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DR. ALAIN LESCOAT (Orcid ID : 0000-0003-2081-8558)

DR. FRANÇOIS MAURIER (Orcid ID : 0000-0002-3222-8566)

DR. BRIGITTE GRANEL (Orcid ID : 0000-0001-7995-8817)

DR. BENJAMIN CHAIGNE (Orcid ID : 0000-0001-5448-7860)

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## **Osteitis in Systemic Sclerosis:**

### **a nationwide case-control retrospective study (SCLEROS Study)**

Cyril Cosse<sup>1</sup> PhD; Solen Kernéis<sup>2</sup> MD, PhD; Alain Lescoat<sup>3</sup> MD, PhD; Gregory Pignet<sup>4</sup> MD, PhD; Marie-Elise Truchetet<sup>5</sup> MD, PhD; Pascal Priollet<sup>6</sup> MD; Elisabeth Diot<sup>7</sup> MD, PhD; Mickael Martin<sup>8</sup> MD, PhD; François Maurier<sup>9</sup> MD; Jean François Viillard<sup>10</sup> MD, PhD; Christian Agard<sup>11</sup> MD, PhD; Brigitte Granel<sup>12</sup> MD, PhD; Sabine Berthier<sup>13</sup> MD; Dorothée Fagedet<sup>14</sup> MD; Bénédicte Watelet<sup>15</sup> MD; Ségolène Toquet<sup>16</sup> MD; David Luque Paz<sup>17</sup> MD, PhD; Cloé Giret<sup>7</sup> MD; Olivier Cerles<sup>1</sup> PhD; Jérémie Dion<sup>1</sup> MD; Christelle Nguyen<sup>18</sup> MD, PhD; Loïc Raffray<sup>19</sup> MD, PhD; Julien Bertolino<sup>12</sup> MD; Wendy Jourde<sup>10</sup> MD; Claire Le Jeunne<sup>1</sup> MD, PhD; Luc Mouthon<sup>1</sup> MD, PhD & Benjamin Chaigne<sup>1</sup> MD, PhD

<sup>1</sup> Service de Médecine Interne, Centre de Référence Maladies systémiques auto-immunes rares d'Ile de France, Hôpital Cochin, Université Paris Descartes, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France.

<sup>2</sup>Antimicrobial Stewardship Team, APHP, Cochin hospital, University of Paris, Paris, France

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<sup>3</sup> Université Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) – UMR\_S 1085, F-35000 Rennes, France; Department of Internal Medicine and Clinical Immunology, Rennes University Hospital, 35203, Rennes, France

<sup>4</sup> Service de Médecine Interne, CHU Toulouse, Toulouse, France ; Centre d'Investigation Clinique 1436, CHU Toulouse, Toulouse, France

<sup>5</sup> Rheumatology department and national center of reference for rare autoimmune diseases, Bordeaux University Hospital

<sup>6</sup> Service de médecine vasculaire, Hôpital Saint Joseph, Paris, France

<sup>7</sup> Service de médecine Interne, Hôpital Bretonneau, Tours Cedex, France

<sup>8</sup> Service de Médecine Interne, Maladies Infectieuses et Tropicales, CHU de Poitiers, Poitiers, France

<sup>9</sup> Centre de compétence des maladies rares, Hôpitaux privés de Metz, Metz, France

<sup>10</sup> Département de Médecine Interne et Maladies Infectieuses, Centre Hospitalier Universitaire Haut Lévêque, Université de Bordeaux, Pessac, France

<sup>11</sup> Service de médecine interne, Hôtel-Dieu, CHU Nantes, Hôpital, Université de Nantes

<sup>12</sup> Service de Médecine Interne, Hôpital Nord, Aix-Marseille Université, Assistance Publique-Hôpitaux de Marseille (AP-HM), Marseille, France

<sup>13</sup> Service de Médecine Interne et Immunologie Clinique, CHU F MITTERRAND, Dijon, France

<sup>14</sup> Service de Médecine Interne – CHICAS, hôpital de GAP

<sup>15</sup> Service de Médecine Interne, CHU Caen, Caen, France

<sup>16</sup> Pôle médecine, CHU Robert Debré, Reims, France

<sup>17</sup> Service des Maladies Infectieuses et Réanimation Médicale, CHU Rennes, France

<sup>18</sup> Service de Rééducation et de Réadaptation de l'Appareil Locomoteur et des Pathologies du Rachis, Hôpitaux Universitaires Paris Centre-Groupe Hospitalier Cochin, Assistance Publique-Hôpitaux de Paris, 75014 Paris, France ; Université de Paris, Faculté de Santé, UFR Médecine Paris Descartes, Sorbonne Paris Cité, 75006 Paris, France ; INSERM UMRS 1124, Toxicité Environnementale, Cibles Thérapeutiques,

Signalisation Cellulaire et Biomarqueurs, UFR Sciences Fondamentales et Biomédicales, Centre Universitaire des Saints-Pères, 75006 Paris, France.

<sup>19</sup> Service Médecine Interne et Dermatologie ; CHU Réunion- Hôpital Félix Guyon, Saint Denis, France

Correspondance: Dr Benjamin Chaigne, Service de Médecine Interne, Centre de Référence Maladies systémiques auto-immunes rares d'Ile de France, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, 75014 Paris, France.

Tel: +33 (0) 1 58 41 20 31 / Fax: +33 (0) 1 58 41 14 50

E-mail: benjamin.chaigne@aphp.fr

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Martin<sup>8</sup> (investigation; writing review and editing); François Maurier<sup>9</sup> (investigation; writing review and editing) ; Jean François Viillard<sup>10</sup> (investigation; writing review and editing) ; Christian Agard<sup>11</sup> (investigation; writing review and editing) ; Brigitte Granel<sup>12</sup> (investigation; writing review and editing); Sabine Berthier<sup>13</sup> (investigation; writing review and editing) ; Dorothee Fagedet<sup>14</sup> (investigation; writing review and editing) ; Bénédicte Watelet<sup>15</sup> (investigation; writing review and editing) ; Ségolène Toquet<sup>16</sup> (investigation; writing review and editing) ; David Luque Paz<sup>17</sup> (investigation; writing review and editing) ; Cloé Giret<sup>7</sup> (investigation; writing review and editing) ; Olivier Cerles<sup>1</sup> (visualization; writing review and editing) ; Jérémie Dion<sup>1</sup> (investigation; writing review and editing) ; Christelle Nguyen<sup>18</sup> (investigation; writing review and editing) ; Loïc Raffray<sup>19</sup> (investigation; writing review and editing) ; Julien Bertolino<sup>12</sup> (investigation; writing review and editing) ; Wendy Jourde<sup>10</sup> (investigation; writing review and editing) ; Claire Le Jeune<sup>1</sup> (conceptualization ; methodology; formal analysis ; writing original draft); Luc Mouthon<sup>1</sup> (conceptualization ; methodology; formal analysis ; writing original draft) & Benjamin Chaigne<sup>1</sup> (supervision; project administration; conceptualization ; methodology; formal analysis ; writing original draft)

## ABSTRACT

*Objective:* Systemic sclerosis (SSc) is an autoimmune (AI) connective tissue disorder characterized by skin fibrosis, vasculopathy and dysimmunity. Data regarding osteitis in SSc are scarce.

*Method:* We performed a nationwide multicentre retrospective case-control study including patients with SSc according to the 2013 ACR/EULAR classification, with a diagnosis of osteitis. The objectives of the study were to describe, to characterize, and to identify associated factors for osteitis in patients with SSc.

*Results:* Forty-eight patients were included. Twenty-six patients (54.1%) had osteitis beneath digital tip ulcers. Physical symptoms included: pain (36/48, 75%), erythema (35/48, 73%), and local warmth (35/48, 73%). Thirty-one (65%) patients had C-reactive protein levels >2 mg/L (8 [2.7 – 44.3] mg/L). On X-ray, CT-scans or MRI, osteitis was characterized by swelling or abscess of soft tissues with acro-osteolysis or lysis in 28 patients (58%). Microbiological sampling was performed in 45 (94%) patients. Most pathogens were *Staphylococcus aureus* (43.8%); anaerobes and *Enterobacteriaceae* (29.1%) and *Pseudomonas aeruginosa* (10.4%). Management comprised antibiotics in 37 (77.1%) patients and/or surgery in 26 (54.2%). Fluoroquinolones were used in 22 (45.8%) patients and amoxicillin + beta-lactamase inhibitor in 7 (14.6%). Six (12.6%) patients relapsed, 6 (12.6%) patients had osteitis recurrence, 15 (32%) sequelae, and 2 patients had septic shock and died.

*Conclusion:* This study confirmed digital tip ulcers as an associated factor for osteitis, and revealed a high rate of functional sequelae. Antimicrobial therapy with oral fluoroquinolone or intravenous amoxicillin and beta-lactamase inhibitor are used as first-line antibiotherapy in SSc patients with osteitis.

## SIGNIFICANCE AND INNOVATIONS

- 54.1% of osteitis in systemic sclerosis (SSc) patients occurred beneath digital ulcers
- Most frequent pathogens in SSc osteitis were *Staphylococcus aureus*, anaerobes and *Enterobacteriaceae*, and *Pseudomonas aeruginosa*
- SSc osteitis is associated with 25.2% of relapse or recurrence, 32% of sequelae and 2 death due to septic shock
- Antibiotic biotherapy with either oral fluoroquinolone or intravenous amoxicillin and beta-lactamase inhibitor were mainly used as first-line antibiotherapy in SSc patients with osteitis

## **INTRODUCTION**

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder characterized by skin sclerosis due to fibroblast activation and extra-cellular matrix synthesis, vasculopathy including vascular hyperactivity and remodeling and dysimmunity (1-3). Because of microangiopathy, patients with SSc have a compromised vascular supply and present with Raynaud's phenomenon and digital ulcers, which put them at risk of osteitis (4-7).

Osteitis is an infection resulting from the contamination of the bone by one or more pathogens. Such infection results either from direct inoculation or from secondary hematogenous spread. It causes an inflammatory reaction with the secretion of proinflammatory cytokines such as tumor necrosis factor alpha (8). Inflammatory cytokines then stimulate the activation of osteoclasts and osteoblasts, which leads to bone resorption and periosteal reaction, respectively. In case of prolonged osteitis or in patients with diabetic foot infection, ischemic lesions enhance the occurrence of an infection and favor bone necrosis and osteolysis (9). Patients are subsequently at risk of gangrene and amputation.

Gangrene has been reported in SSc and occurs mainly in smoking, anti-Scl70 positive patients with digital ulcers and a history of previous infection, including osteitis (10). Oppositely, osteitis has been less described in SSc. Even though it is a severe infection, which inevitably impacts patients' quality of life and is responsible for a high morbidity, very few studies have focused on its description and management in patients with SSc.

Herein, we report the nationwide SCLEROS study, which aimed at characterizing osteitis in patients with SSc.

## **PATIENTS AND METHODS**

### **Study design**

SCLEROS is a retrospective, multicentre, nationwide case-control study performed in France. Between January and June 2019, physicians belonging to the following scientific societies: GFRS



(Groupe Francophone de Recherche sur la Sclérodermie), SNFMI (Société Nationale Française de Médecine Interne); SPILF (Société de Pathologie Infectieuse de Langue Française) and CRI (Club Rhumatismes et Inflammations) were asked to recall and report all cases with SSc and osteitis managed between 2000 and 2019.

### **Objectives**

The primary objective of the study was to describe and characterize osteitis in SSc patients. The secondary objective was to identify associated factors for osteitis in patients with SSc.

### **Study population**

Inclusion criteria were: male or female patients over 18 years old, diagnosis of systemic sclerosis according to the 2013 ACR/EULAR classification (11), diagnosis of osteitis according to the physician in charge of the patient suspected on the basis of clinical, laboratory, and confirmed by radiological findings or surgical bacteriological sampling, namely, the presence of clinical signs/symptoms (local pain, swelling, erythema around the skin ulcer, warmth, purulent discharge, fever), blood chemistry alterations (C-reactive protein, and/or increased white blood cell count), positive microbiological surgical sample or radiological findings. The latter included the following: soft-tissue swelling, periosteal reaction or elevation, loss of cortex with bone erosion, focal loss of trabecular pattern, new bone formation, bone sequestrum, involucrum, and/or cloacae (12, 13). For each case, 4 controls with SSc according to the 2013 ACR/EULAR classification without osteitis were randomly extracted from the SSc database of the national referral centre for AI and systemic disease (14, 15).

### **Data source**

Data comprised subset classification of SSc (limited or diffuse cutaneous SSc) according to LeRoy and Medsger classification (16); disease duration; clinical profiles (modified Rodnan skin score, digital vasculopathy and other visceral impairment); antibody profile and patients' comorbidities.

Collected data related to osteitis were the following: location, clinical and biological presentation of osteitis, microbiological data and management. Superficial samples were defined as thin-needle aspiration, deep samples were defined as bone biopsies performed during surgery. A new episode of osteitis was defined as another osteitis at a different location within 6 months.

## **Statistical analysis**

Quantitative variables were expressed as the mean  $\pm$  standard deviation (SD) or (for a non-Gaussian distribution) the median [interquartile range] [IQR] and compared with Mann-Whitney test. Qualitative variables were expressed as the number (n) and percentage (%) and compared with Chi-square test.

Associated factors for osteitis occurrence and osteitis healing were identified according to a two-step logistic regression. First variables with a p value  $<0.15$  in the univariate analysis were included in the multivariate analysis. These variables were considered as independent associated factors if the p value after the multivariate analysis was  $\leq 0.05$ .

Statistical analysis was performed with STATA 15.1 software (StataCorp LLC, Texas, USA). Results are reported according to the STROBE guidelines reporting data of observational studies (17).

## **Ethics**

The study was approved by the local ethics committee (CER Paris Descartes) n° 2018-93.

## RESULTS

Forty-eight patients with SSc and osteitis were included in the SCLEROS study. No case was removed from the analysis because of data lacking. Populations' baseline characteristics are showed in *table 1*. SCLEROS cases comprised typical SSc patients with 77.1% of Caucasian female (median [interquartile range] age of 58.5 [48.5 – 68.5] years old). Eighty-five per cent had puffy fingers, 79.4% sclerodactyly, 95.8% Raynaud's phenomenon and 54.2% abnormal nailfold capillaries on capillaroscopy. Fifty-two percent of patients had positive anti-centromere autoantibodies and 6.3% positive anti-RNA polymerase III autoantibodies. Only 25% patients had been treated with immunosuppressant drugs at the time of osteitis. Five (10.4%) patients were treated with bosentan (3 with digital tip ulcers and 2 without).

When compared to SSc controls (n = 192), SCLEROS cases had higher mRSS (modified Rodnan skin score) (7 [4 - 18] vs 4 [2 - 8], p = 0.008). The occurrence of interstitial lung disease was less frequent (35.4% vs 53.4%, p = 0.03). Osteitis occurred mostly in patients with a long disease duration of SSc (110 [30 - 204] vs 44 [17 - 109] months, p = 0.004) and predominantly in patients with dSSc (35.4% vs 20.8%, p = 0.03).

### Description of osteitis episodes

Osteitis characteristics are showed in *table 2*.

#### *i/ Clinical presentation*

Osteitis in the SCLEROS population occurred predominantly in distal portions of the limbs (91.7% patients), mainly hands (52.1%). Five (10.4%) patients had osteitis over the proximal phalangeal joints. Other locations included toes (n=19), elbows (n=2), femur (n=1) and sternum (n=1). Digital ulcers and calcinosis were reported overlying the osteitis location in 26 (54.1%) and 13 (27.1%) cases, respectively. Physical symptoms included pain (75%), erythema (72.9%), and local warmth (72.9%). In most cases (44/48, 91.7 %), fever was absent. Purulent discharge was reported in 56.3% of patients.

The patient with sternum osteitis (a fifty-six years-old male) presented with a 6-month diagnostic of dSSc and positive anti-topoisomerase I antibodies. He had history of calcinosis, interstitial lung disease and gastroesophageal reflux disease. Osteitis was suspected on local pain associated with

local warmth, functional disability and erythema and confirmed on X-Ray. C reactive protein was 60 mg/L. He was successfully managed with antibiotics, with no sequelae and no recurrence. The patient with femur osteitis (a seventy-two years-old female) presented with a 4-year diagnostic of ISSc and positive anti-centromere antibodies. She had history of calcinosis and gastroesophageal reflux disease. Osteitis was suspected on local pain on the amputation site on her femur associated with local warmth, functional disability, purulent discharge and erythema and confirmed on MRI. C reactive protein was 66 mg/L. She was successfully managed with antibiotics and surgical joint cleansing, with no sequelae. She presented a new episode of osteitis at the same location 6 months after the first episode and was successfully managed with antibiotics.

When comparing osteitis beneath digital ulcers to other osteitis (i.e. those without underlying digital ulcer), osteitis beneath digital tip ulcers mostly resembled other osteitis (*tables 2, 3*) but osteitis beneath ulcers were more frequently associated with local swelling and erythema (73.1%,  $p = 0.004$ ; 84.6%,  $p = 0.04$  respectively).

#### ii/ *Laboratory investigations*

Thirty-one (64.6%) patients had an increased C-reactive protein (CRP) with a median [IQR] CRP value of 8 [2.7 – 44.3] mg/L ( $N < 5$  mg/L). Hyperleukocytosis ( $>8000$  leukocytes /  $\text{mm}^3$ ) was present in 27.1% of patients. Other blood count parameters were within the normal range. No difference was reported for biological documentation for osteitis beneath digital tip ulcers when comparing with osteitis without (w/o) digital tip ulcers.

#### iii/ *Imaging manifestations*

In the SCLEROS population, only two (4.2%) patients did not have any imaging performed. Standard X-ray ( $n = 36$  patients) reported osteolysis or acro-osteolysis in 17 patients; subcutaneous calcifications in 6 patients and thickening of soft tissues in 5 patients. MRI ( $n = 17$  patients) reported localized collection in 3 patients, soft tissues swelling in 12 patients, thickening of soft tissues in 10 patients; loss of tissue surrounding in 2 patients and acro-osteolysis in 5 patients. CT-scan ( $n = 8$  patients) reported cortical osteolysis with loss of tissue surrounding in 6 patients. Fifteen patients (31.3%) had either X-ray and MRI or X-ray and CT-scan or MRI and CT-scan. On X-ray, CT-scan or MRI, osteitis were characterized by swelling or abscess of soft tissues with acro-osteolysis or lysis in 28 patients (58.3%). Additional osteitis' description

included localized collection and swelling of soft tissues w/o acro-osteolysis that were only reported in 6.3% of radiological reports.

iv/ *Microbiological documentation*

Out of 48 patients, 40 (83.3%) patients had microbiological sampling. Sampling was performed either superficially or deeply. Seventy-seven per cent of superficial samples and 88.9% of deep samples allowed the identification of at least one pathogen species. Out of 40 patients with samples, 3 had sterile samples (7.5%) including 2 surgical samples and 1 needle-guided sample. Out of 37 seven samples with identified microorganisms, 18 samples (48.6%) had more than one identified microorganism. Overall, the most frequent pathogens were *Staphylococcus aureus* (43.8%); anaerobes and *Enterobacteriaceae* (29.1%) and *Pseudomonas aeruginosa* (10.4%). No difference was found in terms of pathogens occurrence considering the presence of digital tip ulcers.

v/ *Osteitis management*

Management of osteitis involved several specialists (internists, infectious diseases specialists, orthopaedic surgeons) in 50% of cases. Management consisted in antibiotics in 77.1% of patients and/or surgery in 54.2% of patients (synovectomy 4.2 % or amputation 22.9%) (*table 3*).

Main antibiotic regimens are summarized in *table 4*. Fluoroquinolones were used in 45.8% of patients, macrolides or lincosamides in 18.8% and amoxicillin and beta-lactamase inhibitor in 14.6%. First-line antibiotics were fluoroquinolone, orally, as a bitherapy for 34 [IQR 10 - 50] days or amoxicillin +/-  $\beta$ -lactamase inhibitor, orally, as a bitherapy for 30 [IQR 12 - 42] days. Second-line antibiotics were fluoroquinolone, orally for 32 [IQR 27 - 42] days or rifampicin, orally, for 42 [IQR 35 - 67] days as a bitherapy. Detailed regimens are presented in the *supplementary table 1*.

After 5 [IQR 2 - 18] months of median follow-up, osteitis healing was reported in 72.9% of patients. Relapse was observed in 6 (12.6%) patients (1 relapse per patient), within two months following the diagnosis of the first episode. Six (12.6%) patients experienced a new episode of osteitis. Noteworthy, such osteitis recurrence location was contralateral to the first episode in 5/6 patients. The time before recurrence was 4 [IQR 2 - 6] months. For 1 patient, the same antibiotic was continued for 3 months (amoxicillin + clavulanic acid). For another, the antibiotic was

switched to piperacillin / tazobactam then cefazolin for 3 months. For the 4 others, an amputation of the affected limb was required.

Thirty-two percent of patients had functional sequelae after management including those related to amputation. Two patients died of septic shock leading to multiple organ failure secondary to osteitis. When comparing osteitis beneath digital ulcers and other osteitis location, management and prognosis were similar.

vi/ *Osteitis management in patients with sterile samples*

Eleven patients were managed without any microbiological documentation. Three patients had sterile samples. The first patient was managed with an oral bitherapy (levofloxacin + clindamycin) for 6 weeks with a clinical healing of osteitis and no recurrence at 2 months. The second patient was managed with an oral monotherapy (cloxacillin), for 20 days then an oral monotherapy (clindamycin) for 6 weeks with a clinical healing of osteitis and no recurrence at 2 months after the beginning of treatment. The third patient was surgically managed. For eight patients, no microbiological sampling was performed. All these patients were treated with antibiotics for 10 days to 6 weeks (penicillin +/- inhibitors in 2 patients; fluoroquinolone for 4 patients and rifampicin for 2 patients). Additional local wound cares with dressing were used until healing. Among the eight patients, two required a surgical management (amputation for both) due to a lack of clinical improvement. Six patients were healed at 6 months and two had functional sequelae because of the amputation.

vii/ *Associated factors for osteitis and osteitis' healing*

Associated factors for osteitis' occurrence are presented in *table 5*. Among the tested variables, digital tip ulcers (RR (95%CI) = 4.26 (1.43 – 12.66), p = 0.009) and calcinosis (RR (95%CI) = 3.13 (1.16 – 8.47), p = 0.03) were found as independent associated factors for osteitis.

Associated factors for osteitis' occurrence on digital tip ulcers are presented in the supplemental *table 2*. Among all the tested variables, age (RR (95%CI) = 1.06 (1.01 – 1.12), p = 0.03) was found as independent associated factor for osteitis on digital tip ulcers.

Among all the tested variables to identify factors with osteitis healing, none was found as an independent associated factor (supplemental *table 3*).

## DISCUSSION

This daily life study confirms that the presence of digital ulcers is an associated factor for osteitis in SSc patients. This finding is in accordance with the series of Giuggioli *et al.*, in 2013, which showed that osteoarticular infections such as osteomyelitis were common in patients with SSc and skin ulcers (18). Moreover, digital ulcers predicted the worsening of SSc and were complicated by osteitis in 5 to 23% of cases (7, 19-22). In their 2016 prospective, observational cohort; Allamore *et al.* sought the clinical features related to the occurrence of gangrene in patients with SSc. The authors found that digital ulcers, as well as smoking status, anti-Scl 70 antibodies, and a history of previous infection (gangrene, osteomyelitis) were associated with increased bone infections (10). The SCLEROS study confirmed that digital ulcers are associated with osteitis and highlighted calcinosis as another associated factor for osteitis.

Our work highlighted the importance of microbiological documentation in osteitis diagnosis and management. In osteitis, the contribution of bone biopsy in the patient's diagnosis is unequivocal (23). Nevertheless, due to the underlying microangiopathy in SSc, physicians are often reluctant to perform surgical microbiological sampling in SSc patients. Our work demonstrated that both superficial sampling and bone biopsy can be performed safely in SSc patients and led to microbiological identification in 37 cases (77.1% of the entire cohort). Imaging is often proposed as an alternative to perform bone biopsy (24, 25). As reported by Giuggioli *et al.*, MRI, CT scan and X-rays studies are already used in daily practice for the diagnosis of osteomyelitis, mostly in the context of diabetes (26-30). The SCLEROS study confirms that such examination can identify swelling or abscess of soft tissues with acro-osteolysis or localized collection and soft tissues swelling w/o acro-osteolysis to confirm osteitis in SSc patients. Still, microbiological sampling remains necessary for the management of osteitis as acro-osteolysis or bone inflammation due to calcinosis can be found without infection in SSc patients. As for any other infections, identification of the pathogens is relevant to avoid over-treatment of patients and to reduce the acquired antibiotic resistance (31). In the SCLEROS study, the identification of pathogens allowed to reduce the antibiotics' spectrum and to shorten the mean duration of antibiotherapy (34 days vs. 6 weeks in patients with sterile samples). In this series, *Staphylococcus aureus*; anaerobes and *Enterobacteriaceae*, and *Pseudomonas aeruginosa* were the most common pathogens. This is consistent with the work of Giuggioli and Bader who reported in 2008 a frequent association with Gram positive bacteria in diabetic foot infection, another infection of distal limb enhanced by

microangiopathy (18, 32). Still, the presence of 29% of bacterial floral culture was unexpected and could hypothetically be linked to specific microbiota, inefficient hand washing or multiple use of antibiotic in SSc patients.

Treating osteitis is challenging as the objectives of its management are to decrease the infection, to reconstruct bone structure and surrounding soft tissue, to preserve the affected joints and from the patient's point-of-view, to return to a normal life as quickly as possible with the minimum functional impairment (23). The SCLEROS study showed that treating osteitis in SSc patients is also extremely challenging. Although most patients had a favourable outcome, it showed that 31.3% SSc patients with osteitis had functional sequelae. Two patients died. Interestingly, the SCLEROS study suggested that after performing microbiological sampling, probabilistic antibiotic with fluoroquinolone or amoxicillin and beta-lactamase inhibitor may be relevant. As it is efficient on staphylococcus spp, streptococcus spp, enterobacteria and pyocyanic, such antibiotherapy is already recommended in diabetic foot infections (33). In the SCLEROS study, patients with microbiological identification had pathogens for which such antibiotherapy was or would have been efficient. Moreover, 6 patients without microbiological identification were managed with such probabilistic antibiotherapy and had a favourable outcome.

The SCLEROS study has some limitations. First, considering the methodology of the call (i.e. a retrospective study), a memory bias could be present. Involved investigators may have reported difficult or severe clinical situations. This possible selection of severe cases might be an explanation for the notified death and sequelae. Moreover, patients with osteitis lacking any clinical symptoms might have been missed in this call. Indeed, some patients with osteomyelitis can be diagnosed with osteitis only on the basis of CT scan or MRI results. Second, due to the retrospective methodology also, radiological examinations were not reanalyzed by a centralized radiologist for the purpose of the study and a prospective study on radiological examination in SSc osteitis should be performed. Third, possible differences regarding the modalities of local care and surgical cleansing may have an impact on osteitis recovery results. Nevertheless, it is difficult to standardize these treatments as they depend on the local presentation of osteitis and physician's practices. Last, no assessment of the disability and the quality of life due to osteitis in SSc was performed. Therefore, we were not able to describe the functional consequences of osteitis in SSc. Despite these weaknesses, this call is the first study describing osteitis in patients with SSc. Moreover, as this study was not tailored for prevalence's calculation, the chosen design was



appropriate to answer the research question i.e. the description of osteitis in SSc patients. Besides, the data presented in SCLEROS reflected daily practice and stood for a homogeneous cohort of osteitis.

## **CONCLUSION**

This study characterized osteitis in SSc patients. It confirmed digital tip ulcers as an associated factor for osteitis and revealed a high rate of functional sequelae. It showed that antimicrobial bitherapy with either oral fluoroquinolone or intravenous amoxicillin and beta-lactamase inhibitor are used as first-line antibiotherapy in SSc patients with osteitis.

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## **TABLES**

**Table 1. Patients' baseline characteristics**

**Table 2. Osteitis characteristics in SSc patients**

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**Supplemental Table 1. Detailed scheme of antibiotherapy regimen**

**Supplemental Table 2. Associated factors for osteitis overlying digital ulcer**

**Supplemental Table 3. Associated factors of osteitis' healing for the entire cohort**

**Table 1. Patients' baseline characteristics**

	<b>Cases N = 48</b>	<b>Controls N = 192</b>	<b>P value</b>
Age, yo, median [IQR]	58.5 [48.5 – 68.5]	56 [42.5 – 68]	0.09
Female, n (%)	37 (77.1)	162 (84.4)	0.23
Ethnicity, n (%)			0.34
<i>Caucasian</i>	43 (89.6)	139 (90.9)	
<i>African</i>	3 (6.3)	9 (5.9)	
<i>Asiatic</i>	1 (2.1)	5 (3.3)	
<i>Hispanic</i>	1 (2.1)	0 (0)	
Body mass index, kg/m <sup>2</sup> , median [IQR]	21.1 [19.7 – 23.7]	23.0 [20.1 – 26.4]	0.94
Active smokers, n (%)	17 (35.4)	49 (32.5)	0.70
Typical features of SSc, n (%)			0.03
dSSc	17 (35.4)	40 (20.8)	
lSSc	31 (64.6)	152 (79.2)	
Duration of SSc, months, median [IQR]	110 [30 – 204]	44 [17 – 109]	0.004
Puffy fingers, n (%)	41 (85.4)	151 (80.8)	0.46
Sclerodactyly, n (%)	38 (79.2)	137 (71.7)	0.54
Mouth opening, mm, median [IQR]	35 [34.5 – 40]	40 [35 – 42]	0.95
mRSS, median [IQR]	7 [4 – 18]	4 [2 – 8]	0.008
dSSc	18 [15.5 – 21.5]	15 [8 – 22.5]	
lSSc	4 [3 – 8]	3 [0 – 6]	
Raynaud's phenomenon, n (%)	46 (95.8)	188 (97.9)	0.41
Abnormal nailfold capillaries, n (%)	26 (54.2)	88 (45.8)	0.30
Digital tip ulcers, n (%)			0.87
<i>Active</i>	20 (41.7)	27 (19.7)	
<i>Healed</i>	10 (20.8)	27 (19.7)	
Telangiectasia, n (%)	23 (47.9)	89 (53.6)	0.49
Calcinosis, n (%)	17 (35.4)	38 (23.5)	0.09
Gastroesophageal reflux disease, n (%)	32 (66.7)	112 (59.3)	0.35
Interstitial lung disease, n (%)	17 (35.4)	78 (53.4)	0.03
DLCO (% of predicted), median [IQR]	63.5 [54 – 72]	64 [43 – 76]	0.15

FVC (% of predicted), median [IQR]	90.5 [82 – 102]	91 [74 – 112]	0.66
Pulmonary arterial hypertension, n (%)	4 (8.3)	22 (15.3)	0.22
PAPs, mmHg, median [IQR]	33 [30 – 39]	31.5 [27 – 37]	0.30
Musculoskeletal disorders, n (%)	19 (39.6)	60 (32.6)	0.36
Scleroderma renal crisis, n (%)	4 (8.3)	22 (15.3)	0.22
Autoantibodies, n (% positive in patients tested)			
<i>Anti-centromere</i>	25 (52.1)	73 (38.0)	0.08
<i>Anti-topoisomerase I</i>	11 (22.9)	46 (23.9)	0.88
<i>Anti-RNA polymerase III</i>	3 (6.3)	6 (3.1)	0.31
Immunosuppressant, n (%)	12 (25.0)	54 (28.1)	0.67
Corticosteroids, n (%)	18 (37.5)	68 (47.6)	0.23

*DLCO: diffusing capacity of the lung for carbon monoxide; dSSc: diffuse systemic sclerosis; FVC: forced vital capacity; IQR: interquartile range; lSSc: limited systemic sclerosis; mRSS: modified Rodnan skin score; PAPs: systolic pulmonary arterial pressure; SSc: systemic sclerosis*

**Table 2. Osteitis characteristics in SSc patients**

	<b>SCLEROS cases N = 48</b>	<b>Patients with osteitis overlying digital tip ulcers N = 26</b>	<b>Patients with osteitis w/o digital tip ulcers N = 22</b>
<b>Clinical manifestations</b>			
Time from systemic sclerosis diagnosis, months, median [IQR]	113 (27 – 201)	90 (6 – 120)	144 (42 – 240)
<i>dSSc</i>	48 (24 – 120)	96 (26 – 131)	45 (28.5 – 48)
<i>lSSc</i>	121 (63 – 210)	108 (48 – 120)	144 (122 – 240)
Osteitis location, n (%)			
<i>Toe (R/L)</i>	19 (39.6)	7 (26.9)	12 (54.6)
<i>Hand (R/L)</i>	25 (52.1)	18 (69.2)	7 (31.8)
<i>Elbow (R/L)</i>	2 (4.2)	1 (3.9)	1 (4.6)
<i>Other location: femur / sternum</i>	1 (2.1) / 1 (2.1)	0 (0) / 0 (0)	1 (2.1) / 1 (2.1)
Overlying calcinosis, n (%)	13 (27.1)	8 (30.8)	5 (22.7)
Duration of osteitis, months, median [IQR]	3 (1 – 6)	3 (1 - 8)	2.5 (1 - 4)
Fever (T>37.8°C), n (%)	4 (8.3)	2 (7.7)	2 (9.1)
Local pain, n (%)	36 (75)	22 (84.6)	14 (63.6)
Functional disability, n (%)	29 (60.4)	17 (65.4)	12 (54.6)
Purulent discharge, n (%)	27 (56.3)	15 (57.7)	12 (54.6)
Local swelling, n (%)	26 (54.2)	19 (73.1)	7 (31.8)
Erythema, n (%)	35 (72.9)	22 (84.6)	13 (59.1)
Local warmth, n (%)	35 (72.9)	20 (76.9)	15 (68.2)
<b>Biological manifestations</b>			
C-reactive protein, mg/L, median [IQR]	8 (2.7 – 44.3)	7.2 (2.7 – 37.5)	12 (2.7 – 60.0)
Increased CRP value, n (%)	31 (65.9)	15 (60.0)	16 (72.7)
Hyperleukocytosis (>8000/mm <sup>3</sup> ), n (%)	13 (27.1)	8 (30.8)	5 (22.7)
Leukocytes, /mm <sup>3</sup> , median [IQR]	7300 (5000 – 8890)	7400 (5435 - 9820)	6385 (4390 - 7900)
Haemoglobin, g/dL, median [IQR]	11.8 (10.6 – 12.8)	12.3 (11.1 – 12.9)	11.4 (10.6 – 12.5)



Platelets, 10 <sup>3</sup> /L, median [IQR]	285 (218 – 341)	284.5 (215 – 341)	288 (219 - 310)
<b>Imaging manifestations</b>			
Localized collection, n (%)	3 (6.3)	0 (0)	3 (13.6)
Bone hypermetabolism, n (%)	3 (6.3)	0 (0)	3 (13.6)
Acro-osteolysis or lysis, n (%)	23 (47.9)	10 (38.5)	13 (59.1)
Swelling or abscess of soft tissues on MRI or standard X-ray, n (%)	28 (58.3)	14 (53.8)	14 (63.6)
With acro-osteolysis	3 (6.3)	2 (7.8)	1 (4.5)
W/o acro-osteolysis			
<b>Sampling</b>			
Peroperative contributive superficial or needle-guided sampling, n (% of performed examination)	14/18 (77.8)	8/10 (80.0)	6/8 (75.0)
Contributive deep or surgical sampling, n (% of performed examination)	24/27 (88.9)	14/15 (93.3)	10/12 (83.3)
<b>Microbiological documentation</b>			
<i>Staphylococcus aureus</i> , n (%)	21 (43.8)	15 (57.7)	6 (27.3)
Coagulase-negative <i>Staphylococcus</i> , n (%)	4 (8.3)	3 (11.5)	1 (4.5)
<i>Enterobacteriaceae</i> , n (%)	14 (29.1)	8 (30.8)	6 (27.3)
Anaerobes, n (%)	14 (29.1)	7 (26.9)	7 (31.8)
<i>Pseudomonas aeruginosa</i> , n (%)	5 (10.4)	1 (3.8)	4 (18.2)
<i>Streptococcus</i> spp, n (%)	4 (8.3)	4 (15.4)	0 (0)
Negative culture, n (%)**	3 (6.5)	1 (3.8)	2 (9.1)

CRP: C reactive protein; dSSc: diffuse systemic sclerosis; IQR: interquartile range; lSSc: limited systemic sclerosis; SSc: systemic sclerosis

\*: contributive exams correspond to exams in which imaging aspects of osteitis were reported.

\*\* : sterile samples were reported on all SCLEROS population (n = 48)

**Table 3. Management and prognosis of osteitis in SSc patients**

	<b>SCLEROS cases N = 48</b>	<b>Patients with osteitis overlying digital tip ulcers N = 26</b>	<b>Patients with osteitis w/o digital tip ulcers N = 22</b>
<b>Management of osteitis</b>			
Multidisciplinary management, n (%)	24 (50.0)	11 (42.3)	13 (59.1)
Surgical treatment, n (%)	26 (54.2)	16 (61.5)	10 (45.5)
Antibiotics, n (%)	37 (77.1)	21 (80.8)	16 (72.7)
Local dressing, n (%)	35 (72.9)	21 (80.8)	14 (63.6)
Surgical joints cleansing, n (%)	8 (16.7)	4 (15.4)	4 (18.2)
Opiates, n (%)	10 (20.8)	7 (26.9)	3 (13.6)
Amputation, n (%)	11 (22.9)	8 (30.8)	3 (13.6)
Synovectomy, n (%)	2 (4.2)	1 (3.9)	1 (4.6)
<b>Re-evaluation</b>			
Follow-up, months, median [IQR]	5 [2 – 18]	3.8 [2 – 12]	8 [2.5 – 24]
Clinical cure, n (%)	35 (72.9)	19 (73.1)	16 (72.7)
Relapse, n (%)	6 (12.6)	4 (15.4)	2 (9.1)
<i>Number of relapse per patient</i>	1 (0 – 1)	1 (0 – 1)	1 (0 – 1)
<i>Homolateral relapse</i>	4/6	3/4	1/2
<i>Time between 2 episodes, months, median [IQR]</i>	2 [1 – 4]	2 [1 – 4]	3 [2.5 – 6]
New episode of osteitis, n (%)	8 (16.6)	7 (26.9)	1 (4.5)
<i>Time to the 2nd episode, months, median [IQR]</i>	6 (5 – 9)	5 (3 – 10)	6 (5 – 7)
Sequelae, n (%)	15 (31.3)	10 (38.5)	5 (22.7)
Death related to osteitis, n (%)	2 (4.2)	2 (7.7)	0 (0)

*DU: digital ulcer; [IQR]: interquartile range; w/o: without*

**Table 4. Antibiotics management in SSc osteitis**

				<b>SCLEROS cases</b>		
				<b>N = 48</b>		
<b>Characteristics of antibiotherapy</b>						
Duration of treatment, days, median [IQR]				41 [5.5 – 55]		
Bitherapy, n (%)				23 (47.9)		
Duration of bitherapy, days, median [IQR]				41 [30 – 49]		
Duration of Intravenous administration, days, median [IQR]				9 [0 – 56]		
Duration of orally administration, days, median [IQR]				29 [0 – 51.5]		
Duration of switch from IVD to orally, days, median [IQR]				1 [0 – 40]		
<b>Main antibiotics regimens</b>						
		<b>Antibiotics</b>	<b>Count</b>	<b>Duration, days, median [IQR]</b>	<b>Orally / IVDD administration</b>	<b>Monotherapy / bitherapy</b>
1 <sup>st</sup> line	1 <sup>st</sup>	Fluoroquinolone	19/48	34 [10 - 50]	15 / 4	4 / 15
	2 <sup>nd</sup>	Amoxicillin +/- Beta lactamase inhibitor	15/48	30 [12 - 42]	14 / 1	4 / 11
	3 <sup>rd</sup>	Macrolides	7/48	35 [15 - 42]	7 / 0	1 / 6
2 <sup>nd</sup> line	1 <sup>st</sup>	Fluoroquinolone	10/48	32 [27 - 42]	8 / 2	2 / 8
	2 <sup>nd</sup>	Rifampicin	4/48	42 [35 - 67]	3 / 1	0 / 4
	3 <sup>rd</sup>	Penicillin +/- inhibitor	3/48	5 [3 - 17]	1 / 2	3 / 0

\* these 2 patients received rifampicin for 40 days

[IQR]: interquartile range; IVD: intravenous; w/o: without

**Table 5. Factors associated with osteitis in SSc patients**

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.01 (0.99 – 1.03)	0.19	/	/
Female sex	0.62 (0.29 – 1.36)	0.23	/	/
Body mass index	0.94 (0.88 – 1.02)	0.12	0.96 (0.87 – 1.07)	0.51
Active smoking	1.14 (0.58 – 2.26)	0.70	/	/
ISSc	0.48 (0.24 – 0.95)	0.04	0.76 (0.17 – 3.35)	0.72
Duration of SSc	1.01 (1.01 – 1.02)	0.02	1.01 (0.99 – 1.01)	0.44
Puffy fingers	1.39 (0.58 – 3.37)	0.46	/	/
Sclerodactyly	1.53 (0.71 – 3.27)	0.28	/	/
mRSS	1.05 (1.01 – 1.09)	0.02	1.02 (0.94 – 1.10)	0.65
Raynaud's phenomenon	0.49 (0.09 – 2.75)	0.42	/	/
Abnormal nailfold capillaries	0.79 (0.09 – 3.19)	0.74	/	/
Digital tip ulcers	2.29 (1.18 – 4.45)	0.01	4.26 (1.43 – 12.66)	0.009
Telangiectasia	0.79 (0.41 – 1.51)	0.49	/	/
Calcinosis	1.49 (0.89 – 3.59)	0.10	3.13 (1.16 – 8.47)	0.03
Gastroesophageal reflux disease	1.38 (0.71 – 2.68)	0.35	/	/
Interstitial lung disease	0.48 (0.24 – 0.94)	0.03	0.62 (0.22 – 1.73)	0.36

Pulmonary arterial hypertension	0.50 (0.16 – 1.54)	0.23	/	/
Musculo-skeletal disorders	1.35 (0.70 – 2.61)	0.37	/	/
Scleroderma renal crisis	0.55 (0.18 – 1.69)	0.29	/	/
Anti-centromere autoantibodies	1.26 (0.98 – 2.17)	0.08	1.17 (0.85 – 3.01)	0.41
Anti-topoisomerase I autoantibodies	0.98 (0.62 – 1.26)	0.31	/	/
Anti-RNA polymerase III autoantibodies	0.83 (0.22 – 1.39)	0.55	/	/
Immunosuppressant w/o CTC	4.20 (0.82 – 2.50)	0.09	2.86 (0.27 – 30.74)	0.39
Corticosteroids	0.66 (0.34 – 1.29)	0.23	/	/

*CTC: corticosteroids; ISSc: limited systemic sclerosis; mRSS: modified Rodnan skin score; SSc: systemic sclerosis*