

# Difficulties in the diagnosis of erysipelas in immunosuppressed patients

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## ABSTRACT

**Introduction:** Erysipelas is an acute inflammatory condition of the skin and subcutaneous tissue caused by *Streptococci*. The lesions usually affect the lower limbs or face unilaterally and are characterized by erythema, oedema and pain. By the definition, the disease is accompanied by high fever. On the laboratory investigations, elevated C-reactive protein and leukocytosis are observed. However, in immunocompromised patients, the diagnosis might be unclear.

**Case description:** This study presents cases of three patients admitted to the department of dermatology with erysipelas: a 51-year-old woman with rheumatoid arthritis treated with tocilizumab, methotrexate and methylprednisolone, a 51-year-old woman with systemic lupus erythematosus treated with methylprednisolone, and a 75-year-old woman with rheumatoid arthritis treated with methotrexate. Clinical pictures shared common symptoms in all cases: oedema, erythema and pain in one of the limbs. However, none of the patients had a fever on admission. On laboratory tests, in two cases, there was no significant increase in inflammatory markers. The treatment with intravenous antibiotics and low-molecular heparin resulted in good clinical improvement.

**Conclusions:** Chronic immunosuppressive treatment acting due to inhibition of pro-inflammatory cytokines reduced patients' immune response, which resulted in the absence of fever and no significant increase in the inflammatory parameters. Presented cases show some peculiarities of erysipelas in the distinct group of immunosuppressed patients and draw attention to unusual manifestations. Nowadays, there are more and more patients treated with biological agents for different diseases, including dermatoses. Hence, the number of atypical erysipelas cases may rise.

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**Keywords:** erysipelas, immunosuppressive therapy, immunosuppression, biological treatment, infection

## CASES DESCRIPTION

### Case 1

A 51-year-old female with a long-standing history of rheumatoid arthritis, treated with tocilizumab, methotrexate, and methylprednisolone was admitted due to oedema, erythema and pain in the area of her left lower leg. Initial treatment with oral amoxicillin did not lead to clinical improvement after 4 days, and the skin lesions expanded in the proximal direction. Importantly, the patient suffered from chronic venous insufficiency, and in the past, she had had erysipelas in the same lower leg.

### Case 2

A 51-year-old female with a history of systemic lupus erythematosus, managed with methylprednisolone, presented to the dermatology department due to oedema, erythema and pain in the upper limb. The symptoms have

been present for two weeks. The patient had been previously treated with amoxicillin with no improvement.

### Case 3

A 75-year-old female with rheumatoid arthritis, treated with methotrexate, presented with oedema, erythema, and pain in the right foot and lower leg (Fig. 1, 2). Despite receiving ciprofloxacin for 3 days, there was no improvement in the skin condition. It was discovered that the patient had suffered an injury to the toes of her right foot two months prior. Notably, the patient had previously suffered two episodes of erysipelas in her right lower limb.

The clinical presentations of all cases displayed common symptoms, characterized by the presence of oedema, erythema, and pain in a single limb (Tab. 1). However, none of the patients exhibited fever, and in two instances (cases 1 and 3), there was an absence of significant elevation in

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**Figure 1.** Erythema and oedema of the left lower limb with the presence of vesicles



**Figure 2.** Oedema and erythema of the right foot and lower leg in a patient on admission

**Table 1.** Comparison of three cases

	1 <sup>st</sup> patient	2 <sup>nd</sup> patient	3 <sup>rd</sup> patient
Patient age and sex	51-year-old female	51-year-old female	75-year-old female
Underlying disease	Rheumatoid arthritis	Systemic lupus erythematosus	Rheumatoid arthritis
Treatment of the underlying disease	<ul style="list-style-type: none"> <li>• Methotrexate 15 mg/week s.c.</li> <li>• Tocilizumab 1 ×/week</li> <li>• Methylprednisolone 2 mg/d</li> </ul>	<ul style="list-style-type: none"> <li>• Azathioprine 150 mg/d</li> <li>• Methylprednisolone 16 mg/d</li> </ul>	<ul style="list-style-type: none"> <li>• Methotrexate 15 mg/week s.c.</li> </ul>
Concomitant diseases	<ul style="list-style-type: none"> <li>• Chronic venous insufficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Arterial hypertension,</li> <li>• Osteoarthritis,</li> <li>• COPD</li> </ul>	<ul style="list-style-type: none"> <li>• Arterial hypertension</li> <li>• Heart failure</li> <li>• Diabetes mellitus</li> <li>• Gastritis</li> <li>• Cardiac achalasia</li> </ul>
Onset of symptoms	For 5 days: erythema, oedema, pain, increased warmth around left ankle joint	For 2 weeks: erythema, pain, oedema, increased warmth of the forearm and right hand	Oedema, erythema and pain in the foot and right lower leg
Treatment applied before admission to the clinic	Amoxicillin 1 g every 12 hours for 4 days (without clinical improvement), expansion of skin lesions in a proximal direction	Amoxicillin 1 g 2×/d, for 9 days (without improvement)	Ciprofloxacin for 3 days (without improvement)
The occurrence of fever before starting antibiotics on an outpatient basis	No fever	No fever	No fever
Occurrence of erysipelas in the past	Erysipelas of the same lower leg	–	2 episodes of erysipelas within the right lower limb
Symptoms on admission to the clinic	<ul style="list-style-type: none"> <li>• Erythema</li> <li>• Oedema</li> <li>• Pain</li> <li>• No fever</li> </ul>	<ul style="list-style-type: none"> <li>• Erythema</li> <li>• Oedema</li> <li>• Pain</li> <li>• No fever</li> </ul>	<ul style="list-style-type: none"> <li>• Erythema</li> <li>• Oedema</li> <li>• Pain</li> <li>• No fever</li> </ul>
Laboratory results (on admission → on discharge) Reference values CRP < 5.0 mg/L WBC 4.0–10.0 k/μL	CRP: 4.3 → (< 1) WBC: 8 → 3.5	CRP: 501.7 → 115.8 WBC: 19 → 10	CRP: 8.2 → 5.8 WBC: 7.7
Imaging tests	Deep vein thrombosis in the lower left limb was excluded from the Doppler ultrasound examination	Deep vein thrombosis in the upper right limb was excluded from the Doppler ultrasound examination	Deep vein thrombosis in the lower right limb was excluded from the Doppler ultrasound examination
Respiratory rate	15/min	19/min	13/min
Pulse	75/min	81/min	66/min
Causative factor of the disease	Unknown	Unknown	2 months earlier, an injury to the toes of the right foot with a skin fissure

s.c. — subcutaneous; COPD — chronic obstructive pulmonary disease; CRP — C-reactive protein; WBC — white blood cell

**Table 2.** Treatment of all cases

	1 <sup>st</sup> patient	2 <sup>nd</sup> patient	3 <sup>rd</sup> patient
Systemic treatment	• Ceftriaxone 2 g 1×/d <i>i.v.</i> (10 days)	• Ceftriaxone 2 g 2×/d <i>i.v.</i> (10 days), next 1×/d <i>i.v.</i> (5 days) • Vancomycin 1 g <i>i.v.</i> (14 days)	• Ceftriaxone 2 g 1×/d <i>i.v.</i> (10 days)
Anticoagulant treatment	• Enoxaparin 0.4 mL 1×/d <i>s.c.</i> (10 days)	• Enoxaparin 0.4 mL 1×/d <i>s.c.</i> (10 days)	• Enoxaparin 0.4 mL 1×/d <i>s.c.</i> (10 days)
Other systemic treatment medications	• Ketoprofen • Ac. Folicum • Omeprazole • Diosmectite	• Omeprazole • NSAIDs	• Ac. Folicum • Spironolactone • Hydroxyzinum • Ramipril • Gliclazide • Naproxen • Tramadol • Isosorbide
Topical treatment	• Aluminium acetate tartrate • Ichthiol ointment • Allantoin	• 10% borax with glycerine	• Aluminium acetate tartrate • Vaselinum album • Fusidic acid
Limb elevation	Applied	Applied	Applied
Treatment effects	The patient responded well to the applied treatment and managed to reduce skin lesions	Significant clinical improvement of general condition, local improvement and decrease in blood inflammatory parameters were obtained	The reduction of oedema and erythema of the lower leg was achieved. The patient was discharged home with the local improvement
Relapse prevention	After discharge, the patient was referred to the clinic for the prevention of recurrent erysipelas with phenoxymethyl penicillin or debecillin	–	After discharge, the patient was referred to the clinic for the prevention of recurrent erysipelas with phenoxymethyl penicillin or debecillin

*i.v.* — intravenous; NSAIDs — non-steroidal anti-inflammatory drugs; *s.c.* — subcutaneous

inflammatory markers such as C-reactive protein (CRP) or leukocytosis. In all cases, clinical improvement was obtained after intravenous antibiotic therapy, encompassing the administration of ceftriaxone, thromboprophylaxis, and topical treatment, along with limb elevation (Tab. 2).

## DISCUSSION

Erysipelas is an inflammatory condition of the dermis and subcutaneous tissue, caused by the infection with streptococci, mainly from group A (*Streptococcus pyogenes*) but also serotypes C and G [1]. It is estimated that a small percentage of infections are caused by Group A *Streptococcal* (GAS) alone, and in most cases, a mixed group of bacteria is the cause [2]. Lipoteichoic acid molecules and F protein are factors facilitating host cell adherence and successful colonization by GAS. The production of streptolysin and hyaluronidase, on the other hand, allows the destruction of host tissues and the dissemination of GAS in the host. Moreover, the M protein found in GAS cells is believed to inhibit phagocytosis by host immune cells [3].

The clinical manifestation of erysipelas is characterized by a well-demarcated, warm oedema, most often involving the lower limbs, while the second most frequently affected site is the face [4]. Lesions are usually asymmetrical. However, sometimes the clinical picture might be atypical.

Studies indicate that the incidence of erysipelas has decreased since the improvement of sanitation and the development of antibiotic therapy. Although erysipelas can affect any age group, it most often occurs at elderly age [5]. Infection can be facilitated due to breaks in the skin barrier, particularly those caused by insect bites or athlete's foot. Other risk factors that predispose individuals to erysipelas development include surgical incisions, obesity, lymphedema, ulcers, poorly controlled diabetes, and liver disease. Noteworthy, cases of recurrent erysipelas are reported, most often within the same site as the primary infection [6, 7].

Laboratory tests are not required to make the diagnosis of erysipelas, however, they may affect the treatment plan [4]. The most important tests are complete blood count with white blood cell count and CRP. Moreover, in more severe cases it is worth performing procalcitonin concentration.

In the case of the presented patients, the course of erysipelas was atypical due to the absence of fever, and in two patients no increase in inflammatory parameters. It can be suspected that the cause of the atypical presentation of the disease was the immunosuppressive drugs taken permanently by each of the three patients. It has been noted that in severely immunocompromised patients, although rare, local or systemic infections may occur without fever. It can also be suppressed by the immunosuppressants themselves [8].

Two of the described patients received methotrexate. It can inhibit the production of pro-inflammatory cytokines: interleukin-4 (IL-4), interleukin-13 (IL-13), interferon-gamma (IFN- $\gamma$ ) and tumour necrosis factor-alpha (TNF- $\alpha$ ) [9, 10]. It can also reduce inflammation by capturing free radicals, suppressing intracellular oxidative stress and inhibiting the formation of immunogenic protein complexes (called MMA adducts) [11]. Similarly, prednisone, which activates certain nuclear receptors, changes gene expression and inhibits the production of pro-inflammatory cytokines. In addition, it reduces the number of circulating lymphocytes, induces cell differentiation, and triggers apoptosis in susceptible cell populations [12].

The presence of fever is associated with endogenous pyrogens such as interleukin-1 (IL-1), tumour necrosis factor (TNF) and interleukin-6 (IL-6), which indirectly increase the body temperature. After reaching the hypothalamus, they stimulate the production of cyclooxygenase 2, which induces the synthesis of prostaglandins (especially prostaglandin E2). In turn, the presence of prostaglandins in the hypothalamus changes the biological set point [13]. The influence exerted on the cytokines by the drugs taken by the study patients may result in a lack of fever and no elevation in inflammatory markers.

Immunocompromised patients are more susceptible to opportunistic infections, which are typically controlled by a healthy immune system but can cause severe illness in individuals with compromised immunity [14]. There are various factors and medical conditions that can lead to immunocompromised states, and these individuals are at a higher risk of developing infections and experiencing more severe illness when exposed to pathogens. Common causes and conditions associated with immunocompromised states include cancer treatment, organ transplantation, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), primary immunodeficiency disorders, and autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis. Moreover, within the category of immunocompromised individuals, some individuals receive immunosuppressive therapy, which includes antimetabolites, biologic drugs, and high doses of glucocorticoids [14, 15]. It's essential to provide extra care and precautions for immunocompromised individuals to reduce their risk of infections and support their overall health. In the treatment of erysipelas in immunocompromised patients, broad-spectrum parenteral antibiotic therapy is recommended according to the following scheme: Intravenous vancomycin plus cefepime 2 g intravenously (IV) every eight hours [16]. Vancomycin loading dose: 20 to 35 mg/kg. Vancomycin initial maintenance dose and dosing interval: 15 to 20 mg/kg every 8 to 12 hours. Once clinical improvement is observed, it is appropriate to switch to

an oral antibiotic regimen. If a specific pathogen is identified during therapy, antibiotics should be adjusted to target that particular pathogen. For immunocompromised patients without an identified pathogen, it is recommended to use amoxicillin-clavulanate (875 mg orally every 12 hours) in combination with either doxycycline (100 mg orally twice daily) or trimethoprim-sulfamethoxazole (TMP-SMX; one to two double-strength tablets orally twice daily). The duration of antibiotic treatment should be adjusted according to the individual's clinical response. If there is a severe infection, a delayed response to treatment, or if the patient is immunosuppressed, it may be necessary to consider an extension of antibiotic therapy for up to 14 days. In certain cases, it can be beneficial to seek a dermatologic evaluation and perform a skin biopsy.

Although the clinical presentation of erysipelas seems to be quite characteristic, there are unusual situations that make accurate diagnosis difficult. Chronic immunosuppressive treatment results in the inhibition of pro-inflammatory cytokines, and thus a decrease in the immune response, hence the absence of fever. Nowadays, there are many subjects treated with immunosuppressants and even more and more patients are treated with biological agents for different diseases, including dermatoses. Hence, the number of atypical erysipelas cases may rise. Physicians should be aware of such possibilities to introduce proper treatment, even despite the obvious symptoms of erysipelas.

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### Author contributions

JN: conceptualization, patient's attending physician, writing — original draft preparation, writing — review and editing; AB: writing — review and editing, supervision; IF: supervision; MC, KB, MD: writing — original draft preparation.

### Conflict of interest

The authors declare no conflict of interest.

### Ethics statement

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