Infections, Cellulitis, and Osteomyelitis

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In systemic sclerosis (SSc), it is well known that infection of digital ulcers (DU) may provoke pain and disability, affecting patients' quality of life and prognosis, thus representing a high socioeconomic cost. In fact, DU may evolve to complications as infection of soft tissue, cellulitis and osteomyelitis, and gangrene, often requiring amputation [1, 2].

In SSc-DU, infection is a very common complication slowing significantly wound healing. In infected DU, some clinical signs are important (pain, heat, redness, and swelling) (Figs. 10.1, 10.2, 10.3, and 10.4) in order to raise the suspicion and adopt a careful approach to identify the nature of the infection. Usually, the development of an infection is favored either by SSc microangiopathy and defective immune system, with the possible contribution of immunosuppressive treatments. The reduction of tissue blood perfusion and the response to systemic antibiotics may further contribute to deteriorate the infected tissues. These factors may represent the most favorable conditions for ulcer infection by different agents (S. *aureus*, *E. coli P. aeruginosa, E. faecalis*, *S. agalactiae*, *S. marcescens*, *S. epidermidis*, *E. aerogenes*, *S. maltophilia*, *P. mirabilis*). Moreover, during the wound care procedures, patients can be exposed to microorganisms. Therefore, the prevention and treatment of preexisting local or systemic infections is of crucial importance.

The most common sources of infectious agents are the patient himself, the contact with other patients and the health care personnel, and also the hospital environment where contaminated medical equipment and/or medications are the most frequent cause of infection [3]. An important reservoir of infective agents is the patient's endogenous flora, in particular bacteria present on the skin, mucous membranes, and gastrointestinal tract. Besides the most common agents such as *S. aureus* and *P. aeruginosa*, the frequent detection of fecal pathogens strongly emphasizes the importance of patient's education to optimize the methodology of home self-medications. In fact, a high incidence (in one-quarter of cases) of fecal pathogens in infected SSc-DU has been shown [4]. For these reasons, a rigorous asepsis is mandatory during all therapeutic procedures. It must include hand hygiene of doctors, nurses, and patients and a careful surveillance of the hospital environment and cross-transmission of infection among patients. Regular sterilization of the rooms where wounds are usually managed is absolutely mandatory [5].

A further complication of a DU is monomicrobial or polymicrobial osteomyelitis (OM) [6], which is an infection and inflammation of the bone or bone marrow. In general, microorganisms may reach the bone via the bloodstream, contiguously from infected areas (as in cellulitis and in DU) or following a penetrating trauma. Although DU occurs very frequently in SSc [7], at the moment, the prevalence of OM in SSc patients is not clearly defined. Only one study on 248 SSc patients has shown a 7.7% (19/248 patients) prevalence of OM [8]. OM was associated with infected DU highlighting the importance of DUs' infection as a main predisposing condition [8]. In addition, patients with DU complicated by OM showed a significantly higher percentage of serum anti-Scl70 autoantibodies and a lower mean age compared to those without OM [8]. These correlations suggest that OM may complicate DU in patients with more severe SSc clinical variants, characterized by more pronounced immune-system depression and marked deterioration of the patient's general conditions, including nutritional status [4]. Moreover, the prevention strategies and treatment of OM complicating SSc-DU are still largely empiric. For the management of OM, a multidisciplinary team is required including infectivologist, orthopedic surgeon, radiologist, and nuclear medicine physician [9]. OM usually manifests with symptoms and signs of acute infection like pain, swelling, and fever [6]. In chronic OM, the presence of fistulas with purulent secre-

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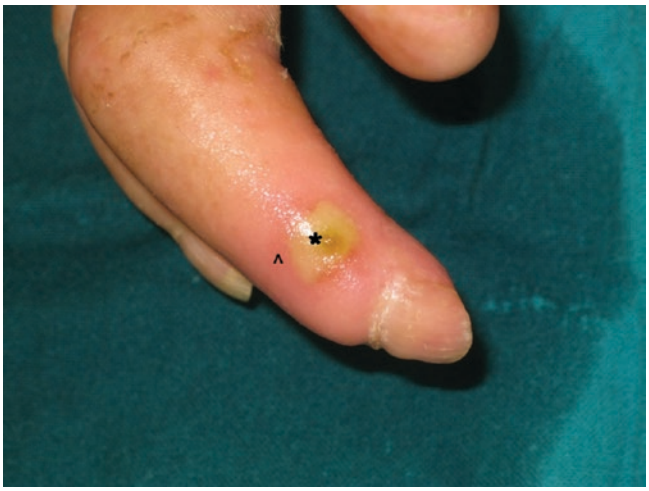

Fig. 10.1 Presence of infection with purulent material (*) and redness (^)

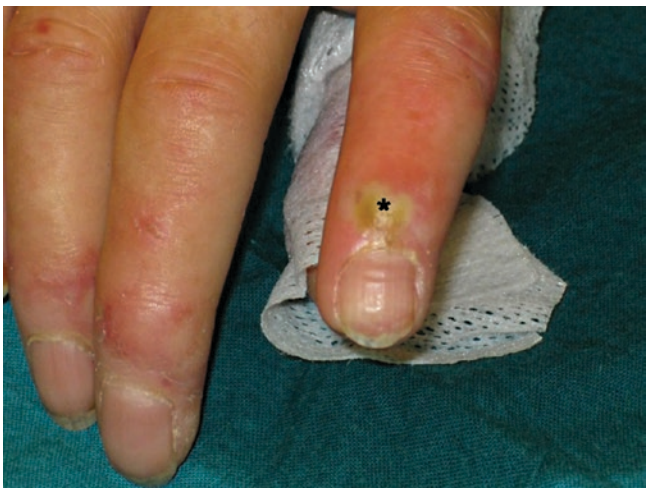

Fig. 10.2 Fibrin (*)

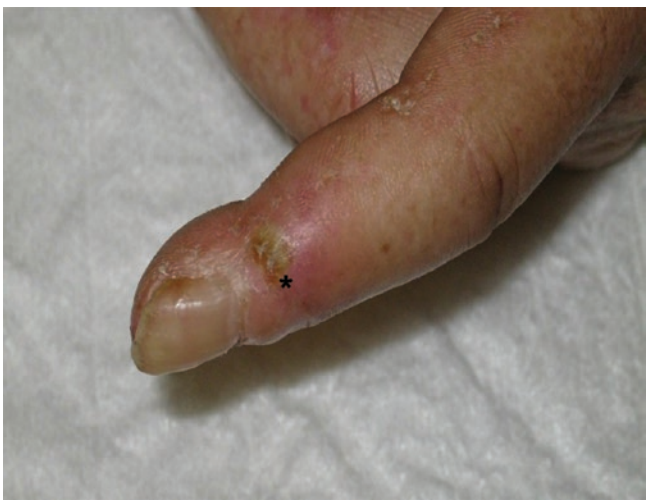

Fig. 10.3 Presence of redness and swelling (*)

tion, skin discoloration and dystrophy, occasional or chronic pain, and fever are observed. These symptoms may alternate with asymptomatic phases. Few data are reported about SSc OM related to complicated DU. In the literature, most of the knowledge about the diagnosis and treatment of OM complicating DU derive from data on diabetic ulcers. Despite the different etiology and pathogenesis of DU, the algorithm to suspect and diagnose OM may be substantially similar. The aspecific laboratory findings (leukocytosis, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) elevation) [6], together with clinical history, are the main signs to suspect an OM in the case of DU. However in chronic OM, leukocyte levels greater than 15.000/mm^3 are rarely found [10]. For this reason, the pathogen identification is crucial for the diagnosis and the choice of the most effective therapy. Surgical sampling or the biopsy of the infected tissue is an efficacious procedure to identify the microbial agent [10]. The culture examination of bone allowed identification of the microorganism in 94% of cases of OM [10, 11]. Often in clinical practice, a DU swab may help in detecting the microorganism and start as soon as possible the best antibiotic therapy. At histopathological examination, OM is characterized by "bone fragmentation or necrosis", with cells' infiltration (inflammatory cells). With Gram staining, the presence of the etiologic agent may be also detected [10]. X-rays may be considered the first instrumental examination in the suspect of OM even if its sensitivity is poor in the first phases of OM as it allows to detect bone alterations after several days (at least 2 weeks) only [6, 10]. Osteopenia, often considered the first sign of OM, and soft tissue's swelling, periostea reaction, and thickening with sclerosis are the x-ray modifications most frequently seen [10, 12] (Fig. 10.5). Magnetic resonance imaging (MRI) is a sensitive tool, in particular in the early phase of bone infection (approximately in the first 5 days), and it provides more information about the extent of the infective process, the soft tissue involvement [12], and marrow edema. In addition, inflammation and alterations of soft tissue (including abscesses, cellulitis, and ulcers) are detected by MRI [6, 12]. Also ultrasound (US) could be useful in the detection of abscesses and fluid collections of soft tissue involved in OM. In fact, US is the first examination when cellulitis, frequently found in OM, is suspected. This complication, as well as OM, often requires patient's hospitalization and a rapid control with intravenous antibiotic therapy to avoid evolution to sepsis [13, 14]. X-rays are not a useful in detecting cellulitis. However, CT is an accurate imaging tool to show the cortical bone and of the soft tissue involvement [14]. Scintigraphy (technetium-99-m-labeled diphosphonates) may be helpful in the early identification of bone infection, usually starting from 2 days after the onset of infectious symptoms and signs. This technique shows not only the infectious process but also the rate of new bone formation. Scintigraphy is helpful to investigate OM when "bone is not affected by underlying conditions" [10]. Gallium

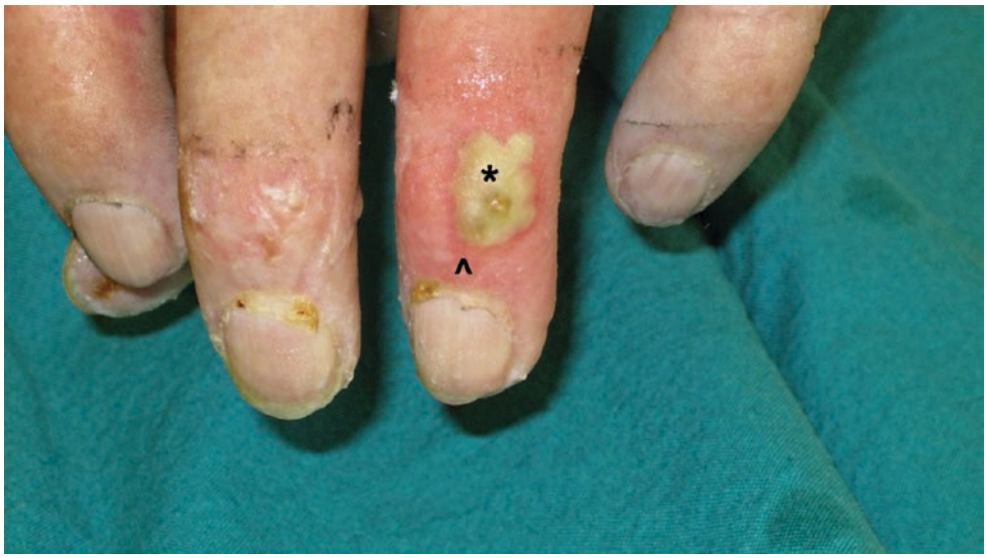

Fig. 10.4 Presence of fibrin (*) and redness (^)

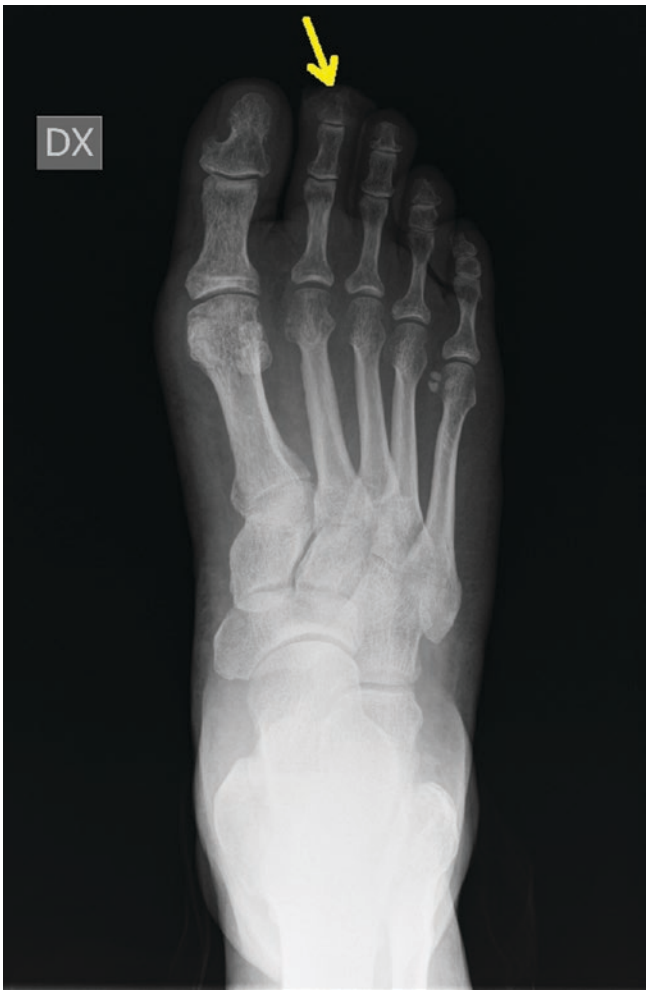

Fig. 10.5 Millimetric area of bone resorption

scan exploits the fact that radiolabeled isotopes attach to phase reactant proteins present in the bone and in the soft tissue. However, in many other conditions (such as malignancy and inflammatory diseases), gallium scans may be positive. It should be also considered that scintigraphy may also provide false-negative results in SSc because vasculopathy may significantly decrease blood perfusion. Recently, FDG-PET has been shown to have a promising role in the detection of bone infection [10, 12].

Conclusions

In SSc, DU may evolve to complications involving soft tissue (cellulitis) and/or the bone (osteomyelitis) representing a great socioeconomic cost. Therefore, an early diagnosis and a prompt treatment are mandatory also to limit the patient's disability and the worsening of quality of life. A crucial element is the self-care education of patients to limit the possibility of contamination and infection. Clinical signs of DU, bone, soft tissue, or systemic infection together with an appropriate use of imaging are most important factors useful to plan a correct management of SSc DUs and of their complications.

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