Acro-osteolysis in systemic sclerosis is associated with digital ischaemia and severe calcinosis

Emma M. Johnstone¹, Charles E. Hutchinson², Andy Vail¹, Aurelie Chevance¹ and Ariane L. Herrick¹

Abstract

Objectives. Acro-osteolysis (bony resorption of the terminal digital tufts) is a well-recognized, but under-researched, manifestation of SSc. Our aim was to investigate the hypothesis that acro-osteolysis is associated with (i) the severity of digital ischaemia and (ii) the presence of calcinosis.

Methods. This was a retrospective study of 101 patients with SSc in whom hand radiographs taken between 2001 and May 2008 were available for review. These radiographs were graded for severity of acro-osteolysis on a 0–4-point scale for each finger (0 = normal bone structure, 4 = severe pencilling of the terminal phalanges). From these scores, patients were subdivided into the following two groups: normal/minimal acro-osteolysis and moderate/severe acro-osteolysis. The presence or absence of calcinosis (mild, moderate or severe) was also documented.

Results. Of the 101 patients, 68 were grouped as normal/minimal acro-osteolysis and 33 as moderate/severe acro-osteolysis. Forty-five had severe digital ischaemia: 25 (76%) of the patients with moderate/severe acro-osteolysis compared with 20 (29%) of those with normal/minimal acro-osteolysis (multifactorial analysis: \( P < 0.001 \)). Patients with moderate/severe acro-osteolysis were more likely to have severe calcinosis (33% vs 13%), but this was not statistically significant after adjustment for potential confounders.

Conclusion. Acro-osteolysis was strongly associated with severe digital ischaemia. The potential association with severe calcinosis merits further study. Prospective studies are required to investigate acro-osteolysis as a marker of digital vascular disease progression and of treatment response.

Key words: SSc, acro-osteolysis, calcinosis, digital ischaemia, Raynaud’s phenomenon, hand radiographs.

Introduction

Digital problems are a major contributor to the morbidity, disability and pain of SSc. They reflect the vascular abnormalities and fibrosis that characterize the disease process and result in digital ischaemia (which can progress to digital-tip ulceration and gangrene), and in sclerodactyly, often with contracture and ulceration over the extensor aspects of the interphalangeal joints. For reasons that are not fully understood, a significant proportion of patients also develop subcutaneous calcinosis, which can ulcerate through the skin; when it is severe, calcinosis in itself causes pain and loss of function.

Acro-osteolysis (resorption of the terminal tuft of the digit) is a characteristic feature of SSc and has been estimated to occur in around 20–25% of patients [1, 2]. It is often assumed that acro-osteolysis results from impairment of blood supply, although pressure from skin tightening may also play a role [3]. Acro-osteolysis has been relatively little researched, although two recent studies of hand radiographs have documented acro-osteolysis and its associations (including with calcinosis) in patients with SSc [1, 2], and an association with secondary hyperparathyroidism has recently been suggested [4]. Similarly, little is known about the pathogenesis of SSC-related calcinosis. Increased understanding of the inter-relationships between digital ischaemia, loss of digital tissue (including bone resulting in acro-osteolysis) and calcinosis may provide further insights into the pathogenesis of the SSc.
disease process. Our specific aim was to investigate the hypothesis that acro-osteolysis is associated with the severity of digital ischaemia (in which case it may serve as a marker of disease severity) and the presence of calcinosis.

Patients and methods

This was a retrospective study of hand radiographs from patients with SSc attending Salford Royal Hospital. Radiographs were selected on the basis that (i) the patient had signed informed consent to his/her data being used for research purposes (study approved by Salford and Trafford Research Ethics Committee), (ii) the radiograph was taken between 2001 and May 2008 and (iii) the radiograph was available for review.

A total of 164 hand radiographs were recorded from 2001 to 2008. Of these, 25 were available to view online using the Picture Archive and Communication System, and the remaining 139 films had been archived. Of these 139, 85 were available for review, giving a total of 110 radiographs. Nine radiographs were repeat films (films from the same patients), meaning that radiographs from 101 patients were analysed. In the case of repeat films, the most recent radiograph was included for analysis in the study.

Patient details were extracted from an electronic database: gender, age and duration of RP at the time of radiograph, disease subtype (limited or diffuse cutaneous [5]), ACA status, smoking status and presence or absence of severe digital ischaemia [defined by a history of one or more of the following: admission for intravenous (i.v.) prostanoid therapy, surgical debridement or amputation].

Analysis of radiographs

Radiographs were examined for the following two features: acro-osteolysis and calcinosis.

Acro-osteolysis

For the purpose of the study, a grading scale for acro-osteolysis was developed. This scale, from 0 to 4, took into account the presence and severity of acro-osteolysis in each finger (including thumbs), with 0 being normal bone structure and 4 being severe pencilling of the terminal phalanx (Fig. 1A). The scoring system was as follows:

0 Normal terminal phalanges. No resorption.
1 Minimal acro-osteolysis, small amount of resorption at the terminal tuft.
2 Resorption of most of the distal tip of the terminal tuft.
3 Resorption of most of the terminal tuft, leaving only one side intact.
4 Complete resorption of the terminal tuft, with obvious pencilling.

Each radiograph was viewed by two observers (one a consultant musculoskeletal radiologist), and a consensus was reached for the score for each finger. Because the presence and severity of acro-osteolysis varied between fingers within any one patient, an overall rating (normal/minimal, moderate or severe acro-osteolysis) was ascribed to each patient on the following basis:

0 Normal/minimal acro-osteolysis: maximum score for an individual finger = 1 and total score (sum of all fingers) \( \leq 8 \).

Fig. 1 Radiographic scoring systems.

(A) Acro-osteolysis scoring system for individual fingertips and (B) examples of calcinosis scores (i) moderate and (ii) severe.
Moderate acro-osteolysis: maximum score for an individual finger ≤2 and total score from 9 to 16 inclusive.

Severe acro-osteolysis: maximum score for an individual finger ≥3 or total score ≥17.

Calcinosis
Presence or absence of radiographic calcinosis was determined by a musculoskeletal radiologist. Calcinosis was further subdivided into mild, moderate and severe depending on the density of calcinosis and the number of separate sites of calcinosis. A single site of low-density calcinosis was grouped as mild, medium density calcinosis at one or more sites or a single site of high-density calcinosis was grouped as moderate and more than one site of high- or mixed-density calcinosis was grouped as severe. Examples are shown in Fig. 1B.

Statistical analysis
Factors were grouped and described using standard summary statistics. Association with acro-osteolysis status was assessed using a single multifactorial regression analysis. All factors for inclusion (listed in Table 1) were determined in advance and were retained in the model regardless of statistical significance to prevent complications of multiplicity or conditionality in the selection of factors. Duration of RP was log-transformed to normalize the distribution, and calcinosis was regrouped, combining the none and mild categories, as no cases of moderate or severe acro-osteolysis were observed in the few patients classified as having mild calcinosis.

Results
Of the 101 patients, 68 (67%) had an acro-osteolysis rating of 0 (normal/minimal), 7 (7%) had a rating of 1 (moderate) and 26 (26%) had a rating of 2 (severe). Because of the small number of patients with moderate acro-osteolysis, those with moderate and severe acro-osteolysis were considered together for the purposes of statistical analysis.

Demographic and clinical features of patients are shown in Table 1 alongside results of the multifactorial analysis. Distributions of age, sex and disease subtype were similar between those with and without moderate/severe acro-osteolysis. Although patients with moderate/severe acro-osteolysis were more likely to smoke than those without, this difference did not reach statistical significance. Patients with longer duration of RP were more likely to have moderate/severe acro-osteolysis. ACA-positive status was associated with increased age and duration of RP, with more severe calcinosis and severe digital ischaemia. The apparent protective effect of ACA-positive status in the multifactorial model, despite the absence of a unifactorial relationship, seems to be an artefact of these associations.

Acro-osteolysis and severity of digital ischaemia
Results are shown in Table 1. Forty-five patients had severe digital ischaemia, of whom 39 had had i.v. prostanoids, 19 debridements and 7 amputations. Patients with moderate/severe acro-osteolysis were more likely to have

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All data are given as n (%) unless specified otherwise. DI: digital ischaemia; OR: odds ratio. aData from 100 patients. bData from 96 patients.
severe digital ischaemia than those without ($P < 0.001$). This was also true for each of the components defining severe digital ischaemia, despite the reduced numbers of observations for each: i.v. prostanoids ($P = 0.008$), surgical debridements ($P = 0.002$) and amputations ($P = 0.04$).

**Acro-osteolysis and calcinosis**

Forty-one patients (41%) had radiographic calcinosis (Table 1). Although patients with acro-osteolysis were more likely to have severe calcinosis, this association was not statistically significant after adjustment for other factors.

**Discussion**

We have demonstrated that acro-osteolysis is associated with digital ischaemia, confirming the findings of Avouac et al. [1] and Koutaissoff et al. [2]. This association is strong ($P < 0.001$) even after adjustment for the potential confounders listed in Table 1. The key new findings from our study, discussed below, are that the association with digital ischaemia is strengthened in an SSc population with a high prevalence of digital problems (including examining for associations with different degrees of severity of digital ischaemia), and that any association with calcinosis may exist only when calcinosis is severe. The major focus of our study was on acro-osteolysis rather than a more comprehensive description of radiographic abnormalities in patients with SSc. We developed an acro-osteolysis scoring system to minimize subjectivity. Although different patterns of acro-osteolysis have been described, in this study we concentrated on distal bone loss.

Although an association between severe digital ischaemia and acro-osteolysis does not indicate causation, nonetheless a possible explanation for the association between acro-osteolysis and severity of digital ischaemia is that impaired blood flow may drive the terminal tuft resorption, which may therefore be a result of ischaemic atrophy. This seems intuitive, given that patients with SSc and severe digital ischaemia develop fingertip ulcers and digital pitting; it seems likely that this soft tissue loss is paralleled by bone loss.

Avouac et al. [1] reported acro-osteolysis in 26 (22%) of an unselected cohort of 120 patients with SSc. The definition of acro-osteolysis (e.g. whether its presence in one finger alone was sufficient for the diagnosis) was not given, but the findings were similar to ours in that patients requiring prostacyclin were more likely to have acro-osteolysis than those without it (10/20 vs 16/100, $P = 0.005$) [1]. In our study, a higher proportion of patients had required i.v. prostanoids than in the cohort of Avouac et al. [1] (39% vs 17%). This higher proportion of patients requiring prostanoids in our study (and the higher prevalence of acro-osteolysis in our study; 33% vs 22% in the cohort of Avouac et al. [1]) most likely reflects its retrospective nature; those patients who had hand radiographs would have been likely to have digital problems. Avouac et al. [1] also reported that acro-osteolysis was associated with digital ulceration, a finding confirmed by Koutaissoff et al. [2], who scored acro-osteolysis in 167 patients with SSc (25% had acro-osteolysis). Koutaissoff et al. [2] also reported (as we too found) that patients with longer disease duration are more likely to have acro-osteolysis, consistent with the clinical observation that clinical features of digital vascular injury in SSc tend to progress over the years.

These three studies (Avouac et al. [1], Koutaissoff et al. [2] and our own) all point to acro-osteolysis being associated with clinical features of digital ischaemia. Although numbers are small, it is of interest that in our cohort, moderate/severe acro-osteolysis was present in 86% of those with amputations and in 68% of those requiring debridement; in other words, those in whom digital ischaemia is most severe. This further supports the hypothesis that acro-osteolysis is associated with severity of digital ischaemia.

Although it seems likely that digital ischaemia plays a key role in the pathogenesis of acro-osteolysis (emphasizing the need for effective vasodilator therapy), prospective studies are required to confirm this. Relevant to this is that a recent longitudinal study by Avouac et al. [6] reported that digital ulcers (and calcinosis) predicted progression of acro-osteoelysis.

Our study also lends limited support for the association between acro-osteolysis and calcinosis previously reported by Avouac et al. [1, 6]. Our cohort had a higher prevalence of calcinosis than that of Avouac et al. [1] (41% vs 23%), again probably reflecting a bias in our population toward patients with clinically significant digital problems. In our study we graded the severity of calcinosis and found an association between acro-osteolysis and severe calcinosis, but not with more minor degrees. The statistical significance of this association lessened with multifactorial analysis. Koutaissoff et al. [2] reported that terminal tuft calcinosis (present in 15% of their cohort) was associated with digital ulceration and pitting scars. Avouac et al.’s [6] study showed that digital ulceration was an independent predictor of calcinosis and acro-osteolysis. An association between calcinosis and nailfold capillaroscopic changes has been reported [7], although we did not confirm this [8]. Further studies are indicated to elucidate the inter-relationships between digital blood flow (using modern imaging techniques), acro-osteolysis and calcinosis.

In conclusion, there is now good evidence to suggest that acro-osteolysis is another ischaemic manifestation of SSc. Acro-osteolysis may also be associated with calcinosis. Although these findings provide increased insight into pathogenesis, perhaps a more important conclusion is that scoring systems for acro-osteolysis (building on that used in this study) should be developed. The scoring system used in this study was ad hoc. Although this has good face validity and was rated independently by two observers who reached consensus on each digit, it remains a weakness of our study that we do not have formal inter- or intra-rater reliability assessments for this scale. A validated acro-osteolysis scoring
system could become a marker in studies of digital vascular disease progression and of treatment response.

**Rheumatology key messages**

- Acro-osteolysis is associated with severity of digital ischaemia.
- Acro-osteolysis may be driven by impaired blood flow.
- Acro-osteolysis should be investigated as a possible marker of SSc-related digital ischaemia.

**Disclosure statement:** The authors have declared no conflicts of interest.

**References**