. Dermatological examination showed multiple dark purple erythematous spots on both lower limbs, which did not fade when pressed. Patches of dark erythematous spots, petechiae, local ulcers, and necrosis were seen on the ankles.

A skin biopsy of the lesion on the patient's right lower limb at the ankle was performed. The histopathological results showed that hyperkeratosis, mild epidermal hyperplasia, and intraepidermal fissures were seen. A mixed inflammatory cell infiltration with more lymphocytes and eosinophils was seen in the superficial dermis and perivascular and subcutaneous tissues (Figure 2a and b). The laboratory results are shown as follows: CRP 15.4 mg/L; anti-hemolytic streptococcus O: 592.6 IU/mL; urine glucose 3+; blood glucose 6.62 mmol/L; Hepatitis B 5: HBcAb(+), HBeAb(+), HBsAg(+); Hepatitis B virus DNA <100 IU/mL. No obvious abnormalities were found in the blood routine, stool routine,

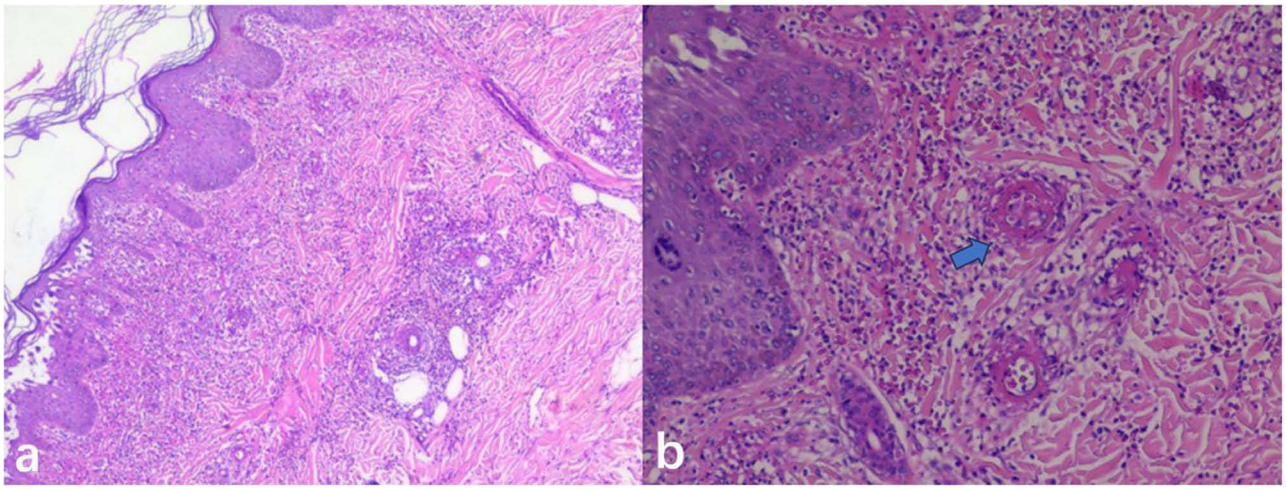

Figure 2 The histological features: Hyperkeratosis, mild epidermal hyperplasia, and intraepidermal fissures were seen. A mixed inflammatory cell infiltration with more lymphocytes and eosinophils was seen in the superficial dermis and perivascular and subcutaneous tissues. Hematoxylin-eosin, ×40 (**a**). Hematoxylin–eosin, ×100 (**b**).

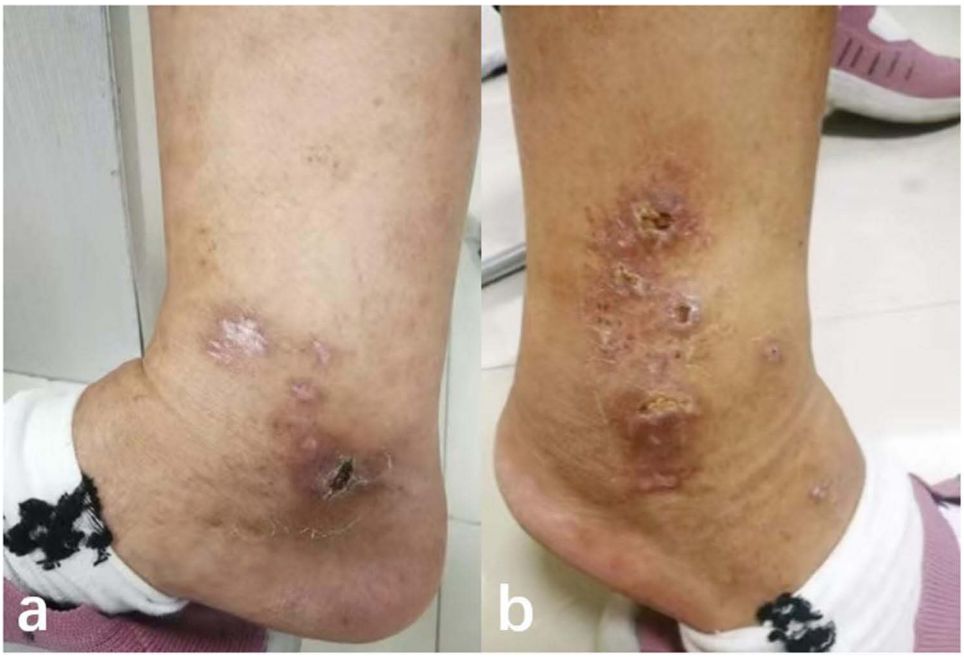

Figure 3 One month after tofacitinib treatment, the erythema subsided, the ulcers were healed, and no new lesion was presented (**a** and **b**).

blood lipids, and coagulation mechanism. The chest CT scan revealed fibrous foci in the upper lobe of the left lung and ground glass nodules in the lower lobe of the left lung. The electrocardiogram revealed sinus arrhythmia, incomplete right bundle branch block, and T-wave changes.

Eventually, the patient was diagnosed with segmental hyaline vasculitis, diabetes mellitus, and hypertensive disease. Then, she was started on tofacitinib citrate tablets, 5 mg orally twice daily on 19 August 2024, and other drugs were stopped. The skin lesions healed from ulceration and necrosis after 1 month of treatment with tofacitinib. The erythematous petechiae subsided (Figure 3a and b). Two months into therapy, the patient experienced substantial relief from the skin pain, and the skin lesions disappeared. After 6 months of follow-up, the patient's disease had no recurrence.

Discussion

Segmental hyaline vasculitis, also known as white atrophy and livedoid vasculopathy (LV), was first reported and named white atrophy by Milian in 1929. Bard et al named it livedoid vasculopathy in 1967.[5] It is a rare disease with an unknown etiology to date. LV is currently considered to be a thrombotic rather than an inflammatory disease, associated with coagulation disorders.[6,7]

LV is most common in young and middle-aged women. Its typical clinical presentation is chronic recurrent painful ulcers on both lower legs, especially ankles. Healing occurs with white atrophy, peripheral hyperpigmentation, and capillary dilatation. The histological features often show intraluminal thrombosis, endothelial hyperplasia, and segmental hyalinization of dermal vessels. Our patient had a history of diabetes mellitus, which can cause microangiopathy. Diabetes mellitus is also often comorbid with peripheral neuropathy.[8,9] Peripheral neuropathy in LV may be associated with an autoimmune etiology, not directly related to the skin lesions. This type of peripheral neuropathy differs from classical vasculitic neuropathy. The latter is usually treated with antithrombotic therapy.[10] The patient in our case had been treated with dipyridamole tablets, which were ineffective. Hypertension, which was comorbid in our patient, is also a potentially relevant condition for LV. Other relevant conditions include connective tissue disease.[11]

The diagnosis of LV is mainly based on histopathological examination, and other types of cutaneous vasculitis need to be excluded. There is no definite treatment for LV. The current treatment focuses on anticoagulation. Other therapies include systemic application of glucocorticoids, thrombolytic agents, hyperbaric oxygen, etc.[1] In this case, the patient was poorly treated with anticoagulation and hormone therapy. Her condition improved significantly after the application

of tofacitinib, a JAK inhibitor. The JAK signaling pathway is an intracellular signaling pathway on which many skin-related cytokines depend, including Interferon alpha/beta/gamma (IFN-α/β/γ), Interleukin 2/4/5/6/7/8/12/13/15/21/23 (IL-2/4/5/6/7/8/12/13/15/21/23). Other cytokines such as tumor necrosis factor alpha (TNF-α), IL-1, and IL-17 do not signal through Janus kinase/signal transduction and transcription activation (JAK/STAT), but JAK inhibitors can indirectly inhibit other STAT-dependent cytokines (IL-23) upstream of these cytokines (IL-17) by inhibiting them.[12] JAK inhibitors have shown good efficacy in treating autoimmune and inflammatory dermatoses. The involvement of the JAK/STAT signaling pathway in the pathogenesis of large-vessel and anti-neutrophil cytoplasmic antibody-associated vasculitis has been well established. In the follow-up study, Ebata et al found that JAK1 and JAK2 were significantly associated with the development of IgA vasculitis and cutaneous leukocyte-crushing vasculitis.[13] This suggested that the JAK/STAT signaling pathway is associated with the pathogenesis of cutaneous small vessel vasculitis. Drugs such as pan-JAK or JAK1/2 inhibitors may have good therapeutic potential in cutaneous vasculitis. In addition, aberrant activation of the JAK/STAT signaling pathway is closely associated with thrombosis and thromboembolic complications.[14] There are few reports on the successful treatment of LV with JAK inhibitors, only a few reports on treatment of LV with baricitinib (JAK1/2 inhibitor),[4] abrocitinib (JAK1 inhibitor).[15] Jia et al reported another case in which a 17-year-old male with a 3-year history of LV. He was treated with tofacitinib for 1 year without disease recurrence after conventional treatment failed.[16] However, there have been few reports about the early application of tofacitinib for the treatment of LV. In our patient, she had a history of skin lesions for only 1 month and was treated with tofacitinib at an early stage.

Tofacitinib reduces the activity of JAK1, JAK2, and JAK3. In vitro, data showed that tofacitinib exhibited the broadest inhibitory effect on cytokines through the JAK signaling pathway among all JAK inhibitors. The Food and Drug Administration (FDA) approved tofacitinib for the treatment of rheumatoid arthritis in 2012. Previous studies have observed a possible increased risk of cardiovascular events, serious infections and cancer in patients receiving higher doses of tofacitinib (10mg twice daily). Therefore, only a dose of 5 mg twice daily is approved for rheumatoid arthritis.[17] Follow-up studies have confirmed a significantly higher risk of venous thromboembolism with tofacitinib at a dose of 10 mg twice daily, and a dose of 5 mg twice daily was safer.[18] In our patient, tofacitinib 5 mg orally twice a day was used. After 2 months of treatment, the skin lesions subsided, and the pain disappeared. The patient's disease did not recur during the next 6-month follow-up. This suggests that this dose of tofacitinib may be safer for the treatment of LV.

Conclusion

Currently, there are fewer reports on the use of JAK inhibitors for the treatment of LV. Through this case report, we assert that early application of tofacitinib may be one of the safe and effective treatment options for LV. However, its effectiveness and safety still need to be confirmed by a large number of clinical randomized controlled trials.

Informed consent

The patient has given informed consent to the publication of her case details and images.

Institutional Approval

As this is a case report, formal institutional review board approval was not required.

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Disclosure

The authors report no conflicts of interest in this work.

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