Dear Editor, a 70-year-old man presented to the emergency department with pain in his right lower extremity. His relevant past medical history included myelodysplastic syndrome (MDS), multilineage dysplasia subtype, initially categorized as low risk (International Prognostic Scoring System Revised version). Active treatment was not indicated. During a follow-up consultation 4 years later, myeloblasts were described for the first time in peripheral blood (<5%) with hemoglobin (Hb) of 12 g/dl, a white blood count (WBC) of $7 \times 10^3/\mu l$, and a platelet count of $200 \times 10^3/\mu l$. A new bone marrow evaluation showed grade 3 myelofibrosis. The treatment proposed was 75 mg/m² of subcutaneous azacitidine for 7 days, every 4 weeks. Twenty four hours after finishing his first cycle, the patient presented with induration, erythema, and progressive pain in the right lower extremity coinciding with the sites of subcutaneous administration. He developed fever ∼48 h after the last dose of azacitidine.

On arrival at the emergency room, he had fever of 39°C, but his other vital signs were normal. Skin examination revealed a lesion in the right thigh that measured ∼5 cm, which was tender, erythematous, with purple areas and a blistered surface (Figure 1, panels A–D). The skin surrounding the lesion felt indurated and swollen. No skin crepitus was noted, and distal pulses were intact. An erythematous painless lesion was observed in the contralateral leg, with a scaling of 200×10³/µl. A new bone marrow evaluation showed grade 3 myelofibrosis. The treatment proposed was 75 mg/m² of subcutaneous azacitidine for 7 days, every 4 weeks. Twenty four hours after finishing his first cycle, the patient presented with induration, erythema, and progressive pain in the right lower extremity coinciding with the sites of subcutaneous administration. He developed fever ∼48 h after the last dose of azacitidine.

Wound and blood cultures were continuously negative throughout the process. During his stay in the ICU, several more debridement procedures were indicated, and the patient eventually reached hemodynamic and clinical stability. Unfortunately, after 22 days of hospital stay, the patient passed away due to a ventilator-associated pneumonia.

Patients with myeloid malignancies may present with a broad range of cutaneous manifestations, including a direct infiltration of tissue by malignant hematopoietic cells or non-specific lesions (infections, neutrophilic dermatosis, paraneoplastic vasculitis, panniculitis, or cutaneous adverse events by antineoplastic drugs, among others) [1].

Hypomethylating agents, such as azacitidine (analog of cytidine), causes transient demethylation of DNA resulting in cytotoxic effects. The common side effects of azacitidine are cytopenia, general malaise, and gastrointestinal events. Injection site reactions are one of the most common non-hematological adverse events [2]. Skin events are typically erythema, pruritus, and rash, but skin nodules and neutrophilic dermatosis (Sweet syndrome and pyoderma gangrenosum) are also reported [3]. When azacitidine is injected subcutaneously, it can cause direct damage to the skin cells, such as keratinocytes and endothelial cells, subsequently leading to skin necrosis: Nicolau syndrome (NS). Clinicians should consider this when an injection-site is ecchymotic and/or develops and erythematous patch, with bulla and intense pain in the immediate post-injection period [4]. The pathogenesis is not well understood; intra-arterial or peripheral-nervous injections might stimulate the sympathetic nerve, causing an acute vasospasm of the vessel, leading to ischemia or inflammation of the vessel structures, followed by thrombosis and necrosis. Various injection administration methods and medications result in NS [4, 5].

NS must be differentiated from NF. The history of a skin lesion secondary to subcutaneous injection with the delayed onset of rapidly progressive local inflammatory changes suggests a closed-space infection. NF is a rapidly spreading life-threatening infection of the subcutis and fascia, which could be polymicrobial (type I: e.g., mixed bacteria, including aerobic and anaerobes) or monomicrobial (type II: e.g., hemolytic streptococci, methicillin-resistant Staphylococcus aureus). Necrotizing infections can occur after minor breaches of the skin or mucosa or nonpenetrating soft-tissue injuries in postsurgical and immunocompromised patients [6]. In this case, the skin lesion caused by a subcutaneous puncture (a seemingly trivial injury) was likely the entry point. The rapid clinical deterioration was probably in the...
context of his condition of immunosuppression due to senescence and MDS. To our knowledge, there are only three published case reports of patients with MDS in which NF occurred after injections of azacitidine, but only in one of them subcutaneously [7, 8]. It is likely that in these cases, the initial mechanism was the same as in NS: vasospasm, ischemia, necrosis, and, subsequently, the development of a deep superinfection (NF).

NF should be considered in patients with intense local pain (in crescendo), erythema of the skin that later becomes purplish or vesiculated (Figure 1, panels C,D), wooden-hard induration of the
For patients with clinical diagnosis of NF, prompt surgical exploration is recommended. The information will be provided if requested in a particular way. The authors received no specific funding for this work. The authors declare they have no conflicts of interest. All authors had access to the data and a role in writing this manuscript. Complications.

In summary, clinical physicians should be aware and have a high suspicious threshold. Expedited diagnosis, prompt surgical intervention, and appropriate antibiotic treatment are essential to limit complications. NF is associated with considerable mortality, even with optimal therapy (ranges between 14% and 34%) [6, 9, 11]. In this case, nosocomial infectious complications led to a fatal outcome. In the other three reported cases, two had a fatal outcome because of poor infection control [7, 8].

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In summary, clinical physicians should be aware and have a high suspicious threshold. Expedited diagnosis, prompt surgical intervention, and appropriate antibiotic treatment are essential to limit complications.

**AUTHOR CONTRIBUTIONS**

All authors had access to the data and a role in writing this manuscript.

**CONFLICT OF INTEREST**

The authors declare they have no conflicts of interest.

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**DATA AVAILABILITY STATEMENT**

The information will be provided if requested in a particular way.

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