



Infectious Emergencies in Dermatology

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Infectious Emergencies in Dermatology are important to consider, and the 'clinical eyes of dermatologists' may save lives and decrease potential morbidities and sequelae of numerous conditions, such as necrotising soft-tissue infections, severe erythema multiforme, purpura fulminans, infective endocarditis, invasive aspergillosis, monkeypox infection, crusted scabies.

NECROTISING SOFT-TISSUE INFECTIONS (NSTI)

Case-Report

A 53-year-old patient without any past medical history presented the 16/09/2022 cough, fever and myalgia. During the night of 17 to 18/09, a left leg erythema with severe pain was noticed and, the 18th, non-steroidal anti-inflammatory drugs (NSAIDs) (self-medication) were taken. The 19th left leg oedema and pain worsened. At the emergency room, hypotension, hypothermia and pain - requesting morphin for the control - were noted, leading to ICU admission. A septic shock was diagnosed, and noradrenalin (15mg/h) administered. Eight hours after admission, a typical presentation of NSTI of the leg appeared. The patient went urgently to the operative room for a large debridement of the leg and finally recovered from a Group A *Streptococcus* (GAS) NSTI with septic shock.

Main features of NSTI

We just published a seminar devoted to NSTI in the *Lancet Infectious Diseases* and the main features are summarized here. [1]

Beyond the classical classifications of NSTI, - historical, microbiological, anatomical -, we suggest to use a more pragmatical classification based on a key question: *Is the soft-tissue infection presenting by the patient necrotising and therefore requesting urgent surgery?* This approach should increase the knowledge of NSTI among care givers and decrease both mortality and morbidities by shortening time to surgery (see below). Fifteen years ago, an epidemiological study showed that a recent blunt trauma was a risk factor for GAS NSTI.

Experimentally, it was demonstrated that a mild nonpenetrating muscle injury would increase vimentin expression which is the receptor for GAS. [2] Pharyngeal carriage of *Streptococcus* might be an endogenous portal of entry of NSTI. [3] NSAIDs are suspected for a long time to be a risk factor for NSTI, based on case-reports, series and case-control studies which were unable to avoid the protopathic bias, i.e., NSAIDs

are more frequently taken because of the initial severity of the condition. [1] However, vimentin may experimentally tether circulating GAS and NSAIDs would enhance the process or mask the initial signs and symptoms of NSTI, delaying its early recognition. [4] Finally, both French and UK authorities made a note of concern regarding the use of NSAIDs in skin and soft tissue infections.

Incidence of NSTI is around 4/100,000 inhabitants/year and a significant decrease was observed during the Covid-19 lockdown period, probably due to hygiene measures and physical distancing (<https://www.gov.uk/government/publications/group-a-streptococcal-infections-activity-during-the-2019-to-2020-season>). For note, a current alert is ongoing regarding invasive GAS infections in Europe.

Each following sign or symptom should evoke NSTI [1]:

necrosis of the skin, crepitation, cyanic/livedoid areas (figure 1), hypoesthesia, rapid extension of signs, - especially despite appropriate antibiotics-, intense pain, lameness and, for sure sepsis-related manifestations.

Ideally, patients with NSTI should be referred to expert centers managing at least 3 NSTI per year as a subsequent reduction of mortality was demonstrated in those settings. [5] Moreover, a time to surgery < 6 hours / < 12 hours confirmed that time is of the essence when managing NSTI. [6] A second-look may be necessary in some situations. Finally, an algorithm for multidisciplinary management of NSTI has been established. [1] A series of 61 patients presenting Fournier's gangrene (abdominoperineal NSTI) came up recently, highlighting that the portal of entry should be systematically searched, including in the mid-term, as Crohn's disease, colic cancer, digestive fistula, urological neoplasia or infection ... self-injections of slimming products purchased on the internet! [7,8]

Finally, all NSTI are not related to bacteria: cryptococcal, mucor, *Histoplasma capsulatum*, ... Pyoderma gangrenosum can be misleading.

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Figure 1. Typical cyanic and livid areas of a patient presenting NSTI of the leg.

SEVERE ERYTHEMA MULTIFORME (EM)

All dermatologists know that the diagnosis of EM is in the rings. [9] However, in a retrospective series, it was shown that signs and symptoms of *Mycoplasma pneumoniae*-related EM (MP-related EM) (n=33) have a distinctive presentation compared with non-MP-related EM (n=100) with more diffuse and atypical targets, more mucositis and respiratory sequelae. [10] Histology data showed an epidermal necrolysis pattern. The link with MIRM (*M pneumoniae*-Induced Rash and Mucositis), recalled RIME (Reactive Infectious Mucocutaneous Eruption), should be discussed. [11] Other infectious agents inducing EM were recently described such as SARS-CoV-2 and adenovirus. Major EM is defined by the involvement of 2 mucous membranes. In fact, we believe that a single involvement of the mouth may also lead to severe EM in case of impairment of food intake/weight loss, intense pain. Although rare, sequelae may occur in severe EM.

We conducted a retrospective survey in France showing that the use of corticosteroids in the acute phase of severe EM, aiming to better control signs and symptoms, may differ from center to center. [12] A randomized controlled trial will be conducted soon in that setting comparing a short cure of corticosteroids, either oral or IV, to placebo.

Chronic EM is defined by recurrent or persistent course of the disease. Antivirals should be used first-line (for instance, valaciclovir 500 mg twice a day for 3-6 months at least). Thalidomide 50-100 mg/day is a main second-line drug in patients presenting more than 3 episodes. In case of failure or side-effects, alternatives include lenalidomide, dapson, immunosuppressive drugs, rituximab, JAK inhibitors, IVIG. [13]

OTHER EXAMPLES OF INFECTIOUS EMERGENCIES IN DERMATOLOGY

Purpura fulminans is characterized by the association of a sudden and extensive purpura together with an acute circulatory failure. Skin biopsy PCR may be very useful for rapid microbiological diagnosis, e.g., *Neisseria meningitidis* or *Streptococcus pneumoniae*. [14]

Dermatological manifestations of infective endocarditis include conjunctival hemorrhage, purpura, Osler node, Janeway lesion. We found a correlation between the presence of cutaneous lesion and the occurrence of cerebral emboli, leading to systematic CT scan imaging accordingly. [15]

Any skin lesion occurring in an immunosuppressed patient,

especially with fever, should be biopsied and investigated microbiologically for various strains. In a retrospective multicenter study of the French-invasive Aspergillosis registry, we found that cutaneous manifestations of this fungal infection may be various. [16]

In a multicenter series of 528 monkeypox patients involving 16 countries, 13% were hospitalised, mostly for severe anorectal pain. No deaths occurred. [17]

Crusted scabies is highly contagious leading to epidemics and may have detrimental consequences in the elderly, such as dehydration and albumin loss. [18] In low and middle-income countries, scabies-related impetigo may lead to severe complications such as glomerulonephritis, rheumatic fever or NSTI which are prevented by mass drug administration using oral ivermectin. [19,20]

CONCLUSIONS

Dermatologists are crucial for the management of infectious emergencies (and non-infectious as well) in acutely ill patients presenting with skin lesions.

LEARNING POINTS / TAKE HOME MESSAGES

- NSTI early recognition is key for shortening time to surgery/improving mortality and morbidities
- Portal of entry of Fournier's gangrene should be systematically searched, including at mid-term
- The use of corticosteroids in severe EM has not yet been demonstrated and a RCT is mandatory
- A brain CT scan should be performed in patients with infective endocarditis presenting with skin lesions
- In low and middle-income countries, impetigo-related scabies and subsequent bacterial complications may be prevented by oral ivermectin through a mass drug administration program.

KEYWORDS

necrotising soft-tissue infection - Fournier's gangrene - erythema multiforme - purpura fulminans - crusted scabies

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