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Chronic Leg Ulceration Associated with Polycythemia Vera Responding to Ruxolitinib (Jakafi®)

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Abstract

We present the case of a 63-year-old white male with bilateral chronic leg ulcers due to polycythemia vera and hydroxyurea therapy who demonstrated dramatic healing of his wounds in response to ruxolitinib (Jakafi®, Novartis), a novel Janus kinase-1 and -2 inhibitor. This patient's wound had previously been refractory to multiple surgical interventions and immunosuppression. After the initiation of ruxolitinib, the patient underwent successful split-thickness skin grafting, with resultant healing of his wounds. He was stable without prednisone and other immunosuppressant therapy and had healed at 6 months. Ruxolitinib therapy could represent a novel option for patients who develop persistent inflammatory wounds in the setting of polycythemia vera and hydroxyurea therapy.

Keywords

chronic wound; hydroxyurea; leg ulcer; polycythemia vera; pyoderma gangrenosum; split-thickness skin graft

Leg ulceration is a known complication of hydroxyurea use in the setting of polycythemia vera (PV) and sickle cell disease that can be very challenging to treat (1–3). Although the ulcers often respond to withdrawal of hydroxyurea, this is not always feasible owing to the underlying hematologic condition (4). Ruxolitinib is an oral selective inhibitor of Janus kinase (JAK)-1 and -2 recently approved by the U.S. Food and Drug Administration for the treatment of intermediate-and high-risk myelofibrosis and PV (5–7). Patients with leg ulcers were excluded from the original studies of ruxolitinib in myelodys-plastic disease because of

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concerns about infection. However, we report the use of ruxolitinib in a patient with resistant PV-associated leg ulceration. The impressive response of this patient was very promising, suggesting a possible role for JAK inhibition in patients with chronic leg ulceration associated with myelofibrotic disorders.

Case Report

A 63-year-old white male with bilateral foot and ankle ulceration associated with PV and chronic hydroxyurea therapy was followed up at our institution from January 2006 to April 2013. At presentation, the patient had had refractory leg ulcers for 1 year. Wound debridement and grafts with biologic alternative tissues had previously been unsuccessful. Because of a presumptive diagnosis of pyoderma gangrenosum, he was started on high-dose prednisone at a dose of 80 mg/day and mycophenolate mofetil (CellCept®, Genentech, South San Francisco, CA) 1.5 g twice daily.

Approximately 6 months before the presentation, the patient had developed a left leg deep venous thrombosis and began anticoagulation with warfarin. Concurrently with this, he also reported development of Raynaud's phenomenon of the digits and erythematous papules on the dorsum of the bilateral digits, consistent with Gottron's papules. He denied muscle weakness, malar and discoid rashes, sicca symptoms, oral ulcers, cough, chest pain, and shortness of breath. The patient had a remote history of colon cancer treated 15 years before presentation with hemi-colectomy and chemotherapy. The gastrointestinal workup was negative for colon cancer recurrence or evidence of inflammatory bowel disease.

He had no family history of autoimmune disease, diabetes, or leg ulceration. The patient worked full time as a defense contractor. He did not smoke, use illicit substances, or drink alcohol.

On the initial examination, the patient was afebrile. He had a blood pressure of 120/56 mm Hg and pulse of 104 beats/min regular rhythm. The head and neck evaluation was remarkable only for bilateral hearing aids; he had no malar or discoid or heliotrope rashes. He had no oral ulcers and had a normal oral aperture and normal salivary pooling. His neck was supple, with no lymphadenopathy or thyromegaly. The cardiovascular, respiratory, and abdominal examination findings were unremarkable. On examination of the hands, he had scaly erythematous lesions over the metacarpophalangeal joints and proximal interphalangeal joints. He had no rash on the torso or chest. His muscle strength was 5 of 5 in all muscle groups. The examination of the legs revealed bilateral deep necrotic ulcers (Fig. 1).

Pathologic examination of the wound biopsy specimen demonstrated necrosis with dense neutrophilic and mixed inflammatory infiltrate. Superficial capillaries demonstrated thick periodic acid-Schiff stain-positive walls, and the dermal capillaries demonstrated thick walls and almost occluded lumens (Fig. 2).

Laboratory Data

At presentation with the leg ulcerations, the laboratory workup revealed mild leukocytosis and hemoglobin of 14.3 g/dL, consistent with his known PV. He was homozygous for the JAK-2 mutation. The autoimmune profile was negative (Table 1). The results of the arterial studies were within normal limits. The venous studies showed an incompetent deep venous system, with reflux involving the common femoral, proximal femoral, mid-femoral, distal femoral, and popliteal veins.

The patient had had several hospitalizations during the course of several years. He was initially treated with prednisone, mycophenolate mofetil, intravenous immunoglobulin, pentoxifylline, and sulfasalazine. He underwent a venous ablation procedure to address the venous insufficiency, with no improvement in the ulcers. Because of the lack of a response to immunosuppression and because of the skin lesions, which were consistent with the amyopathic vasculitic rashes known to be associated with hydroxyurea therapy, an attempt was made to wean the patient off the hydroxyurea. However, his ulcers worsened, and the hydroxyurea had to be increased back to 1500 mg/day.

In conjunction with the intravenous immunoglobulin therapy, the patient developed an additional deep venous thrombosis, and the warfarin therapy was changed to low-molecular-weight heparin (enoxaparin) at a dose of 1 mg/kg twice daily. Despite all these measures, the ulcers remained refractory to therapy. Immunosuppression was changed to methotrexate and tumor necrosis factor-α inhibition. He underwent repeated debridement, repeated attempts at bioengineered alternative tissue grafting, split-thickness skin grafting, hyperbaric oxygen therapy, local wound care, and low-frequency ultrasound therapy (MIST®, Celleration, Eden Prairie, MN), but the ulcers continued to worsen. Amputation was discussed, but the patient declined.

Approximately 5 years after the initial presentation, because of the persisting leg ulceration, another attempt was made to stop the hydroxyurea. The patient developed progressive leukocytosis, weight loss, splenomegaly, and headaches. Magnetic resonance imaging of the brain revealed a 6 × 5-mm hypothalamic mass, which was thought to be consistent with extramedullary hematopoiesis secondary to postpolycythemia myeloid metaplasia. The tumor necrosis factor-α inhibitor was discontinued, and hydroxyurea was reinstituted. A bone marrow biopsy was not performed, but peripheral blood cytogenetic testing was negative for acute myeloid leukemia.

After a discussion of the risks, ruxolitinib was added at a dose of 10 mg twice daily, and the hydroxyurea dosage was decreased. Approximately 5 weeks after beginning this therapy, the white blood cell count began to decline; as a result, the hydroxyurea was discontinued. The wounds began to heal, and the patient underwent split-thickness skin grafting with a more than 80% take. The methotrexate dose was tapered and then withdrawn. The residual wound healed by secondary intention. Fig. 3 shows the timeline of the patient's total wound surface area as it covaried with the hemoglobin and total white blood cell count, with the dates of the surgical interventions and medication exposures superimposed. At 6 months of ruxolitinib therapy, the wounds had entirely healed (Fig. 4). The other skin manifestations attributed to hydroxyurea use, including the Gottron papules on the digits persisted, but the Raynaud phenomenon, which was likely related to hyperviscosity, had totally resolved. The headaches had also resolved, and repeat imaging demonstrated stability of the hypothalamic mass. At the 12-month visit, the patient was mobilizing independently and regaining full function and range of motion at the ankle through physical therapy. However, 15 months after the final surgery and 18 months after initiation of ruxolitinib, the patient died of a cerebral hemorrhage.

Discussion

PV is a chronic myeloproliferative disorder characterized by an increased red blood cell mass with a low erythropoietin level and the presence of the JAK-2 mutation (V617F) in 92% of cases (8–10).

Hydroxyurea is an antimetabolite used in the treatment of PV that impairs DNA repair by inhibiting ribonucleotide reductase. It has been recommended for PV therapy in conjunction

with phlebotomy for patients who are older than 60 years and those with previous thrombosis. Hydroxyurea is usually fairly well tolerated but is known to be associated with a variety of dermatologic side effects, including alopecia, diffuse hyperpigmentation, erythema, skin atrophy, an amyopathic dermatomyositis presentation (11), nail changes, poikilodermatous dermatitis (11,12), and resistant leg ulcers (1–3,13–15). Leg ulceration occurs in approximately 9% of patients receiving hydroxyurea in the setting of myeloproliferative syndromes and in approximately 29% of patients taking hydroxyurea for management of sickle cell anemia (1). This complication seems to be dose dependent, with studies reporting an association with a mean cumulative exposure to hydroxyurea of 3.2 (range 1.4 to 5.5) kg and mean duration of hydroxyurea treatment of 6.1 (range 2 to 15) years. Biopsy specimens have shown nonspecific changes, with 1 series reporting epidermal atrophy, dermal fibrosis, and occasional fibrin occlusive vasculopathy similar to that seen in livedoid vasculitis (2). Although it has been postulated that the pathogenesis of leg ulcers relates in part to the underlying prothrombotic state (4,16–19), to date, the only effective therapy for these ulcers has been withdrawal of hydroxyurea (2,13,14,20); however, the underlying hematologic state often precludes this.

The JAK signal transducer and activator of transcription pathway is a final common pathway of signal transduction for various cytokines and growth factors, including erythropoietin, thrombopoietin, granulocyte macrophage colony-stimulating factor, granulocyte colony-stimulating factor, and interleukin-3, -5, and -6 (10). Under normal conditions, JAK-2 becomes activated in response to growth factor or cytokine binding; however, in myelodysplastic syndromes such as PV, the acquired gain of function mutations in JAK-2 result in constitutive activation in the absence of any ligand (8,21).

Ruxolitinib is an oral selective inhibitor of JAK-1 and -2 recently approved by the U.S. Food and Drug Administration for the treatment of intermediate- and high-risk myelofibrosis (5–7). Patients with leg ulcers were excluded from the original studies of ruxolitinib to treat myelodysplastic disease because of concerns about infection. However, we report the use of ruxolitinib in a patient with resistant PV-associated leg ulceration. The impressive wound healing seen in the present case merits additional investigation and suggests a possible role for JAK inhibition in patients with chronic leg ulceration associated with myelofibrotic disorders.

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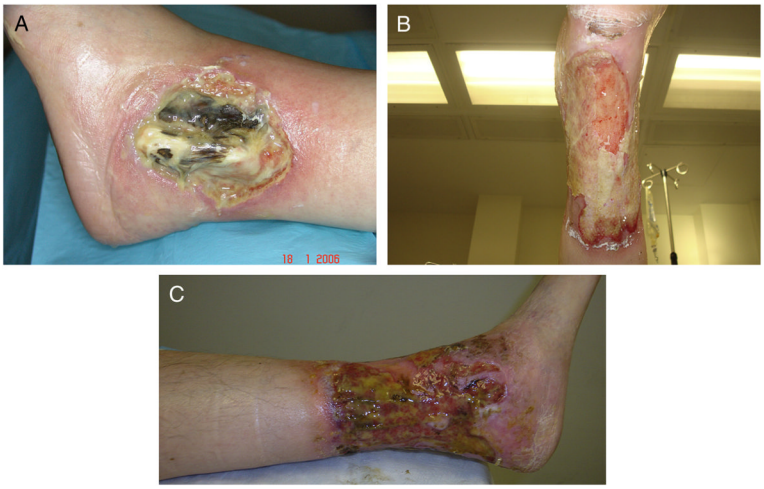

Fig. 1.
(*A*) Lateral malleolar ulcer at presentation demonstrating central necrosis of the tendons with extensive inflammatory slough and deep overhanging gunmetal gray borders consistent with pyoderma gangrenosum. (*B*) and (*C*) Progression of ulceration to become circumferential by 3 years after presentation.

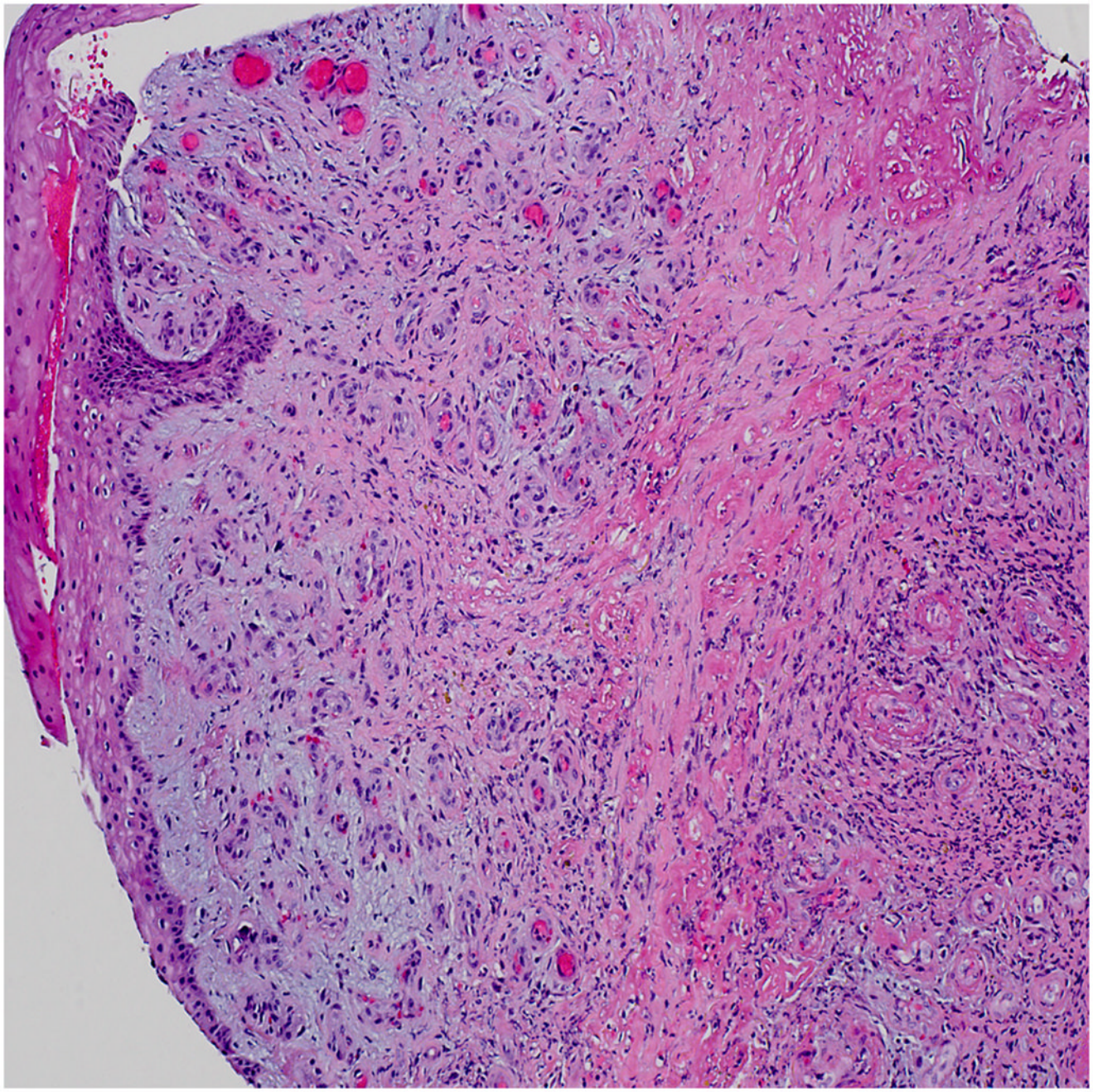

Fig. 2.
Histopathologic findings from wound biopsy specimen demonstrating ulcer border showing mixed inflammatory infiltrate, including prominent neutrophils, granulation tissue formation, and fibrinous occlusive vasculopathy (hematoxylin and eosin stain, original magnification ×10).

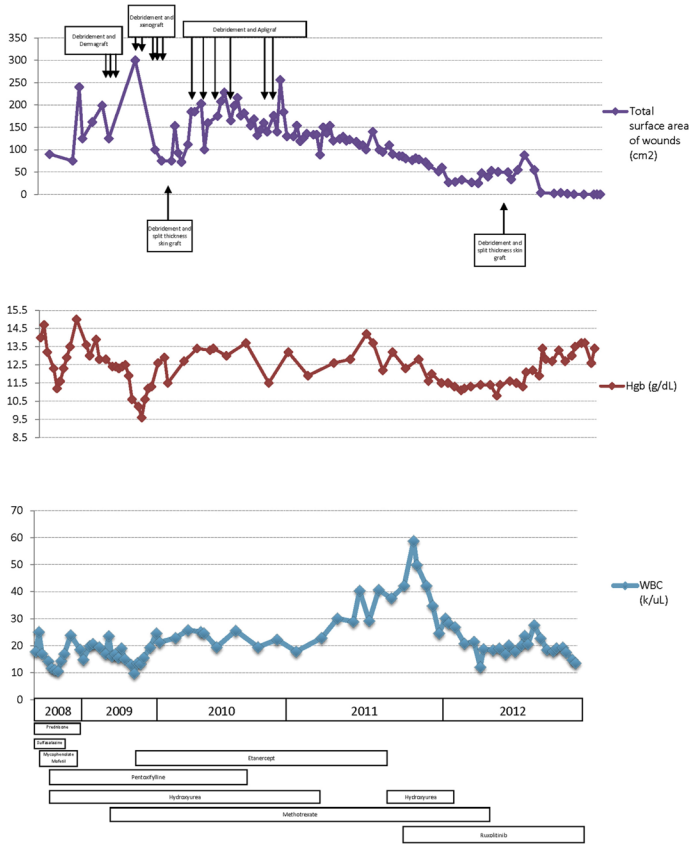

Fig. 3.

Graphic timeline of *(top)* total surface area of wounds, *(middle)* hemoglobin, and *(bottom)* total white blood cell count, along with a timeline of medication exposures *(bars)* and surgical interventions *(arrows)*.

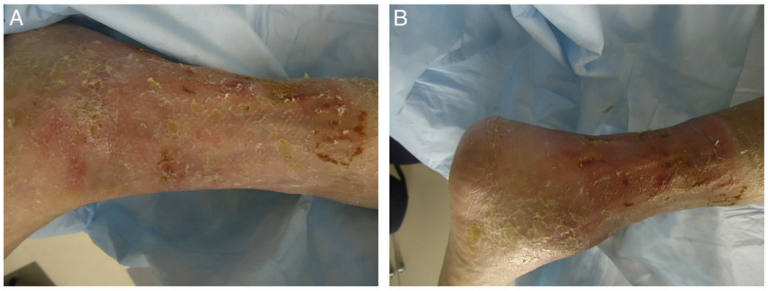

Fig. 4.
Photograph of leg demonstrating complete healing of the wounds after split-thickness skin grafting and initiation of ruxolitinib therapy.

Table 1

Hematologic parameters and autoimmune profile at presentation

Variable	Patient's Findings	Normal Range
Janus kinase-2 mutation	Homozygous	
White blood cell count (k/μL)	14.3	4.0–10.8
Differential (%)		
Neutrophils	93.9	
Lymphocytes	4.0	
Hemoglobin (g/dL)	14.3	12.5–16.5
Hematocrit (%)	37.4	41–53
Red blood cell distribution width (%)	16.6	11–15
Platelet count (k/μL)	398	145–400
Sodium (mmol/L)	136	137–145
Potassium	4.7	3.5–5.1
Blood urea nitrogen (mg/dL)	20	9–20
Creatinine (mg/dL)	0.9	0.66–1.50
Alkaline phosphatase (U/L)	93	38–126
Aspartate aminotransferase (U/L)	23	3–34
Alanine aminotransferase (U/L)	29	15–41
ANA immunofluorescence	Negative	Negative
dsDNA antibodies	Negative	Negative
Antineutrophil cytoplasmic antibodies	Negative	Negative
Sjögren's antibodies (SSA and SSB)	Negative	Negative
Sm antibody	Negative	Negative
RNP antibody	Negative	Negative
Thyroid-stimulating hormone (IU/mL)	1.58	0.40–4.0
Uric acid (mg/dL)	2.4	3.5–7.2
Hemoglobin A1c (%)	4.7	4.2–5.6
β2-Glycoprotein I antibodies IgG (U/mL)	<4.0	<10.0, negative
β2-Glycoprotein I antibodies IgA (U/mL)	<4.0	<10.0, negative
β2-Glycoprotein I antibodies IgM (U/mL)	<4.0	<10.0, negative
Anticardiolipin antibodies IgG (U)	<23	<23, negative
Anticardiolipin antibodies IgA (U)	<11	<11, negative
Anticardiolipin antibodies IgM	<11 units	<11, negative
Lupus anticoagulant ratio	Negative	1.2–1.5 (weakly positive) 1.5–2.0 (moderately positive) >2.0 (strongly positive)
Sedimentation rate (mm/hr)	10	0–16
C-reactive protein (mg/L)	1.2	0.00–3.00
Human immunodeficiency virus 1 and 2	Negative	Negative
Hepatitis B surface antibody	Negative	Negative
Hepatitis C antibody	Negative	Negative

Variable	Patient's Findings	Normal Range
Plasminogen activator inhibitor mutation	4G/5G, heterozygous	5G/5G
Factor V Leiden (R506Q) mutation	Negative	Negative
Methyl-tetrahydrofolate reductase C677T mutation	C677T, homozygous	Negative
Prothrombin gene (G20210A) mutation	Negative	Negative

Abbreviations: ANA, antinuclear antibody; dsDNA, double-stranded DNA; RNP, ribonucleoprotein.