Leg Ulceration in Rheumatoid Arthritis – An Underreported Multicausal Complication with Considerable Morbidity: Analysis of Thirty-Six Patients and Review of the Literature

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Key Words

Rheumatoid arthritis · Leg ulcer · Chronic venous insufficiency · Vasculitis · Inactivity

Abstract

Background: Rheumatoid arthritis (RA) is a systemic inflammatory disease which may present with extra-articular symptoms, including cutaneous manifestations. Ulcerated rheumatoid nodules, necrotic vasculitic lesions and pyoderma gangrenosum are fairly characteristic and well-recognized causes of skin ulcers in RA. However, most RA patients develop leg ulcers due to other pathophysiological factors posing a diagnostic and therapeutic challenge and leading to considerable morbidity. **Methods:** A retrospective chart analysis of all patients with RA and leg ulcers hospitalized at our Dermatology Department between January 1998 and March 2008 was performed to evaluate risk factors and identify underlying conditions that predispose RA patients to the development of leg ulcers. **Results:** A total of 36 patients with RA and leg ulcers were identified. Three patients presented with necrotizing vasculitis and 2 with pyoderma gangrenosum. Chronic venous insufficiency was diagnosed as the underlying cause of

leg ulcers in 8 patients, peripheral arterial disease in 4 patients, and combined arterial and venous malfunction in 3 patients. Five patients suffered from pressure ulcers. Interestingly, in 11 patients (31%) other underlying causes besides constricted mobility followed by secondary lymphedema could not be identified, and these ulcers were classified as 'inactivity leg ulcers'. **Conclusions:** The majority of leg ulcers in patients with RA are due to underlying venous/arterial malfunction while vasculitic or traumatic ulcers are less common. Additionally, we identified a relevant subgroup of patients with 'inactivity ulcers' due to impaired mobility and consecutive lymphedema. Morphology and localization of ulcerations as well as duplex sonography provide the most important clues for accurate diagnosis, ensuring adequate treatment.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting about 1% of the population. It is clinically characterized by joint inflammation, progressive joint destruction and decreasing function-

al ability. Systemic involvement may present with extra-articular manifestation of various organs, including the lung, heart, kidney and skin [1]. Recent studies focusing on dermatological conditions in RA patients have identified a high prevalence of rheumatoid nodules (34%) and Raynaud phenomenon (17%) [2–5]. According to different studies, the frequency of leg ulceration in patients with RA may be up to 10% [6, 7] compared to the prevalence of venous leg ulceration in the general population of approximately 1% [8]; thus, implying that patients with RA are at increased risk of developing ulcerations of the lower extremities leading to considerable morbidity.

In this study, a cohort of 36 RA patients with leg ulcers was retrospectively analyzed to identify underlying conditions and risk factors for development of chronic lower extremity ulcerations.

Case Report

We present a 69-year-old woman with a 7-month history of leg ulceration located on the lateral malleolus. The ulceration developed after incidental trauma

and slowly progressed. Upon presentation, the size of the ulceration was 3 × 2 cm in diameter and 2.2 cm in depth. The patient had suffered from RA for 15 years leading to considerably impaired mobility. RF was 14.7 U/ml (reference interval 0–14 U/ml). The current treatment regimen consisted of methotrexate (15 mg weekly), low-dose prednisolone (5 mg daily), leflunomide and etoricoxib. The leg ulceration was colonized with *Pseudomonas aeruginosa* and Gram-positive bacilli. Dysfunction of the deep and superficial venous system was excluded by color duplex ultrasonography. She had a normal ankle-brachial index and no peripheral arterial disease (PAD). Lymphedema of the lower leg could be observed. The ulceration was treated by shave excision of the ulcer margins (histological examination of the obtained specimen did not show vasculitic changes) and vacuum-assisted closure. The immunosuppressive therapy was retained unchanged. With this treatment regimen, the ulceration slowly healed.

Methods

Patients

Between January 1998 and March 2008, a total of 36 consecutive patients with RA fulfilling the criteria of the American College of Rheumatology [9] were treated as inpatients at the Department of Dermatology, University of Würzburg, with leg ulcerations. A retrospective chart analysis of RA patients was performed and the following data were recorded: duration of RA, treatment for RA, smoking habits and additional systemic diseases (e.g. diabetes mellitus, hypertension). Body mass index was calculated according to the height and weight of the individuals. RA patients with coexisting connective tissue diseases were excluded.

Diagnostic Workup

Leg ulcer duration, relapse rate, horizontal and vertical localization of the ongoing ulceration, number and size of ulcers, as well as unilateral or bilateral leg involvement were documented. Results of clinical exams were recorded, including venous arterial disease and PAD, occurrence of polyneuropathy and lymphedema, and degree of immobility (i.e. restricted ankle movement, difficulties walking or wheelchair-bound). Venous function

was assessed by color duplex ultrasonography of reflux of the deep and superficial venous system using LOGIQ™ 500 (GE Medical Systems, Milwaukee, Wisc., USA). The deep venous system was judged by compressibility of the veins, filling defects, recanalized intraluminal channels and wall thickening. Arterial examination included determination of the ankle-brachial index and extent of atherosclerotic plaques in the femoral artery by color duplex ultrasonography. Venous and arterial examinations were performed by the same physician (N.B.); only 3 patients had been examined by a different physician. Additional data in selected cases included results of histological analysis of perilesional biopsy, direct immunofluorescence and radiological examination to rule out vasculitis or underlying osteomyelitis, respectively.

Laboratory Parameters

Laboratory tests included complete blood count, rheumatoid factor, antinuclear antibody, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and testing for bacterial colonization of the ulcers.

Results

Patients

The studied series consisted of 30 women and 6 men with a median age of 71 years (range 45–92 years). The majority of patients (23/29, 79%; 7 patients with unknown duration) had suffered from RA for more than 10 years and 52% (15/29) for more than 20 years. Thirty-five patients received various systemic treatments (table 1), including disease-modifying antirheumatic drugs, oral steroids, methotrexate, combination of methotrexate and oral steroids, or others including azathioprine (n = 2), azulfidine (n = 1), combination of azulfidine and hydroxychloroquine (n = 1), leflunomide (n = 1), mycophenolate mofetil (n = 1), etanercept (n = 1) and adalimumab (n = 2). One patient was without specific treatment. The average BMI was 27 (range 19–44). Eight patients (21%) suffered from diabetes, 23 patients (64%) had arterial hypertension.

Clinical Characteristics of Ulcers

The mean duration of the leg ulceration was 12 months (range 1–60); 28% of patients had a history of recurrent leg ul-

Table 1. Clinical characteristics of the studied RA patients

Patients, n	36
Mean age, years (range)	71 (45–92)
Females/males	30/6
Medication	
DMARDs	6
Oral steroids	7
Methotrexate	7
Methotrexate/oral steroids	6
Biologicals	3
Others	6
No treatment	1
Disease duration	
Up to 5 years	2
6–10 years	4
11–20 years	8
More than 20 years	15
Unknown	7
Mobility	
Normal	2
Restricted ankle movement	9
Crutches	16
Wheelchair	7
Unknown	2

DMARDs = Disease-modifying antirheumatic drugs.

Table 2. Size and localization of leg ulcerations in the studied RA patients

Number of ulcers	
1	17
2	8
>2	11
General localization	
One leg	26
Both legs	10
Gaiter area	27
Foot	6
Multiple sites	3
Horizontal axis	
Medial	6
Anterolateral	17
Dorsal	2
Multiple locations	11
Size (cm ²)	
<10	9
10–20	7
21–30	6
31–100	5
>100	9

Fig. 1. Algorithm for classification of leg ulcers in RA.

ceration; 47% of patients had 1 ulcer, 22% had 2 ulcers, and 31% had >2 ulcers. Further ulcer characteristics are summarized in table 2. The ulcerations were located on 1 leg in 72% of patients; in 28% of patients both legs were affected. Ulcers were located in the gaiter area in 75% of cases (according to classification by Callam et al. [10]), 17% cases had ulcerations on the foot, and 8% of cases presented with ulcers at multiple locations. On the horizontal axis, ulcers were located medially in 17%, anteriorly/laterally in 47%, and dorsally in 6% of patients. In total, 30% of patients presented with ulcers at multiple sites. The size of the ulcer varied considerably as shown in table 2. Underlying osteomyelitis was excluded in 10 cases. Biopsies of ulcer margins were performed in 14 of 36 patients. In 3 patients, vasculitis was histologically evident, while 11 patients did not show vasculitic changes. The final diagnosis and classification of leg ulcers in our

patients has been summarized in a flow-chart (fig. 1).

Immunological Ulcers

Necrotizing vasculitis was identified by histology and direct immunofluorescence in 3 cases. In 11 patients, vasculitis was ruled out by biopsy of the ulcer margin. An additional 2 cases were diagnosed as pyoderma gangrenosum (fig. 2D).

Vascular Malfunction

Chronic venous insufficiency was identified in 33% of patients (12/36), post-thrombotic syndrome in 17% of patients (6/36), and dysfunction of the superficial and deep venous system was found in 8% (3/36) (fig. 2A). Atherosclerotic plaques were identified by ultrasound in 52% of patients. Approximately 20% of patients (7/36) had relevant PAD (fig. 2C). Combined venous and arterial ulcer was diagnosed in 3 patients (8%).

Traumatic Ulcers

In 3 patients (8%), pressure ulcers due to deformities of the foot were identified. In 2 patients, ulcerations were caused by trauma and underlying polyneuropathy.

Inactivity Ulcers

A total of 11 patients (31%) had neither a venous, arterial nor vasculitic disorder, nor any of the other previously mentioned underlying disorders. This group was classified as 'inactivity ulcer due to RA' (fig. 2B). In this subgroup, 64% of patients (7/11) had lymphedema and/or showed significantly impaired mobility. The 'inactivity ulcers' were located anteriorly/laterally in 36% (4/11, including the presented case report; fig. 2B), medially in 9% (1/11), posteriorly in 9% (1/11) and mixed in 46% (5/11) of cases. In this subgroup, 18% of patients (2/11) had a history of recurrent leg ulceration. There was no significant difference concerning duration and clinical activity of RA, laboratory parameters, or size of the ulceration compared to the rest of the cohort.

Laboratory Parameters

Blood count showed normal values for thrombocytes in the majority of cases, thrombocytosis was found in 19% (7/36) of patients. In total, 78% (28/36) of patients suffered from mild-to-moderate anemia (10–11.5 g/dl), 14% (5/36) had severe anemia (<10 g/dl) with 1 patient requiring blood transfusion. CRP was moderately elevated (between 1 and 5 mg/dl) in 58% (21/36), in 17% (6/36) of patients CRP was >5 mg/dl. ESR was between 50 and 80 mm/h in 58% (21/36) of patients, 11% (4/36) had an ESR of >100 mm/h. Furthermore, 61% of tested patients (22/36) had a positive rheumatoid factor, 50% of them with a high titer. Positive antinuclear antibody results were found in 22% (8/36) of patients, predominantly with a low titer (<1:160). Ulcers were colonized with *Staphylococcus aureus* in 31% (11/36), *Pseudomonas aeruginosa* in 14% (5/36), a combination of both in 14% (5/36), or other Gram-negative bacteria in 8% (3/36).

Discussion

Chronic ulceration of the lower extremity is a fairly common medical problem affecting approximately 1% of the general population. For patients with RA, the prevalence of leg ulceration has been esti-

mated in several studies to be up to 10% [6], rising to 34% in patients with systemic rheumatoid vasculitis (RV) [7, 11]. In the general population, ulcers due to venous dysfunction contribute to 70–90% of all cases; however, in patients with RA the underlying causes are oftentimes multifactorial. In our series of patients, vascular dysfunction and immobility accounted for the majority of cases, whereas RA-specific vasculitic ulcerations or pyoderma gangrenosum were rather rare. Our cohort consisted of patients admitted to the hospital because ambulatory treatments had failed in the past. Therefore, studied patients may have been affected more severely than the general RA population and bias including overestimation of average size of ulceration as well as several co-factors, such as inactivity or arterial dysfunction, cannot be excluded.

RV is a severe complication of RA with increased morbidity and mortality affecting between 0.7 and 7.9% of RA patients depending on the studied cohort (community-based versus hospitalized) [12–15]. In our study, we identified a relatively low number of patients with ulcers of vasculitic etiology (8%) compared to 18% [16], 37% [17] and 50% [18] of patients in comparable studies. Diagnosis of cutaneous vasculitis is usually established by skin biopsy. However, biopsies of ulcer margins may show secondary changes due to bacterial superinfection as well as ongoing inflammatory stimuli mimicking vasculitis [19, 20]. Due to these confounding factors, margin biopsies of ulceration may have led to overestimation of vasculitic changes in previous studies. Patients with long-standing disease, severe joint erosions and deformities, presence of rheumatoid nodules, and with high levels of rheumatoid factor are at higher risk of developing RV [1]. Predilection sites for these types of ulcers are the lateral malleolus or the pretibial area. RV ulcers are characterized by pronounced painfulness and a punched-out appearance. The considerable morbidity of RV, however, depends on the involvement of peripheral nerves (mononeuritis multiplex or distal symmetric sensory neuropathy), as well as CNS, heart, lung, kidney, bowel and ocular involvement [21]. Treatment options for RV leg ulcerations include systemic steroids, methotrexate [22] and leukocytapheresis [23].

Pyoderma gangrenosum is clinically characterized by ulceration with necrotic undermined borders and a tendency for

Fig. 2. Clinical appearance of leg ulcers in RA patients due to different underlying conditions. **A** Venous ulcer located at the medial malleolus surrounded by varicosis. Blue staining of the surrounding skin is due to gentian violet. **B** Deep 'inactivity ulceration' located on the lateral malleolus. **C** Coalescing ulcerations and black eschar necrosis on the dorsal aspect of the thigh due to PAD. **D** Pyoderma gangrenosum showing bizarre configuration of the ulceration rims, undermined edges, and a soft edematous ulcerated area.

rapid progression after minor trauma (fig. 2D). Due to these typical clinical features, we diagnosed pyoderma gangrenosum in 2 patients. Although pyoderma gangrenosum may be associated with RA, this type of skin ulceration may be found more often in patients with chronic inflammatory bowel disease and paraproteinemia [4].

In our study, insufficiency of the superficial and deep venous systems was identified as the main cause in 22% patients (12/36), 3 of these suffered from a combination of venous and arterial malfunction. Pun et al. [16] identified venous dysfunction as the most common cause of leg ulceration, accounting for 45% in a cohort of

patients with underlying RA. The predilection sites of venous ulcers in RA patients correspond to those of venous ulcers in the general population: solitary or bilateral shallow ulcerations with a fibrinous base and irregular margins on the medial aspect of the lower leg, just above the malleolus, accompanied by typical cutaneous changes such as hemosiderin pigmentation, dermatosclerosis, atrophie blanche or obvious varicosis (fig. 2A) [8]. Rarely, venous ulcers are found laterally or proximally. In the majority of cases, aggravation of venous ulceration and impaired healing is due to concomitant impairment of the venous pump due to dysfunction of the ankle joint [24]. Accordingly, in our study 82% of patients with ulcers due to impaired venous function showed various degrees of constricted mobility. Standard treatment of patients with venous ulcers in our department includes shaving of the sclerotic areas/fasciotomy and subsequent vacuum-assisted split skin grafting. Concomitantly, a peri- and postoperative increase in immunosuppressive therapy by increasing the basic prednisolone dosage to 1 mg/kg body weight followed by slow tapering of the dose over a period of 3 weeks. An alternative treatment option of minor and painful ulcerations may be pinch grafting [18]; however, larger prospective studies are mandatory to identify optimal treatment options of venous ulcers in patients with RA.

RA patients tend to have an increased risk of developing atherosclerosis due to the disease itself and the long-standing immunosuppressive therapy with corticosteroids leading to increased morbidity by coronary, cerebral and PAD [25, 26]. Relevant PAD is considered in patients with an ankle-brachial index <0.9 [27]. In our study, we identified 4 patients with PAD-induced ulcers. Additionally, 3 patients suffered from combined arterial/venous ulcers. Typical clinical features of PAD include intermittent claudication induced by exercise, and relieved after 10 min of rest. However, many RA patients with movement restrictions due to their bone deformities may not experience these exercise-induced symptoms. Progression of PAD with ischemic rest pain may eventually lead to stage IV of PAD (according to classification of PAD by Fontaine and Rutherford), with gangrene affecting the digits, distal part of the forefoot and heel. In our patients, we observed arterial ulcerations of the leg predominantly on the

anterior and lateral aspect of the lower leg (fig. 2C).

Deformities of the foot also represent a predisposition for skin ulcerations due to pressure, friction and minor trauma usually induced by ill-fitting shoes, e.g. flexion deformities of the toes predispose people to ulcerations on the dorsum of the toes [19]. A recent study by Firth et al. [28] suggests that the overall prevalence of foot ulcerations in patients with RA may be up to approximately 10%. In this study, ulcers were most commonly found at the dorsal aspect of the hammer toes (48%). Other critical areas of the foot are the plantar region around the metatarsal heads (32%) (subluxation of metatarsophalangeal joints), the lateral and medial aspects of the forefoot adjacent to the metatarsophalangeal joint (20%), and the heel [28]. In addition to increased skin fragility, polyneuropathy may also contribute to lesions of the foot. Therefore, podiatry care in patients with long-standing RA should be reserved to specialists, and personalized wide-fitting and extra-depth footwear is mandatory to prevent secondary ulcerations.

Infrequently, onset of leg ulcerations may develop during treatment with antiproliferative drugs [29]. In this context, development of vasculitis changes [30] and skin ulcerations [31, 32] has been observed in a few RA patients treated with the pyrimidine-synthesis inhibitor leflunomide, suggesting that leflunomide may play a role in the pathogenesis of a specific subset of leg ulcerations.

In 11 RA patients with leg ulcers, no underlying vascular or immunological condition could be identified. The majority of these patients including the presented case had restricted ankle movement, were immobile or wheelchair dependent and concomitantly displayed clinical signs of moderate-to-severe lymphedema of the leg (63%) suggesting a secondary lymphedema due to constricted mobility. This group was termed 'inactivity ulcer due to RA' (fig. 2B). Interestingly, lymphedema predominantly affecting the upper extremities has been sporadically reported in long-standing RA [33]. However, a few cases of exclusive lower limb involvement have also been reported [34]. There is usually no correlation of lymphedema with seropositivity for rheumatoid factor or disease activity [34, 35]. The cause of edema in RA is currently unknown; however, immobility, inflammatory exudates around affected joints, hypo-

proteinemia, increased capillary permeability and filtration as well as pre-existing abnormalities of the lymphatic vessels have been discussed in this context [36, 37]. Future detailed studies of the lymphatic system including lymphoscintigraphy in patients with RA and leg ulcerations may identify pathophysiological mechanisms in these patients. Clinically, the subgroup of patients with inactivity ulcers did not significantly differ from the remainder of RA patients. Our data show that peripheral edema may have been an underestimated cause of leg ulcers in RA in the past, and all efforts should be taken to minimize lymphedema in patients with RA by elevation of the affected extremity and application of adequate compression bandages [38].

Lower leg ulcerations in RA patients are oftentimes resistant to conventional therapies, and therefore pose a diagnostic and therapeutic challenge for the treating rheumatologist. Morphology, localization, time course, co-morbidity and clinical symptoms of the ulcerations give important hints for the exact diagnosis ensuring adequate treatment. Beside vascular malfunction, in our study we identified a relevant subgroup of patients with 'inactivity ulcers' presenting with mild-to-moderate lymphedema and reduced mobility. It is tempting to speculate that lymphedema is a consequence of impaired mobility. However, whether lymphedema in individual patients with RA and leg ulcerations is primary or secondary in nature has to be addressed by future studies including lymphoscintigraphy.

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