Rheumatoid Ulcers

3

Sankha Shubhra Chakrabarti

3.1 Introduction

Rheumatoid arthritis is the most common type of autoimmune arthritis characterised by pain, swelling, and tenderness of peripheral joints in a symmetrical pattern. It is also characterised by prominent extra-articular manifestations. These include rheumatoid nodules, pulmonary involvement, vasculitis, and systemic effects [1]. Ulcers of the extremities have been reported in around 10% cases of rheumatoid arthritis, but in contrast, rheumatoid arthritis is a rare cause of ulcers of the extremities [2]. When one thinks of rheumatoid limb ulcers, the general idea that comes to mind is of cutaneous ulcers related to rheumatoid vasculitis. However, there may be other aetiologies of limb ulcers in rheumatoid arthritis, with ulcers due to imbalances in foot pressure resulting from deformities being some of the common ones [3]. Infective and iatrogenic ulcers, ulcers resulting from co-existent diseases such as chronic venous insufficiency, atherosclerotic peripheral vascular disease, ulcers resulting from cutaneous dystrophic calcinosis, and multifactorial ulcers have also been observed in large retrospective studies involving patients of rheumatoid arthritis [4, 5]. A particularly interesting entity is pyoderma gangrenosum, which is responsible for chronic non-healing ulcers in the limbs. Pyoderma gangrenosum is an uncommon inflammatory disorder of the skin characterised by neutrophilic infiltration. The spectrum of skin manifestations ranges from papules or pustules to painful ulcers. Rheumatoid arthritis is one of the major systemic inflammatory conditions associated with pyoderma gangrenosum [6]. In this chapter, we will discuss the epidemiology of rheumatoid

S. S. Chakrabarti (✉)
Department of Geriatric Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India
e-mail: sankha.chakrabarti1@bhu.ac.in

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ulcers of the extremities, the pathogenesis of major aetiologies of rheumatoid limb ulcers, their presenting clinical manifestations, diagnostic approach to them, and treatment options for such ulcers.

3.2 Epidemiology of Rheumatoid Limb Ulcers

Rheumatoid arthritis is the most common autoimmune arthritis and affects around 0.5–1% of the world population [7]. Higher prevalence has been reported for some native American populations such as the Pima Indians and Chippewa Indians. On the other hand, Chinese and Japanese populations have reported lower prevalence and some studies on rural populations in South Africa and Nigeria failed to identify any cases of rheumatoid arthritis despite good sample sizes [7]. Like most autoimmune diseases, rheumatoid arthritis has a female preponderance with a two–threefold higher prevalence [8]. Previously thought to be a disease of younger adults, it is now widely accepted that the elderly are also affected by rheumatoid arthritis. In fact, rheumatoid arthritis is one of the most common inflammatory diseases of the elderly. Elderly onset rheumatoid arthritis is defined as having an onset above 65 years of age, and like rheumatoid arthritis of the young, also has a predilection for females [9].

As far as ulcers of the extremities are concerned, rheumatoid arthritis and other inflammatory conditions are rare aetiologies overall but do account for a considerable proportion of non-healing chronic limb ulcers. Experience from a multidisciplinary wound healing and limb preservation clinic from the University of Pittsburgh revealed that around 7% of leg ulcerations had a reasonably certain collagen vascular aetiology [10]. While the experience from less specialised and more peripheral centres may turn up lower numbers, autoimmune diseases must be suspected as potential causes of non-vascular chronic limb ulcers. Foot ulcer prevalence is around 10% in patients of rheumatoid arthritis in the course of their disease. Prevalence of extremity ulceration may be higher if upper limb vasculitic ulcers are also included. Those developing rheumatoid foot ulcers have a nearly 50% recurrence rate at same and different sites [3]. The major classes of ulcers of the extremities in rheumatoid arthritis patients are ulcers due to co-existent arterial or venous insufficiency, ulcers due to deformities leading to differential load distribution on the limbs, and vasculitic ulcers. Besides contributing to the pathogenesis of ulcers of the extremities, rheumatoid arthritis is also a cause for impaired healing of the ulcers, leading to chronicity.

3.3 Pathogenesis

The pathogenesis of a rheumatoid limb ulcer is complex and multifactorial. It is depicted in Fig. 3.1 and can be discussed under varied sub-headings.

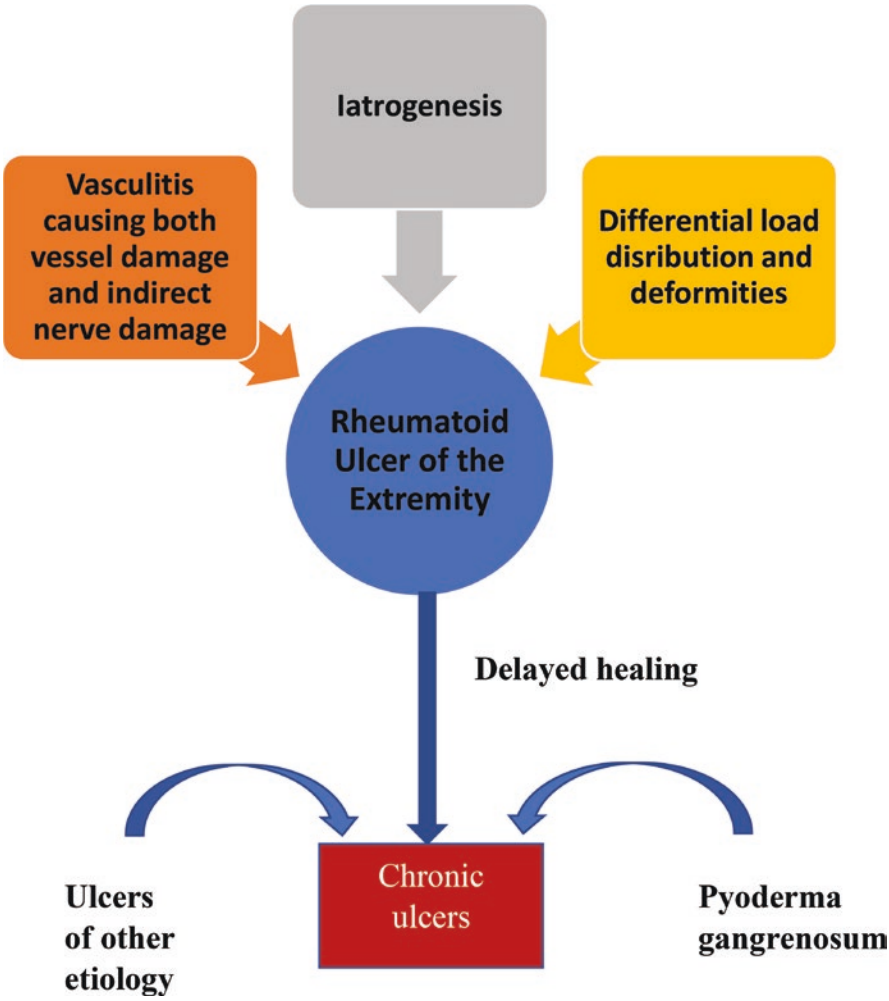

Fig. 3.1 Pathogenesis of rheumatoid limb ulcer

3.3.1 Vasculitis and Inflammation

The hallmark of a non-healing rheumatoid limb ulcer is inflammation and vasculitis, albeit as a subtype these ulcers are rarer. Rheumatoid vasculitis is undifferentiable from other causes of vasculitis. It is classified as a "vasculitis associated with systemic disease" as per the 2012 revised Chapel Hill consensus conference nomenclature criteria [11]. Rheumatoid vasculitis affects vessels of any calibre but more frequently small and medium-sized vessels and is characterised by infiltration of vessel walls by mononuclear cells or neutrophils [12]. An association with specific genotypes of the *HLA-DRB1* shared epitope has been reported, and markers of immune involvement such as high titres of rheumatoid factor and anti-cyclic

citrullinated polypeptide (anti-CCP) and decreased complement levels are also observed [12, 13]. Mononeuritis multiplex is another typical feature of rheumatoid vasculitis. This may result in sensory loss in the extremities, leading to both development of new neuropathic ulcers and non-healing of existing ones [13].

3.3.2 Differential Load Distribution

Foot deformities are a common feature of rheumatoid arthritis. These lead to differential load bearing on the feet, predisposing some parts to undergo damage due to higher pressures. The concomitant sensory neuropathy also aggravates the problem. A unique British study on determinants of foot ulceration in rheumatoid arthritis patients determined loss of protective sensations, abnormal ankle brachial pressure index, and forefoot deformities to be strongest risk factors [3].

3.3.3 Associated Conditions

Even in patients of rheumatoid arthritis, the majority of limb ulcers are not attributable to disease-related vasculitis and inflammation but rather to presence of comorbidities. A 7-year retrospective case review of all patients with leg ulcers seen at the National Skin Centre at Singapore identified venous disease as the most common aetiology of leg ulcers in those with rheumatological conditions [4]. Other ulcers identified included multifactorial ones, those due to atypical mycobacterial infection, and ulcers due to pyoderma gangrenosum, ischaemic microangiopathy, and iatrogenic ulcers [4]. Since the burden of comorbidities may be high in rheumatoid arthritis patients, especially in elderly patients, chronic venous ulcers in the setting of varicose veins and ulcers of diabetic foot due to neuropathy and atherosclerotic vascular disease may be quite common.

Pyoderma gangrenosum is a complex neutrophilic dermatosis. It may be often seen in association with cases of rheumatoid arthritis as also other autoimmune and inflammatory disorders. The pathogenesis of this entity is complex, not fully elucidated, and involves not only neutrophils but T cells, inflammasomes, keratinocyte apoptosis, and epigenetic changes [14]. There is an increased migration of neutrophils to the dermis which is the hallmark of this disease. In this it resembles other entities such as Behçet's disease and Sweet's syndrome. Genetic susceptibility plays an important role in pyoderma gangrenosum.

3.3.4 Iatrogenic

While several medications and therapeutic interventions may cause chronic extremity ulcers, two noteworthy agents are methotrexate and leflunomide. These two disease-modifying anti-rheumatic drugs (DMARDs) form the cornerstone of the usual triple drug regimen utilised for rheumatoid arthritis [15]. They are also

extensively used as first-line monotherapy. Both methotrexate and leflunomide are known to cause leg ulcers. Methotrexate-induced skin ulcers in patients of rheumatoid arthritis have been reported mostly in the elderly. They often develop after years of therapy, and have a predilection for the lower limbs, hands, and elbows. The pathogenesis is related to the inhibition of the folate biosynthesis pathway, and DNA replication [16, 17]. Other agents such as steroids, biologicals, and non-steroidal anti-inflammatory drugs (NSAIDS) may have an accelerant role if taken simultaneously [16]. Leflunomide induces cutaneous ulcers by inhibiting dihydroorotate dehydrogenase involved in pyrimidine synthesis, as well as by blunting the action of growth factors such as the epidermal derived growth factor (EDGF). Inflammation in the dermis and subcutaneous tissue with necrosis of collagen fibres, presence of granulation tissue, and giant cell granulomas are visualised on histopathological examination [18, 19].

3.3.5 Impaired Healing

Rheumatoid arthritis is a systemic inflammatory disease and results in a state of chronic inflammation which is inevitably characterised by the typical features of anaemia and hypoalbuminemia especially in the elderly, loss of muscle mass, and delayed wound healing [20, 21]. Impaired wound healing adds to the chronicity of limb ulcers which increase prevalence rates. Steroids which are often part of treatment protocols for acute flares of rheumatoid arthritis may also impair healing.

3.4 Clinical Features

In this section, we will primarily discuss the presentation of classical vasculitic ulcers of the extremities which are observed in patients of rheumatoid arthritis. Some salient features of ulcers due to comorbid illness or iatrogenic ulcers are briefly mentioned in Table 3 .1. Pyoderma gangrenosum is discussed separately.

3.4.1 Vasculitic Ulcers of the Extremities

Although the most common extremity ulcers in patients of rheumatoid arthritis are of other aetiology, vasculitic ulcers are the pathognomonic ulcers of any connective tissue disorder. Notably, vasculitic rheumatoid ulcers may affect both the lower and upper extremities, unlike the commoner venous ulcers which have a definite lower limb predilection. However, these ulcers are again commoner on the lower limbs and in the sacral region, sometimes giving a false diagnosis of bedsores (pressure sores/decubitus ulcers) [31]. The spectrum of cutaneous manifestations varies from palpable purpura to nodules to ulcers, and digital necrosis [12]. Deep, painful ulcers may suggest a vasculitic origin, but histopathological evidence is usually needed to make a definitive diagnosis, and even then, it may not be always feasible [32].

Table 3 .1 Salient features of non-vasculitic ulcers in rheumatoid arthritis [3, 5, 16, 19, 22–30]

Ulcers due to differential load distribution	These occur in the setting of foot deformities which are common in rheumatoid arthritis, especially if left untreated. Common deformities of the feet in rheumatoid arthritis include hallux valgus, hallux rigidus, mallet toe, claw toe, splay toe deformities (forefoot), pes planus (mid foot), and calcaneal varus and valgus deformities (hind foot). Raised plantar pressures, and ill-fitting footwear due to deformities may also contribute to these ulcers
Venous ulcers	These are seen mostly in the setting of a long history of varicose veins, especially neglected ones. They are shallow, painful, poorly demarcated ulcers located over bony prominences. The medial malleolus is a common site. Associated skin changes such as itching and scaling may be present
Ulcers due to peripheral arterial disease	These are a common finding in smokers or patients with other risk factors for atherosclerotic peripheral vascular disease. Those with history of coronary or cerebrovascular atherosclerosis or acute events may have such ulcers. A history of limb claudication may also exist. Common sites are the toes, heels, and bony prominences of the foot. These ulcers are usually deep, round or punched out, with a clearly demarcated edge. There may be absent or feeble peripheral arterial pulses or audible bruits. Gangrene of digits or limb may be associated
Diabetic foot ulcers	Diabetic foot ulcers are usually multifactorial. Diabetes is a risk factor for both peripheral arterial diseases leading to arterial ulcers as described above, and neuropathy. Autonomic neuropathy, small fibre sensory neuropathy, and large fibre neuropathy combine with arterial disease to cause the characteristic diabetic foot. There is associated paresthesias, hypoesthesia, and anhidrosis due to autonomic neuropathy. While ulcers due to predominant peripheral arterial disease follow the patterns described above for arterial ulcers, neuropathic ulcers commonly occur over the weight-bearing areas such as the plantar metatarsal head, great toe, and heels
Ulcers due to ischemic microangiopathy	Occlusive microangiopathy due to thrombotic or anatomic occlusion is seen in rheumatoid arthritis if there are associated conditions such as livedo reticularis, calciphylaxis, or antiphospholipid antibodies syndrome. The ulcers may be similar in location and morphology to inflammatory microangiopathic ulcers which are seen in classical vasculitis and in pyoderma gangrenosum. However, minor variations in clinical features may be present depending on the aetiology
Ulcers in the setting of co-existent other connective tissue/ inflammatory disorders	Rheumatoid arthritis may be associated with other connective tissue disorders such as systemic lupus erythematosus, scleroderma, Behçet's disease (as part of overlap syndromes), or other conditions such as calcinosis cutis, inflammatory myositis, or psoriasis. The ulcers specific to these disease types may be seen in such cases. Leukocytoclastic vasculitis is a generally skin-limited vasculitis which may be idiopathic or secondary to rheumatoid arthritis or other systemic diseases. It may lead to skin ulceration on the extremities in patients of rheumatoid arthritis
Iatrogenic ulcers	Methotrexate-induced skin ulcers are commonly located over the lower limbs, hand, and elbows. These resolve well within weeks after drug discontinuation. Cutaneous ulcers on lower limbs and forearms have been reported with leflunomide use, mainly in elderly females after months of therapy. The healing of these ulcers after drug withdrawal is delayed

Suspicion should be strong when the ulcers do not heal with standard vascular interventions and local wound care [33]. Sometimes, an association with vasculitic involvement of other organs may exist, and this portends a poor prognosis [12]. Necrotising vasculitis and associated vasculitic nerve involvement may also be observed in some cases of rheumatoid arthritis with cutaneous ulcers [34].

3.4.2 Pyoderma Gangrenosum

Pyoderma gangrenosum, as described above, is a neutrophilic dermatosis which may be idiopathic but is usually seen associated with immune-inflammatory conditions such as rheumatoid arthritis [35]. In the ulcerative variant of pyoderma gangrenosum, tender inflammatory nodules or pustules are the initial manifestations developing most commonly at sites of trauma, especially on the anterior lower extremities. The pre-tibial region is commonly affected [36]. They rapidly evolve into necrotic ulcers with violaceous undermined borders and surrounding erythema. Pyoderma gangrenosum also has bullous, pustular, vegetative, peristomal, postoperative subtypes [35].

3.5 Diagnosis

The diagnosis of an ulcer of the extremity in a patient of rheumatoid arthritis is clinical. History of pre-existing disease and presence of associated skin lesions and examination findings as described for the individual entities above allows an empirical diagnosis of the cause of the ulcer. A detailed neurological examination may be warranted in cases of co-existing morbidities such as diabetes when ruling out neuropathic ulcers is important. A 10G monofilament test may be performed to identify loss of protective sensation [37]. Histopathological evidence from a biopsy of the lesion may have additive value in pin-pointing the exact diagnosis. The salient feature of a typical vasculitic ulcer of the extremity is mononuclear cell or neutrophilic infiltration of the vessel wall of small and medium vessels. The vessel wall may be destroyed, with necrosis, and disruption of the internal and external elastic lamina [12]. Leukocytoclasis or the presence of debris of neutrophils within the blood vessel walls may be seen. A sensitive and specific finding for vasculitis in rheumatoid arthritis is perivascular infiltrates of mononuclear or polymorphonuclear cells with greater than/equal to three cell layers [38].

In suspected cases of pyoderma gangrenosum, biopsies taken early in the course from the border show an infiltrate of chronic inflammatory cells confined to the dermis. A perivascular lymphocytic infiltrate and fibrinoid necrosis of the vessel wall may be noted. Later in the course of ulceration, a polymorphonuclear cell infiltrate with features of ulceration, infarction, and abscess formation is more common [39]. Histopathological examination also allows the exclusion of chronic mycobacterial infections and malignancies which may develop in the setting of long-standing wounds [33].

Some additional diagnostic tests are often needed to evaluate the status of comorbidities which are a common cause of ulcers of the extremities in rheumatoid arthritis. A doppler ultrasonographic imaging of the arterial and venous systems of the lower limbs is useful to diagnose venous insufficiency, concomitant deep venous thrombosis as well as peripheral arterial atherosclerotic lesions. A routine haematological and biochemical panel including metabolic parameters such as glycosylated haemoglobin and lipid profile may be useful. Serology to rule out overlap connective tissue disorders and systemic vasculitis syndromes may also be needed. Common serological investigations include estimation of anti-nuclear antibody (ANA), anti-double-stranded DNA antibody (anti-ds-DNA), anti-Smith antibody (anti-Sm), anti-centromere antibody, anti-Scl-70 antibody, anti-Ro/La antibodies, cytoplasmic and perinuclear anti-neutrophil cytoplasmic antibodies (c- and p-ANCAs). The details of the connective tissue disorders identified by these tests are not within the domain of this chapter. Pus culture from the wound site with antibiotic sensitivity testing against bacterial and fungal pathogens may also guide the therapeutic protocol.

3.6 Management

The management of rheumatoid ulcers of the extremities is based on three planks—local wound care, coverage for secondary infections, and immunosuppression targeting the underlying disease. Additional therapy may be warranted in case of specific co-existent aetiologies. In venous disease, compression stockings and limb elevation strategies may be useful. In atherosclerotic peripheral arterial disease, use of antiplatelets, statins, dual antiplatelet-vasodilator medications (cilostazol), and hemorheological medications such as pentoxifylline may be beneficial. Anticoagulants may be needed lifelong in case of associated antiphospholipid antibody syndrome resulting in thrombosis and ulcers of vascular origin. A trained podiatrist may be able to design a therapeutic and prophylactic plan for deformity-related ulcers which are caused by differential load distribution. Endovascular therapy for occlusive vascular lesions is being attempted in recent times and may be useful in select cases.

3.6.1 Local Wound Care

The local care of vasculitic ulcers is based on eliminating necrotic tissue, control of infection, maintenance of moistness of the wound, and eliminating pockets from the wound margin. Cadexomer iodine ointment aids in achieving the first two goals whereas silver sulfadiazine cream and povidone iodine ointment are useful for infection control. Occasionally, if the ulcers are extensive and evidence of systemic (blood stream) infection exists, systemic antibiotics may be added. Moistness of the wound may be ensured using Cadexomer or povidone iodine when exudates are excessive and using silver sulfadiazine cream when exudates are lacking.

Occasionally in cases of painful ulcers, white petrolatum or a petrolatum-based ointment may be useful. Debridement may be useful in patients with significant dead and necrotic tissue. Both debridement and use of occlusive dressing must be done with added care, considering the tendency of these ulcers to rapidly deteriorate [40]. Innovative solutions are being developed to enhance healing of vasculitic ulcers. These include the use of bovine collagen glycosaminoglycan matrices, split thickness skin grafting and corrective operations for foot deformities [41–43]. A consultative approach between a surgeon with expertise in chronic non-healing wounds, a physician with expertise in rheumatology, and a dermatologist may provide the best outcomes.

3.6.2 Coverage for Secondary Infections

Local site infections are usually bacterial but may rarely be caused by fungi, mycobacteria, and also viruses or leishmania in exceptional cases. Systemic antibiotic coverage usually is targeted against locally prevalent organisms [44]. A broad-spectrum beta lactam covering both gram positive and negative organisms may be the standard of care. Anti-pseudomonal coverage with fluoroquinolones (levofloxacin) or anti-pseudomonal beta lactams (piperacillin-tazobactam, ceftazidime, or meropenem) for hospitalised patients may be needed, especially in patients with co-existent diabetes. Piperacillin-tazobactam, meropenem, amoxycillin-clavulanate, metronidazole, and clindamycin provide good coverage against anaerobic organisms. Coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) is needed if culture reports suggest MRSA or if there is a history of prolonged hospitalisation or surgical interventions. Linezolid may be a good oral option in such cases [44]. Guidelines recommend the use of dapsone, an anti-mycobacterial antibiotic useful in the treatment of leprosy, in the management of rheumatoid vasculitis. However, it plays a mainly immunomodulatory role [40].

3.6.3 Systemic Immunosuppression

Systemic immunosuppression is the cornerstone of the treatment of rheumatoid arthritis. Since the vasculitic process is intricately linked with the core pathogenesis of rheumatoid arthritis, treatment of rheumatoid vasculitic ulcers also utilises immunosuppressants. These include both standard disease-modifying anti-rheumatic drugs (DMARDs) as well as biological DMARDs, and other immune-suppressants. The first-line management for rheumatoid vasculitis is high-dose steroids, such as prednisolone 0.5–1 mg/kg/day. Methotrexate is the DMARD of first choice for management of rheumatoid arthritis and may be used similarly in management of skin ulcers due to rheumatoid vasculitis. If non-responsive to these therapy, cyclophosphamide and azathioprine have been suggested as additional therapeutic options [12, 40]. Newer biological DMARDs such as anti-TNFα therapies (infliximab, adalimumab, etanercept, etc) may also be useful sometimes, though concerns

have been raised regarding ulcers and vasculitis developing or worsening occasionally while on anti-TNF therapy. Stoppage of these agents or switching to safer options has been recommended in guidelines for such cases [40, 45]. The guidelines of the Japanese Dermatological Association also advice the use of cyclosporine, cyclophosphamide, and intravenous immunoglobulin (IVIg) in non-responsive cases [40].

3.6.4 Management of Pyoderma Gangrenosum

The management of this condition is non-specific and mostly focused on treating the underlying systemic disease and local wound care. Topical steroids, topical tacrolimus and pimecrolimus are sometimes used. Systemic immunosuppression with high-dose prednisolone (1–2 mg/kg/day) and high-dose cyclosporine either alone or with steroids may be utilised. Dapsone, sulfasalazine, and the other immunosuppressants discussed above in the management of rheumatoid vasculitis may also be effective in certain cases [36].

3.7 Conclusion

Ulcers of the extremities are common in patients of rheumatoid arthritis. Chronic non-healing limb ulcers are a major source of morbidity in these patients and adversely affect the quality of life. Although vasculitic ulcers are pathognomonic, the more common ulcers are venous and arterial ulcers, and also those related to deformities. Histopathological examination usually provides support to what is commonly a clinical diagnosis. The management of rheumatoid ulcers of the extremities rests on local wound care, coverage of secondary infections, and adequate use of disease-modifying anti-rheumatic drugs and other systemic immunosuppressants.

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