Leg ulcers in patients with rheumatoid arthritis—a prospective study of aetiology, wound healing and pain reduction after pinch grafting

R. F. Öien¹,², A. Håkansson² and B. U. Hansen³

¹Lyckeby Health Centre, S-371 62 Lyckeby, ²Department of Community Medicine, Malmö University Hospital, S-205 02 Malmö and ³Department of Internal Medicine, Section of Rheumatology, Karlskrona Central Hospital, S-371 85 Karlskrona, Sweden

Abstract

Objective. To study the aetiology of leg ulcers in patients with rheumatoid arthritis (RA) and to study healing and pain relief after pinch grafting.

Methods. Twenty patients with RA and leg ulcers were studied. Diagnosis of the ulcers was founded on the clinical picture and measurements of the ankle–brachial pressure index. To detect vasculitis, skin biopsies were taken for immunohistochemistry and histopathology. Pain severity was assessed pre- and post-operatively using a visual analogue scale.

Results. Ten of the 20 patients had ulcers with multifactorial aetiology. Fifteen had signs of venous insufficiency, 11 had histopathological evidence of vasculitis, four had reduced arterial circulation and two patients had diabetes. Healing after pinch grafting was found in eight patients, all of whom had an ulcer area less than 15 cm². Eleven out of 18 patients had pain reduction after pinch grafting.

Conclusion. The causation of leg ulcers in patients with RA was found to be multifactorial, with vasculitis and venous insufficiency as the main determinants. Pinch grafting seems to be a good alternative to conservative treatment for minor leg ulcers for these patients, regarding both wound healing and pain relief.

Key words: Rheumatoid arthritis, Leg and foot ulcers, Vasculitis, Pinch grafting, Pain relief.

Patients with rheumatoid arthritis (RA) are predisposed to developing chronic leg ulcers [1–4]. The aetiology is frequently multifactorial but often associated with venous insufficiency [1, 2, 5, 6]. In one study, 9% of patients with RA had a leg ulcer [4] while 22% of patients with Felty’s syndrome [7] and 38% of patients with systemic rheumatoid vasculitis [8] were reported to have leg ulcers. In contrast, the prevalence of chronic leg ulcers in the adult population is estimated at 1% [2].

The role of vasculitis in cutaneous ulcers in RA is controversial [1, 2, 9–11]. Systemic vasculitis may be suspected clinically, on the basis of the development of painful, deep ulceration, but skin biopsies examined histopathologically and immunohistochemically would help to verify the diagnosis. It is important to recognize that, even when biopsies are performed, indisputable histological proof of vasculitis may be difficult to obtain [2, 12, 13].

Vasculitic ulcers are known to be more resistant to treatment and also more painful than ulcers of other aetiologies [10, 11, 14–17]. It has also been shown that patients with RA and vasculitic ulcers, i.e. malignant RA, have higher mortality and thus poorer prognosis than other patients with RA [1, 7, 8, 11, 18–21].

The aetiology of leg and foot ulcers in patients with RA and the effect of vasculitis on wound healing has not yet been studied adequately [2, 3], and the same can be said for pinch grafting as an alternative to conservative treatment [14, 22, 23].

The aim of our study was to clarify the aetiology of chronic leg ulcers in patients with RA and to describe the effect of the pinch graft operation on healing and pain in these patients.

Patients and methods

Patients

Twenty patients with RA and leg ulcers were studied. They were treated as out-patients (9) or in-patients (11) by the same general practitioner (R.F.O.) in cooperation...

with a single rheumatologist (B.U.H.) in Karlskrona, Sweden. The patients were enrolled consecutively in the study because of a non-healing leg ulcer. Venous ulcers had been treated with compression therapy and a trial of immunosuppressive agents (Table 1) whenever vasculitis was suspected clinically or on biopsy. All patients satisfied the American College of Rheumatology criteria for RA [24].

Associated diseases, medical and ulcer histories and medication were assessed. Laboratory variables, such as the serum level of immunoglobulin (Ig) M rheumatoid factor, Hb, erythrocyte sedimentation rate, B-glucose and S-creatinine, were analysed. A bacterial culture from the ulcer was taken but antibiotics were given only in cases of clinical cellulitis.

The blood level of anticoagulant was adjusted for two patients who were using this medication. All changes of the patient’s medication were made on clinical grounds, e.g. increased dose of corticosteroids or change in disease-modifying anti-rheumatic drugs (DMARDs) for those with more aggressive arthritis.

Assessment of ulcer aetiology

The ulcer diagnosis was established by taking into account the clinical findings and the results of measuring the arterial circulation and of skin biopsies. The ulcer was classified as arteriosclerotic in patients in whom the ankle–brachial pressure index (ABPI), measured with a hand-held ultrasound Doppler instrument, was < 0.9 [3, 25] and there were no clinical signs of oedema or history of venous insufficiency. The ulcer was classified as diabetic in insulin-treated patients with diabetes mellitus and a normal or high ABPI. The diagnosis of venous ulcers was founded on a history of previous deep vein thrombosis (DVT), a typical clinical picture and a long history of recurrent ulcers and oedema of the leg, and no signs of impaired arterial circulation.

Vasculitis was assessed by skin biopsy. One biopsy was taken from the edge of the ulcer for histopathological analysis (HPA) and examined at the Department of Pathology, Karlskrona Central Hospital. Another skin biopsy from intact skin surrounding the ulcer was taken for immunohistochemical analysis, using the direct immunofluorescence (IF) method for complement component 3 (C3) and Ig A, G and M. This biopsy was analysed at the Department of Pathology, Malmö University Hospital. The evaluation of biopsies followed the routines for each department. An additional one to three biopsies for HPA were taken on different occasions for nine patients. In this study a solitary finding of abnormal IF was not considered diagnostic for vasculitis, whereas at least one positive HPA, i.e. perivascular fibrinoid necrosis and leukocyte infiltration, was regarded as evidence of vasculitis [1, 13].

To test the specificity and sensitivity of IF and HPA, skin biopsies were taken from another 13 patients treated by pinch grafting in primary care. All of these patients had venous ulcers and no evidence of chronic inflammatory disease. However, two biopsies (15%) were positive when tested by IF.

The ulcers were recorded by photographing them and tracing them onto a sheet of plastic film placed on the wound. Ulcer size was measured in square centimetres by digital planimetry.

Operation technique

The skin transplantation method used was the pinch graft technique described by Reverdin and later by Davis [26, 27]. The method was recapitulated in a recent review [23]. All operations were done by the same operator and each operation took approximately 30 min. Pinch grafting was performed on one leg in patients with bilateral ulcers. In patients with large ulcers, part of the ulcer area was covered with grafts, whereas in patients with minor ulcers the whole ulcer area was covered.

After the operation the patient remained relatively still, but not immobilized, for a few days. At the check-up 1 week after the operation, the dressing on the donor site, which had been left untouched, was removed. The donor site healed completely within 10–14 days in all patients.

Only the outer dressing was changed daily on the grafted ulcer. After the first post-operative week the wound was treated according to normal dressing principles, thus avoiding dryness.

Healing and pain

Complete ulcer healing was the endpoint of the study. At the first check-up 1 week after the operation, the number of grafts which had taken was documented. The patients were then examined every third month for 1 yr or until the ulcer had healed completely.

Pain severity was assessed twice daily for 5 days immediately before and after the operation, using a visual analogue scale (VAS). The mean value of the pre-operative and post-operative pain assessments was then calculated.

Ethics approval

Ethics committee approval was obtained and informed consent was required from all patients before participation in the study (University of Lund, LU 37–95).

Results

Ulcer aetiology

Features of RA and the assessment of ulcer aetiology and healing are given in Table 1. The total number of patients was 20 (15 women and five men) and their median age was 71.0 yr (range 51–84). The median duration of RA was 19.5 yr (range 9–48).

Ten patients had extra-articular manifestations, two had Felty’s syndrome, two had Sjögren’s syndrome and two had pericarditis. One patient in each of these groups had a positive HPA for vasculitis. Two patients
Table 1. Features of RA and ulcer aetiology and healing in 20 patients with RA and leg ulcers treated by pinch grafting

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of RA (yr)</th>
<th>DMARDs</th>
<th>Duration of ulcer (months)</th>
<th>HPA</th>
<th>IF</th>
<th>Vasculitis</th>
<th>Non-inflammatory ulcer aetiology</th>
<th>Treated in hospital or primary care</th>
<th>Size of grafted ulcer (cm²)</th>
<th>Healing time (weeks)</th>
<th>Dropout (within months)</th>
<th>Unhealed after 1 yr</th>
<th>Unhealed at death (within months)</th>
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<td>M</td>
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<td>-</td>
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<td>+</td>
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<td>-</td>
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<td>Hospital</td>
<td>10.2</td>
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</table>

a1, myocrisin; 2, methotrexate; 3, azathioprine; 4, cyclosporin; 5, pulse treatment with methylprednisolone; 6, pulse treatment with cyclophosphamide + methylprednisolone. ND, not done.
Leg ulcers in patients with rheumatoid arthritis

![Venn diagram showing the relationship between arterial/diabetic, venous, and vasculitis ulceration.]

Fig. 1. Ulcer aetiology for 19 patients with RA and leg ulcers. For one patient no certain aetiology could be established for the ulcer.

with pleuritis, one with scleromalacia and five with rheumatoid nodules, had a negative HPA.

Figure 1 illustrates the ulcer aetiology. A venous component was found in 15 patients and an arterial component in four patients, and two patients had insulin-treated diabetes mellitus. Eleven patients had evidence of vasculitis, i.e., biopsy-positive HPA. For one patient vasculitis was the only aetiologic factor detected and for another patient no certain aetiology of the ulcer could be established.

**Ulcer healing**

There was complete healing in eight patients and the median healing time was 12 weeks (range 3–35) (Table 1). The median age of patients with healed ulcers was 74.0 yr and the median duration of RA was 17.5 yr. The median size of the grafted ulcer was 5.8 cm² (range 0.4–13.2) for the eight ulcers that healed and 24.4 cm² (6.7–356.6) for the other twelve ulcers (Wilcoxon rank sum test, \( P = 0.003 \)), while the median duration of the ulcer was 5 months (2–180) and 10.5 months (3–114) respectively (\( P = 0.08 \)). For patients with unhealed ulcers the median duration of RA was 20.5 yr.

Five patients, all treated at hospital, with a median age of 75.0 yr, died during the study. The cause of death, which in four cases was a clinical and probable diagnosis (no autopsy was done) was myocardial infarct, septicaemia, pulmonary embolus and RA with vasculitis. The fifth patient, on whom an autopsy was performed, died of nephropathy.

**Pain and pain relief**

For the 18 patients who followed the study protocol, there was a statistically significant reduction in pain (Wilcoxon signed rank test, \( P = 0.02 \)). Eleven patients had decreased pain (mean 2.2 units; range 0.6–5.0) and five had increased pain (0.8; 0.2–1.9), whereas there was no change in pain intensity for two patients.

**Discussion**

In the present investigation we found the causation of leg ulcers in patients with RA to be multifactorial—predominantly a mixed vasculitic and venous aetiology (Fig. 1). Chronic leg ulcers in general have a multifactorial aetiology and result mainly from venous insufficiency [5, 6, 28], which is also known to be the case for leg ulcers in patients with RA [1, 2, 10, 29]. McRorie et al. [6] found an indication of venous disease in 78% of rheumatoid ulcer patients. Venous insufficiency can be caused by DVT or by muscle pump dysfunction due to suppressed movement in the ankle or immobility [1, 4, 6, 29, 30].

The role of vasculitis in leg ulceration in RA remains controversial [3], with a reported incidence ranging from 0.6 to 38% [4, 8, 10–12, 31]. The difficulties in assessing and defining vasculitis have been elucidated earlier [1, 2, 8–10, 32]. It has been emphasized that the diagnosis of a vasculitic leg ulcer rests principally on the appearance of the ulcer and clinical evidence of systemic vasculitis [3]. Skin biopsies for HPA and IF would help in verifying a clinical suspicion of vasculitic ulceration. However, even when biopsies are performed, indisputable evidence of vasculitis may be difficult to obtain [2, 12, 13], which is why such analyses have rarely been done in a systematic manner [2, 8, 9, 12, 13].

In the present study, the diagnosis of vasculitis, found in 55% of the cases, was restricted to patients with at least one biopsy positive for HPA. We found biopsy-verified vasculitis for IF in 65% of the ulcers (13/20) and for IF as well as for HPA in 40% (8/20). It is known that biopsies for IF have high sensitivity but low specificity for vasculitis [33]. Biopsies for HPA, on the other hand, have high specificity but low sensitivity.

We found that one important predictor of ulcer healing was ulcer size—there was a successful outcome only for smaller ulcers. Another predictor of ulcer healing was ulcer duration. Restricted mobility is known to be an important factor in poor ulcer healing for both venous and rheumatoid ulcers [6, 30]. This aspect was not considered in the present study.

Although bed-rest is believed to aid the healing of chronic ulcers [1], we do not consider immobilization imperative for ulcer healing after pinch grafting, which can be performed easily on out-patients [22, 33, 34].

Ulcers caused by vasculitis are often described as extremely painful [2, 10, 14, 16]. We noted a significant reduction in pain after pinch grafting of chronic leg ulcers in patients with RA. Our findings of pain relief after operation confirm what was suspected by other researchers [23, 35].

This study shows that pinch grafting is a clinically effective and simple method for treating minor, painful leg ulcers. However, larger prospective studies including controls are needed in order to come to a definite
conclusion regarding the response to pinch grafting of leg ulcers in RA patients.

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