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ORIGINAL ARTICLE

Lower Limb Refractory Ulcers and Postoperative Nonhealing Wound: Review of the Literature

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ABSTRACT

Lower limb ulcers including nonhealing postoperative wounds are challenging problems, especially to orthopedic surgeons. Such ulcers are recognized complications of rheumatoid arthritis but the scenario has changed for the better since the advent of aggressive disease-modifying antirheumatic drugs (DMARDs). Out of different types of lower limb ulcerations including venous, arterial, lymphatic, malignancies, infection, medication induced and inflammatory, autoimmune inflammatory conditions need to be delineated. They can be improved, though slowly with DMARDs. The pathogenesis is multifactorial but most prevalent are vasculitis. The various investigative tools for diagnosing the causes of these ulcers include plethysmography, ultrasound, angiography, computed tomography, magnetic resonance imaging, chromosomal analysis, and, most importantly, skin biopsy. Clinical presentation of the patient still remains the supreme disease tracker. Review of the literature is presented to ascertain the evidence for best clinical practice.

Keywords: Disease-modifying antirheumatic drugs, Immunomodulators, Immunosupressants, Infection, Limb ulcers, Pain, Rheumatoid arthritis, Vasculitis.

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INTRODUCTION

Lower limb ulcers (Fig. 1) are challenging problems to orthopedic surgeons, especially when postoperative wounds even without any evidence of local sepsis is not healing and anxiety is writ large on surgeons' face in such a situation.

With orthopedic surgeons' increasing awareness of rheumatology, lower extremity nonhealing wounds, including postoperative ulcers, are now better understood. It simultaneously also reflects on clinical experiences of orthopedicians' successful use of antitubercular treatment in nonhealing postoperative wounds. Ponseti's polyarticular rheumatism is also a known clinical entity in which a patient with tuberculosis gets polyarticular involvement, signifying autoimmune factors' initiation even with tubercular infection. Finally, a question definitely remains to be answered – role of antitubercular drugs as immunosuppressants and immunomodulators in wound healing.

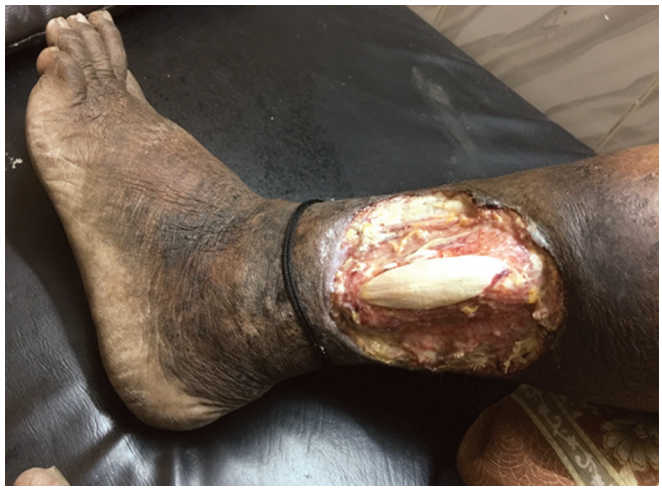

Fig. 1: Giant nontraumatic ulcer

Lower extremity ulcers are a recognized complication of rheumatoid arthritis. The involved pathogenesis is multifactorial,[1,2] and all the following are reported to play a role:

- Vasculitis[3]
- Felty's syndrome (swollen spleen, decreased white blood cell count, and repeated infections)[4]
- Posttraumatic deformity, neuroarthropathy, venous insufficiency
- Arterial disease

Prevalence of approximately 8 to 9% of leg ulceration in rheumatoid arthritis is reflected in historical cohorts. Seropositive and erosive rheumatoid arthritis is associated with ulceration. Vasculitis and its other extra-articular vasculitic manifestations of rheumatoid arthritis are mainly responsible for these nonhealing ulcers.

Differential Diagnosis

Factors attributing to various causes are enumerated in Table 1.[5] A list of whole gamut of other causes not included in Table 1 is detailed in Table 2. Flow chart 1 to proceed after history and clinical examination to differentiate painful and painless ulcers.

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Table 1: Causes of leg ulcers

Vascular	Venus
	Arterial
	Mixed
Neuropathic	Diabetes
	Tabes
	Syringomyelia
Metabolic	Diabetes
	Gout
	Prolidase deficiency
Hematological	Sickle cell disease
	Cryoglobulinemia
Trauma	Pressure
	Injury
	Burns
Tumors	Basal cell carcinoma
	Squamous cell carcinoma
Infection	Bacterial
	Fungal
	Protozoal
Panniculitis	Necrobiosis lipoidica
	Fat necrosis
Pyoderma	Gangrenosum
Special	Hypertensive ulcer/obesity

Table 2: Other causes of limb ulcers

Physical or chemical injury	Pressure (decubitus), pressure by shoes, plaster of Paris, orthopedic appliances, compression bandages, trauma, burn wounds, freezing, electricity, intra-articular injection of yttrium-90, chemical (corrosive agents) sclerotherapy, artificial (automutilation)
Malignancy	Sarcoma, lymphoma, squamous cell carcinoma, basal cell carcinoma, metastatic cancer, Kaposi's and pseudo-Kaposi's sarcoma, cutaneous T-cell and B-cell lymphoma, Hodgkin's disease
Drug induced	Steroid ulcus (intralesional injection), vaccination ulcer (Bacillus Calmette–Guérin), halogens, ergotamine, methotrexate, hydroxyurea, paravasal injection of cytostatic and other drugs, granulocyte colony-stimulating factor
Ulcerating skin diseases	Pseudoepitheliomatous hyperplasia, epithelioma, pyoderma gangrenosum, pemphigoid, panniculitis, periarteritis nodosa, erythema induratum, Behcet's disease, cutaneous discoid and systemic lupus erythematosus, scleroderma, lichen planus, keratosis actinica, contact dermatitis, fat necrosis, or pancreatic fat necrosis
Autoimmune	Dermatitis, lupus, rheumatoid arthritis, vessel: small-vessel leukocytoclastic vasculitis, microscopic polyangiitis, Wegener's granulomatosis, allergic granulomatosis (Churg-Strauss), Henoch-Schonlein purpura, essential cryoglobulinemic vasculitis, erythema induratum Bazin, livedo reticularis, livedo vasculitis and Sneddon syndrome, polyarteritis nodosa, Kawasaki disease
Metabolic	Diabetes mellitus, necrobiosis lipoidica, porphyria cutanea tarda, gout, calciphylaxis, calcinosis cutis, homocysteinuria, prolidase deficiency, hyperoxaluria
Hematologic disorders	Thalassemia, hereditary spherocytosis, glucose-6-phosphate dehydrogenase deficiency, essential thrombocythemia, thrombotic thrombocytopenic purpura, granulocytopenia, polycythemia, leukemia, Waldenstrom's disease, multiple myeloma, cryofibrinogenemia, purpura, hyperglobulinemia, cold agglutinins
Clotting disorders	Factor V Leiden, lupus anticoagulant, antiphospholipid syndrome, disturbed fibrinolysis, factor XIII deficiency, antithrombin III deficiency, protein C or S deficiency, Marcoumar necrosis, large hematoma, purpura fulminans, diffuse intravasal coagulation

Investigation

Diabetes venous insufficiency and vascular disease must be looked for. Biopsy of the ulcers may be inconclusive in some, but evidence of vasculitis can be delineated. Cholesterol emboli syndrome unusually can also be visible.[6] Leukocytoclastic vasculitis in tissue adjacent to the ulcer border with an area of intact epidermis can be visualized in positive cases. Common sites for vasculitis are foot (malleolar, dorsal foot, plantar foot) and calf regions. Chromosome analysis, antiphospholipid profile, lupus anticoagulant titers, antiphospholipid antibodies [anti-cardiolipin immunoglobulin A (IgA) antibody and beta-2 glycoprotein 1 IgA] should be routinely investigated. Genetic prothrombotic study should also be performed. Factor V Leiden mutation, MTHFR C677T PAI-1 mutation details can be part of this genetic observation.

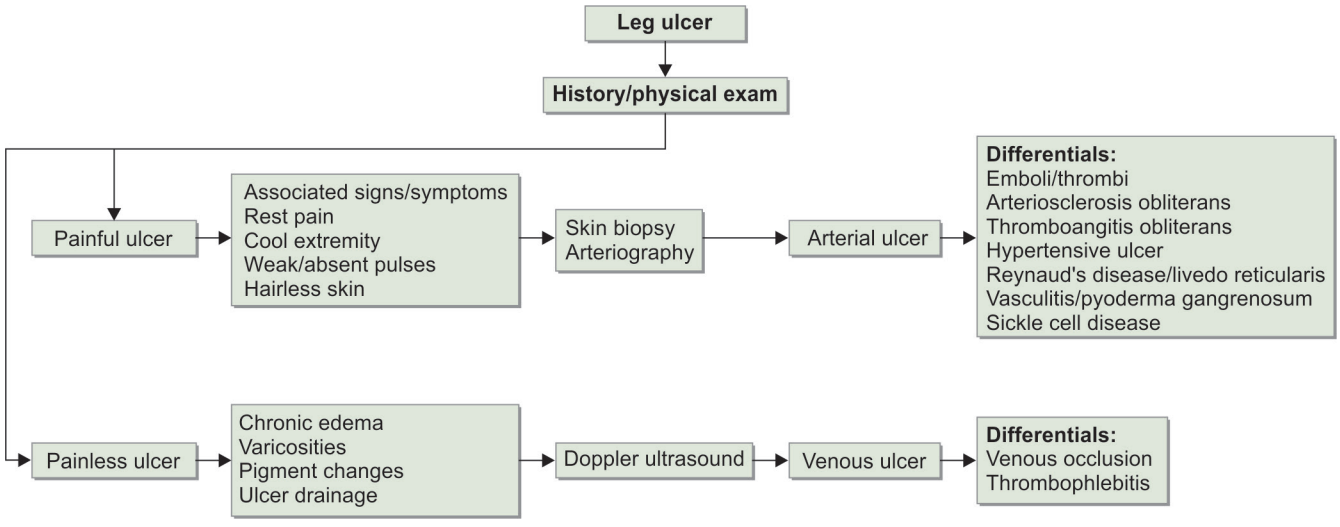
Treatment

Nonbiologic DMARD, biologic antitumor necrosis factor-alpha (anti-TNF alpha) agents are used, but evidence suggests that rheumatoid arthritis-associated ulcers benefit from addition of anti-TNF alpha agents with improved outcome.

Final statistics shows that ulcers remain an important clinical problem (only 30% of cases had healing in approximately more than 2 months follow-up) although ulcer prevalence has improved with the use of above treatment. In these autoimmune ulcers, it must again be emphasized that pathologic features of vasculitis are not always evident of tissue biopsy. All these patients with ulcers in rheumatoid arthritis had radiographic evidence of erosive disease and 63% were seropositive, suggesting definite correlation of these ulcers with extra-articular rheumatoid disease.

Center for wound healing recommends to adopt a multidisciplinary approach in the management of complex wounds including comprehensive evaluation for venous and arterial disease and aggressive management

Flow chart 1: Differential diagnosis for lower limb ulceration



of diabetes, if present.[2,3] Even in well-controlled diabetics, the wounds refuse to heal; hence, the ulcers are not thought to be due to diabetes.

Other autoimmune diseases like antiphospholipid antibodies, other prothrombotic states, scleroderma ulcers can be prevalent. The endocrinopathy associated with Klinefelter's syndrome has recognized complication of developing lower extremity ulceration, so should be considered as nonhealing lower limb ulcer. Testosterone level and its administration are important in evaluation and its management.

Vasculitis needs special mention: Vasculitis is a term used to describe a group of uncommon diseases which produce inflammatory changes and necrosis in the blood vessel walls. Loss of integrity leads to bleeding, and compromise of the lumen leads to tissue ischemia and necrosis Langford.[7]

The outcome of this inflammation depends on the size, type, and location of the vessels involved. Inflammation can affect the aorta and its branches, or may affect medium-sized arteries through to small arteries, venules, and arterioles Scott.[8] It is small vessel vasculitis that is most commonly associated with cutaneous changes, including nail fold infarct and potentially leg ulceration.

Vasculitis may occur as a primary process or may be secondary to another underlying disease, e.g., rheumatoid arthritis, lupus, or Sjögren's syndrome. Other general features, such as fever, weight loss, and anorexia may accompany widespread inflammation. Therefore, patients often feel systemically unwell.

Diagnosis of Vasculitis

The diagnosis of vasculitis is often very difficult. If it occurs in combination with another illness, such as rheumatoid arthritis, lupus, or Sjogren's syndrome, then it may be suspected if new or worsened symptoms appear, e.g., weight loss, fever, fatigue, palpable purpura, or nail fold infarcts. A mononeuritis multiplex (i.e., asymmetric neuropathy) is often suggestive of vasculitis in the absence of diabetes Hellmann.[9]

In addition to detailed history and examination, laboratory tests help identify the existence and type of vasculitis and are also useful in identifying any infective influence on the condition. These are often carried out through a specialist unit and are not always available via general community services.

Immunosuppressive Therapies

Treatment will depend on the type, nature, and severity of the vasculitis. In proven serious vasculitic conditions, powerful therapy is indicated. In initial stages, high-dose oral steroid is generally initiated and may be accompanied by 2 to 6 weekly pulses of intravenous cyclophosphamide, an immunosuppressant drug used under specialist direction. It is important not to ignore the potential side effects of these agents. Complications of steroid therapy are well documented Griffiths.[10] Careful monitoring of opportunistic infection, bone marrow suppression, and hemorrhagic cystitis is necessary. There needs to be awareness of the potential for the subsequent development of bladder tumor and increased risk of other neoplasia Brzeski.[11] Mortality data suggest that while early deaths in vasculitis are the result of the active disease, late deaths may be caused by the complications of therapy Langford.[7]

The goal of initial treatment is to induce remission of the disease. Once this has been accomplished, the drug dose is lowered to reduce side effects. Low-dose oral steroid, azathioprine, and methotrexate have been used in less severe forms of vasculitis and as maintenance therapy after remission has been induced.

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