Prevalence and clinical association with acro-osteolysis in early systemic sclerosis

A. Sakchaikul[1], P. Chowchuen[1], C. Foocharoen[2], P. Thammaroj[1]

[1]Department of Radiology, [2]Division of Rheumatology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.

Abstract

Objective

Acro-osteolysis is often associated with systemic sclerosis (SSc). However, the severity of acro-osteolysis and its clinical association among SSc patients is limited. Our aims were to assess the prevalence of acro-osteolysis and the clinical association with acro-osteolysis among SSc patients at early onset of the disease.

Methods

A cross-sectional study of 120 newly diagnosed SSc patients with the onset of less than 4 years were evaluated on clinical characteristics and hand radiographs. Acro-osteolysis was graded on a 0–4-point scale based on the severity and the patients were subdivided into mild, moderate and severe.

Results

Among all SSc patients enrolled, 62.5% were females, 56.1% dcSSc and the vast majority of them (84.1%) were positive for anti-topoisomerase I antibody (anti-topo I). The mean disease duration was 2.0±1.3 years. Acro-osteolysis was noted in 77 patients with a prevalence of 64.1% (95%CI 54.9–72.7), of which 16.7% were defined as severe acro-osteolysis. Logistic regression analysis revealed that acro-osteolysis was positively associated with anti-topo I (OR 13.96), hand deformity (OR 3.81) and dysphagia (OR 6.66), but negatively associated with oedematous skin (OR 0.05). Analysis stratified by severity of acro-osteolysis showed significant differences between subgroup in terms of the presence of digital gangrene (p=0.02), ischaemic ulcer (p=0.001), oedematous skin (p=0.001), and hand deformities (p=0.01).

Conclusion

Acro-osteolysis was common in SSc at the early onset of disease. While the presence of anti-topo I, hand deformity and esophageal involvement were strongly associated with acro-osteolysis, oedematous skin was the protective factor for acro-osteolysis.

Key words

systemic sclerosis, scleroderma-related disease, acro-osteolysis, hand radiography, skin involvement

Aornnicha Sakchaikul, MD
Prathana Chowchuen, MD
Chingching Foocharoen, MD
Punthip Thammaroj, MD

Please address correspondence to:
Punthip Thammaroj,
Department of Radiology,
Faculty of Medicine,
Khon Kaen University,
123 Mittraphap Road,
Nai-Mueang, Mueang District,
Khon Kaen 40002, Thailand.
E-mail: wpunth@kku.ac.th

Introduction

Systemic sclerosis (SSc) is a complex disorder characterised by the involvement of small arteries, microvessels and connective tissue, with deposition of fibrotic tissue and microvascular obliteration in the skin and internal organs. The worldwide prevalence is 10-34.1 per 100,000 populations. Based on the clinical features, SSc is divided into 2 large groups, limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) groups. The aetiology and pathogenesis of SSc have not been elucidated, the disease appears to be the results of multisteps and multifactors including immune system alterations, genetic and environmental factors. The clinical feature of SSc varies depending on the extent of the skin and internal organ comorbidities [1, 2].

Acro-osteolysis is the resorption of the terminal tuft of the digit, which is frequently seen in SSc. It has been estimated to occur at around 20–76% of SSc patients [3-5]. It starts at the tip of finger and can produce the destruction of a large portion of the distal phalanx that leads to the finger looked like a conical aspect, particularly in severe cases. Acro-osteolysis was associated with severe Raynaud's phenomenon and calcinosis [1], suggesting that impairment of blood supply and skin tightening could be a pathogenesis of acro-osteolysis. However, the exact pathogenesis of acro-osteolysis remains unknown.

Most of the literature on SSc with acro-osteolysis included patients with a wide range of disease duration [1, 3-6]. Although internal organ involvement commonly occurred in an early phase within 4 years after onset of SSc, to our best knowledge, investigation on the severity of acro-osteolysis and its clinical association in SSc patients in an early onset of disease has never been reported. Therefore, we aimed to determine the prevalence of acro-osteolysis and identify the clinical association with acro-osteolysis among SSc patients at the early onset of disease.

Materials and methods

This was a cross-sectional study of hand radiographs and clinical features from patients with SSc attending the Scleroderma Clinic, Khon Kaen University Hospital, Thailand from April 2019 to June 2020.

Description of study population

We considered eligible any patients over 18 years of age who met the update criteria of the American College of Rheumatology for SSc [7]. The time interval after the diagnosis of SSc of these patients have not exceed 4 years, which was defined as an early onset of SSc. We excluded the patients diagnosed as having an overlap syndrome.

Sample size was calculated based on the prevalence of acro-osteolysis that was around 20–76% of SSc patients from the previous studies [3-5, 8] We estimated sample size by using prevalence of 50%, the precision of 10% and level of confidence of 95%. The sample size should be 97 cases but we included totally 120 cases into our study in order to increase statistical power in case of missing data was detected. Therefore, the new cases of 120 SSc patients were included in this study and were screened for acro-osteolysis by hand radiography.

Clinical variables

We carried out a general evaluation of these patients. The data included age, sex, type of SSc (diffuse or limited), presence of anti-topoisomerase I antibody (anti-topo I), anti-centromere antibody, SSc clinical characteristics, modified Rodnan skin score (mRSS), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Hand radiographs

All eligible patients underwent hand radiographs in 2 positions; posteroanterior and oblique views using a general radiography system; Hitachi, Radnext 80, 50 kVp, 1 mAs.

Operation definitions

Diagnosis of SSc was based on 2013 ACR/EULAR Classification Criteria for Scleroderma [7]. The SSc patients were classified into dcSSc or lcSSc groups according to LeRoy *et al.* [9]. The onset of SSc was defined as the time of first development of non-Raynaud SSc symptom reported by the patient.
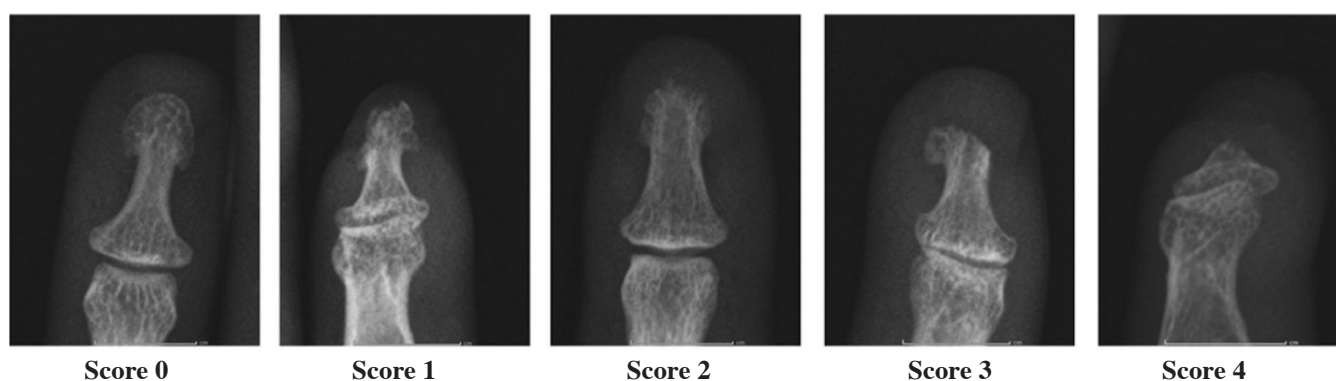
Fig. 1. Scoring of acro-osteolysis. Score 0: normal terminal phalanges. No resorption; Score 1: minimal acro-osteolysis, small amount of resorption at the terminal tuft. Score 2: resorption of most of the distal tip of the terminal tuft. Score 3: resorption of most of the terminal tuft, leaving only one side intact. Score 4: complete resorption of the terminal tuft, with obvious pencilling.

Pulmonary arterial hypertension (PAH) is defined by a mean pulmonary arterial pressure >20 mmHg confirmed by right heart catheterisation (10). Interstitial lung lesion was considered present when interstitial fibrosis was detected by either chest radiography or high-resolution computed tomography (HRCT). The definition of oesophageal involvement was fulfilled when any oesophageal symptoms of SSc were revealed (*i.e.* oesophageal dysphagia, heartburn, or reflux symptoms). Stomach involvement included dyspepsia, early satiety, and bloating (11). Oedematous skin was characterised by feature of puffy hand or non-pitting oedema of fingers. Hand deformity is defined when the finger joints are flexion contractures resembling claw deformities (12).

Analysis of radiographs
All hand radiographs were recorded and reviewed using the Picture Archive and Communication System. Radiographs were examined for acro-osteolysis by two 10-year experienced musculoskeletal radiologists. Any discrepancy was given in a consensus.
Acro-osteolysis was defined by bone resorption at the terminal tuft of the fingers. A grading scale for acro-osteolysis was used referring to the scale from 0 to 4 that 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 (4) (Fig. 1.). The scoring system was as follows (4):

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.

The overall rating including normal, minimal, moderate or severe acro-osteolysis was described to each patient on the following basis:
0. Normal.
1. Mild acro-osteolysis: maximum score for an individual finger = 1 and total score (sum of all fingers) ≤8.
2. Moderate acro-osteolysis: maximum score for an individual finger ≤2 and total score from 9 to 16 inclusive.
3. Severe acro-osteolysis: maximum score for an individual finger ≥3 or total score ≥17.

Statistical analysis
Continuous variables were presented as mean (standard deviation) or median (interquartile range [IQR]), as appropriate. Categorical variables were reported as number and percentage. Continuous variables were compared between two groups (no acro-osteolysis *vs.* acro-osteolysis) using two sample t-test or Wilcoxon rank-sum as appropriate. Chi-square test or Fisher's exact test were used for categorical variables.
Binary logistic regression was used to analyse the association of acro-osteolysis with the clinical features. To build a

multivariable regression model, univariable regression was first analysed. The variables significant at $p<0.1$ in univariable analysis were identified as potential factors variables and entered into a logistic regression model. The level of statistical significance was set at $p<0.05$. Data analyses were performed using STATA v. 16.0 (StataCorp., College Station, TX, USA).

Ethical consideration
This study was designed by the authors and approved by the Human Research Ethics Committee of Khon Kaen University with approval number HE621325 as per the Helsinki Declaration and the Good Clinical Practice Guidelines. All eligible patients signed informed consent before enrolment.

Results
A total of 120 SSc patients were included, of whom 75 (62.5%) patients were females and 64 (56.1%) were dcSSc. The respective mean age at the onset and the mean age at the study date was 54.8±10.6 years and 56.8±10.5 years, respectively. The mean disease duration was 2.0 (±1.3) years. The majority of patients (84.1%) were positive for anti-topo I antibody. The overall clinical characteristics of the patients were presented in Table I.
Acro-osteolysis was detected in 77 SSc patients with the prevalence of 64.1% (95% CI 54.9–72.7). By univariate analysis, older age and dysphagia at the onset were associated with acro-osteolysis, while oedematous skin at the onset and on the study date were not

Table I. Clinical characteristics of overall patients and clinical association with acro-osteolysis.

Data	Overall n=120 (%)	No acro-osteolysis n=43 (%)	Acro-osteolysis n=77 (%)	OR (95%CI)	*p*-value
Female sex	75 (62.5)	28 (65.1)	47 (61.0)	0.84 (0.36-1.95)	0.66
Age at onset (years)					
(mean ± SD)	54.8 ± 10.6	52.3 ± 10.5	56.2 ± 10.4	-	0.05
Age on study date (years) (mean ± SD)	56.8 ± 10.5	54.2 ± 10.3	58.3 ± 10.3	-	0.04[a]
Disease duration (year) (mean ± SD)	2.0 ± 1.3	1.9 ± 1.2	2.1 ± 1.3	N/A	0.50
Diffuse cutaneous systemic sclerosis	64 of 114 (56.1)	24 (60.0)	40 (54.0)	0.78 (0.33-1.83)	0.54
Anti-topoisomerase I antibody positive	90 of 107 (84.1)	29 (74.4)	61 (89.7)	3.00 (0.92-10.22)	0.04[a]
Anti-centromere antibodies positive	6 of 120 (5.0)	2 (4.7)	4 (5.2)	1.12 (0.15-12.9)	0.90
Clinical characteristics at onset					
Ischaemic ulcer	22 of 118 (18.6)	4 (9.3)	18 (24.0)	3.08 (0.91-13.35)	0.049[a]
Oedematous skin	75 of 118 (63.6)	36 (83.7)	39 (52.0)	0.21 (0.07-0.57)	<0.001[a]
Oesophageal involvement	46 of 118 (39.0)	10 (23.3)	36 (48.0)	3.05 (1.23-7.90)	0.01[a]
Clinical characteristics on study date					
Oedematous skin	27 of 118 (22.9)	16 (37.2)	11 (14.7)	0.29 (0.11-0.77)	0.01[a]
Hand deformity	43 of 118 (36.4)	9 (20.9)	34 (45.3)	3.13 (1.24-8.42)	0.01[a]

[a]statistically significant; n: number; SD: standard deviation.

associated with acro-osteolysis (Table I, Supplementary Table S1). According to the results of logistic regression analysis, the clinical features positively associated with acro-osteolysis were anti-topo I (adjusted OR 13.96; 95% CI 2.29–85.10), hand deformity on the study date (adjusted OR 3.81; 95%CI 1.03–14.07), and dysphagia at the onset (adjusted OR 6.66; 95% CI 1.77–25.05). While oedematous skin at the onset had a negative association with acro-osteolysis (adjusted OR 0.05; 95% CI 0.01–0.32) (Table II, Suppl. Table S2).

Among the patients with acro-osteolysis, 37 cases (48.0%) were defined as mild acro-osteolysis, 20 (26.0%) moderate, and 20 (26.0%) severe. When the patients were stratified according to the severity of acro-osteolysis, significant differences were observed between subgroups in terms of the presence of digital gangrene at the onset (*p*=0.02), ischaemic ulcer on the study date (*p*=0.001), oedematous skin on the study date (*p*=0.001), and hand deformities on the study date (*p*=0.01). Disease subsets, severity of skin thickness by mRSS and internal organ involvement were not significantly different. (Table III, Suppl. Table S3).

Discussion

Acro-osteolysis is a bone involvement in SSc and it is frequently observed in SSc patients with longer duration of disease (4, 5). According to our findings, however, acro-osteolysis was commonly presented as early as at the onset of the disease. The majority of acro-osteolysis was mild but about one third of the patients had moderate to severe acro-osteolysis. When compared to the previous study which included mostly patients with lcSSc, the prevalence of acro-osteolysis among Thai was similar to those of the previous reports (64% *vs*. 20–76%) (3-5, 13). In addition, in this study, the prevalence of overall acro-osteolysis as well as moderate to severe acro-osteolysis was comparable between dcSSc and lcSSc group at the early onset of disease, although skin thickness assessment by mRSS of dcSSc group was significantly higher than that of lcSSc group (*p*=0.01) (data not shown). The pathogenesis of acro-osteolysis is not fully understood, our results show that acro-osteolysis might not be affected by the SSc disease subset or the severity of the disease. In addition, not only mild acro-osteolysis but also moderate to severe acro-osteolysis can be occurred even at the early stage of SSc.

Skin thickness is a cardinal feature of SSc. One of the first syptoms of SSc is puffy hands or skin oedema. The oedematous skin or oedematous phase usually comes prior to skin thickness or indurative phase. The oedematous phase may last for years or shorter before progression to the indurative phase (12). In

this phase, hand deformity and internal organ involvements (PAH, cardiac involvement and pulmonary fibrosis) are less frequent than in the indurative phase (14). In this study, the oedematous skin was the only factor that had negative association with acro-osteolysis in SSc patients, while hand deformity was strongly associated with acro-osteolysis. These findings might be explained by the fact that the very early stage of the disease is the oedematous phase and is generally mild and less frequently involved hand lesion. In fact, hand deformity is a less frequent clinical feature during the oedematous phase (14), so the oedematous phase is not a risk factor for the development of acro-osteolysis.

On the other hand, once hand deformity is detected, acro-osteolysis is frequently presented. Because this study is a cross-sectional study, there is an uncertainty whether acro-osteolysis would occur later when the skin turns to the indurative phase and acro-osteolysis could be prevented or not. Further investigation for longitudinal hand radiographs performed at onset during the oedematous phase and thereafter in the indurative phase should be performed in order to evaluate the natural progression of acro-osteolysis or bone change during SSc progression. Even so, our data provide the initial information to the attending physicians that SSc patients should pay attention to and be aware of the presence of acro-osteolysis

Table II. Logistic regression analysis of clinical associated with acro-osteolysis.

Data	Crude OR (95%CI)	Adjusted OR (95%CI)	p-value
Anti-topoisomerase I antibody positive	3.00 (0.92-10.22)	13.96 (2.29-85.10)	0.01[a]
Oedematous skin at onset	0.21 (0.07-0.57)	0.05 (0.01-0.32)	0.01[a]
Oesophageal involvement at onset	3.05 (1.23-7.90)	6.66 (1.77-25.05)	0.01[a]
Hand deformity on study date	3.13 (1.24-8.42)	3.81 (1.03-14.07)	0.045[a]

[a]statistically significant; OR: odds ratio.

Table III. Clinical differences stratify by severity of acro-osteolysis.

Data	No	Mild	Moderate	Severe	p-value
Clinical characteristics at onset					
Digital gangrene	0	0	0	2	0.02[a]
Clinical characteristics on study date					
Digital ulcer	0	7	0	4	0.001[a]
Oedematous skin	16	10	1	0	0.001[a]
Hand deformity	9	13	12	9	0.01[a]

[a]statistically significant.

when oedematous change of the skin disappears.

Anti-topo I is a well-known specific autoantibody in SSc and has been used for diagnosis and risk assessment of SSc patients. It also can be used as a surrogate maker for fibrosis, active disease and worsen prognosis (15). Anti-topo I is associated with acro-osteolysis (16, 17). In this study, we also have found the association between the presence of anti-topo I and acro-osteolysis in SSc patients of less than 4 years of onset. Our results show that the risk of acro-osteolysis in anti-topo I-positive SSc patients is 14 times higher than those who were negative for anti-topo I. According to the high prevalence of anti-topo I among Thais (18-20), it is uncertain whether the association between acro-osteolysis and anti-topo I might be happened by chance or not. Since our study is a cross-sectional study, longitudinal study is necessary to see whether acro-osteolysis is progressively worsening in anti-topo I-positive SSc patients. At least, our results clearly show that routine screening of hand radiographs of the SSc patients at baseline at the very beginning is necessary, particularly for those positive for anti-topo I for an early detection of acro-osteolysis, since the prevention for acro-osteolysis currently remains unclear.

In this study, acro-osteolysis was not associated with most of internal organ involvement, except for oesophageal involvement which showed 6 times of risk of acro-osteolysis development among early stage of SSc patients. As we know, oesophageal involvement is a common clinical feature of SSc and can be a clinical presentation of SSc (18). The association between esophageal involvement and acro-osteolysis in an early onset of disease might be a random chance event, because data concerning any causal link between oesophageal involvement and acro-osteolysis among SSc patients are lacking.

The aetiology and pathogenesis of acro-osteolysis still remains unclear. Many studies proposed that acro-osteolysis could be a) a vasculopathy and hypoxia that lead to digital ischaemia and b) a retractile pressure from skin thickness (8, 12). In this study, we found the association between the severity of acro-osteolysis and clinical features that represent vasculopathy (digital ulcer and digital gangrene). However, we were unable to see the association between acro-osteolyis with skin thickness by mRSS or with inflammatory markers (ESR and CRP). According to our findings, vasculopathy and tissue hypoxia can be a part of pathogenesis of acro-osteolysis in SSc, while inflammation has no possible role of acro-osteolysis development. Since we have limitation to do skin biopsy or assess the local skin thickness at fingertip, we cannot conclude whether

acro-osteolysis is related to the retractile pressure from skin thickness of finger.

The strength of our study are a) we included the newly diagnosed SSc patients at an early onset of disease, so we can have the baseline data of bone involvement in the earliest time; b) clinically important data such as specific autoantibodies and inflammatory markers were included into analysis, so that our results would be helpful for exploration of the aetiology or pathogenesis of acro-osteolysis and c) the sufficient number of patients according to sample size calculation was included, so that the results can validate the prevalence of having acro-osteolysis and had a power of analysis of the clinical association with acro-osteolysis in SSc.

On the other hand, limitations of our study are; a) evaluation of the presence of acro-osteolysis is difficult in cases of severe hand deformity. However, the hand radiographs interpretation was based on the consensus of 2 radiologists to reduce any error of the assessment; and b) there is no longitudinal data of the progression of acro-osteolysis because our study was a cross-sectional study design. We therefore cannot provide the additional information about the nature of acro-osteolysis among SSc with early onset of disease. Nevertheless, the preliminary data can give some interested point for the attending physicians in order to perform a better care and monitoring of acro-osteolysis in SSc patients in daily practice.

Conclusion

Acro-osteolysis was common among SSc at the early onset of disease and about one-third were moderate to severe acro-osteolysis. Oedematous skin was the protective factor, while the presence of anti-topo I, hand deformity and oesophageal involvement were strongly associated with acro-osteolysis.

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