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Case Presentation

Hydroxychloroquine-induced fatal toxic epidermal necrolysis complicated by angioinvasive rhizopus

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Abstract

The majority of toxic epidermal necrolysis (TEN) cases are provoked by "high risk" medications (e.g. allopurinol, aromatic anticonvulsants, nevirapine, oxicam non-steroidal anti-inflammatory agents, and sulfonamides). TEN usually occurs 1 to 8 weeks after initial administration of the offending agent, but re-administration can evoke TEN within hours to days [1]. Hydroxychloroquine has rarely been associated with TEN, with one case proving fatal [2-4]. Herein, we report a case of hydroxychloroquine-induced fatal TEN complicated by angioinvasive Rhizopus. To our knowledge, this is the first case report of angioinvasive Rhizopus in a TEN patient. Initial misidentification of the offending agent causing TEN also serves as an important teaching point worth highlighting.

Case synopsis

A 30-year-old woman with systemic lupus erythematosus (SLE) presented with a worsening rash four weeks after initiation of hydroxychloroquine and phenytoin for SLE-associated seizure disorder. She was on no other medications. She was diagnosed with Stevens-Johnson syndrome (SJS) secondary to phenytoin. Hydroxychloroquine and phenytoin were discontinued and the patient improved clinically. At discharge, she was switched to levetiracetam for seizures with re-initiation of hydroxychloroquine.

Three days later, she presented with worsening tender rash and was transferred to our Burn Center for further management. On exam, there was diffuse erythema with overlying bullae and erosions involving greater than 90% body surface area. Nikolsky and Asboe-Hansen signs were positive. Erosions were present on ocular, oral, and vaginal mucosae. SCORTEN scale for severity of TEN was calculated as 4, carrying an estimated mortality rate of 58.3%. A TEN-like presentation of acute SLE was considered, but normal serum complement levels, negative double-stranded DNA antibody, and lack of other organ involvement made this diagnosis unlikely. Skin biopsy showed a subepidermal vesicle with confluent epidermal necrosis, minimal infiltrate, and negative direct immunofluorescence, consistent with TEN. Despite hydroxychloroquine cessation, intravenous immunoglobulin, broad-spectrum intravenous antibiotics, and supportive care, the patient developed chronic septic shock secondary to persistent polymicrobial bacteremia, likely related to gastrointestinal involvement based on radiologic findings.

Three weeks after initial presentation with re-epitheliazation slowly under way, she developed a sharply demarcated, necrotic plaque on her forehead and frontal scalp. Skin biopsy revealed vascular invasion by broad, non-septate hyphae branching at wide

angles, suggestive of zygomycosis. Fungal culture showed evidence of Rhizopus species. Owing to progressively worsening multiorgan failure, surgical debridement was not pursued and the family withdrew care.

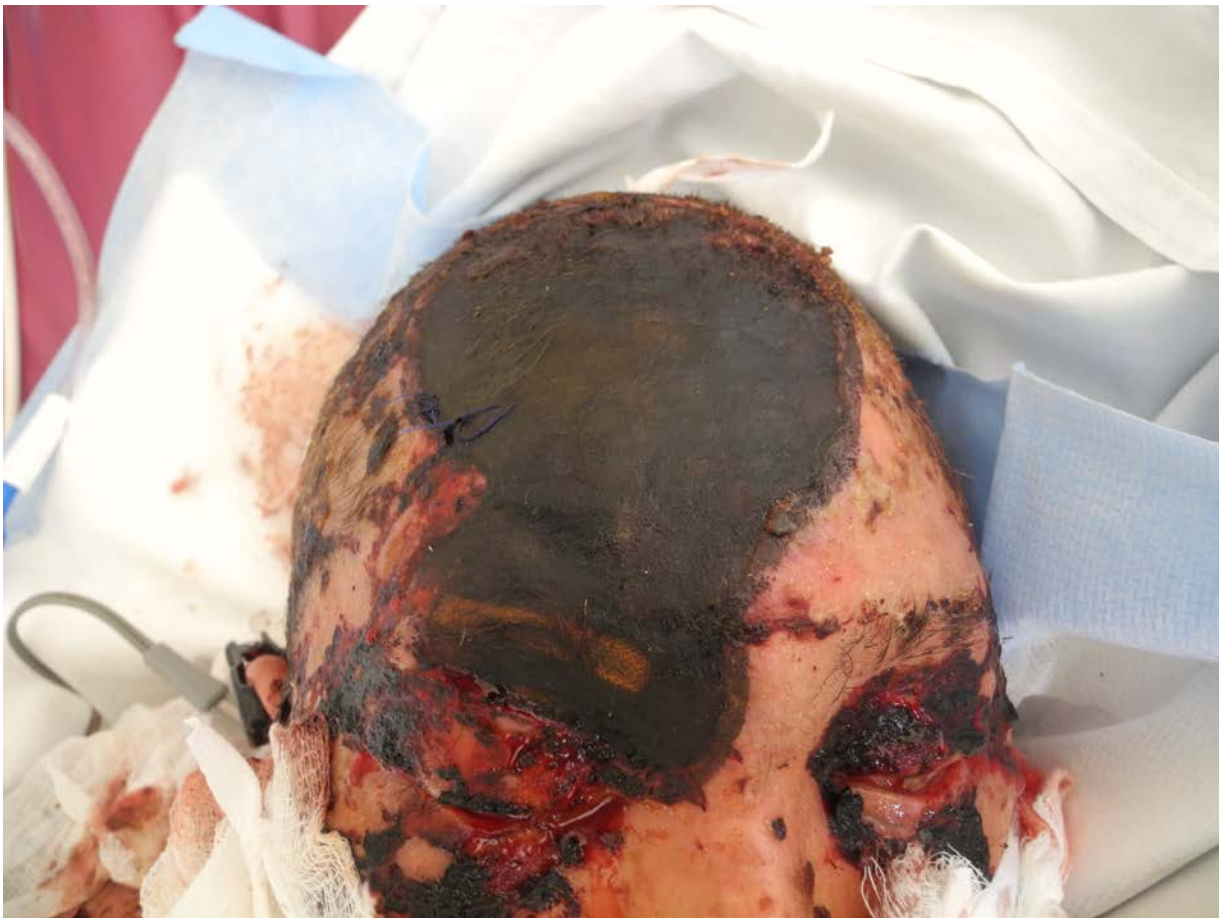

Figure 1. Sharply demarcated, necrotic plaque on her forehead and frontal scalp, later proven to be angioinvasive Rhizopus

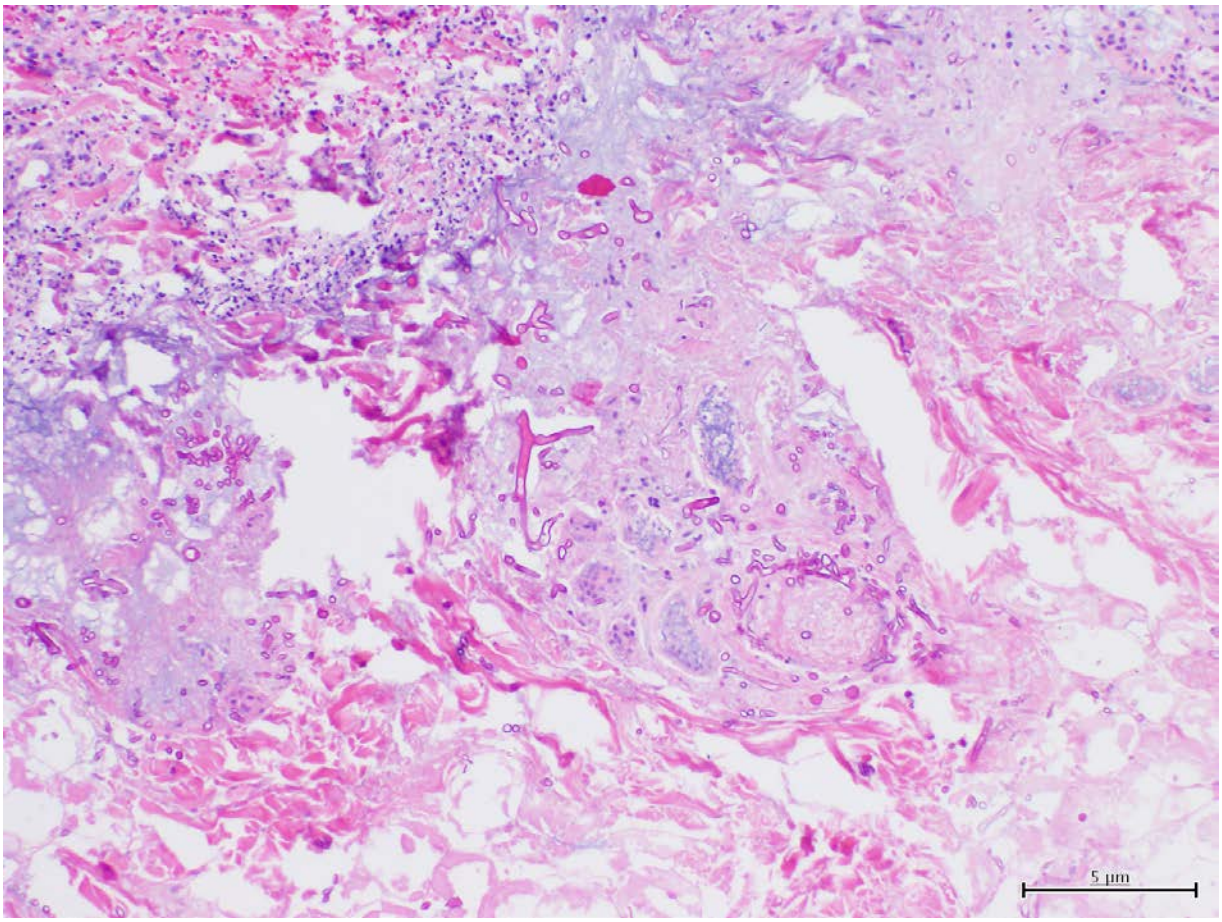

Figure 2. High power magnification of skin biopsy revealing vascular invasion by broad, non-septate hyphae branching at wide angles, suggestive of zygomycosis

Discussion

Angioinvasive zygomycotic infections commonly occur in immunocompromised patients owing to neutropenia, systemic steroids, or poorly controlled diabetes mellitus. Our case highlights the importance of recognizing TEN as an immunocompromised state. Such an approach allows for early detection of life-threatening infections followed by appropriate management, which in invasive zygomycosis includes systemic antifungals and prompt surgical debridement. Invasive zygomycosis should be suspected in TEN patients presenting with necrotic plaques or ulcers, even if at site of previous desquamation [5].

Phenytoin, a far more likely culprit than hydroxychloroquine, was initially labeled as the causative medication of SJS/TEN. However, three days after re-challenge with hydroxychloroquine, the patient presented with eruptive TEN. In retrospect, it is highly unlikely that the patient had two separate drug hypersensitivities to agents with no cross-reactivity (phenytoin and levetiracetam), but rather an initial and subsequent sensitized hypersensitivity reaction to hydroxychloroquine. This case illustrates that physicians must consider all possible medications rather than only “high risk” culprits when identifying causative agents of SJS/TEN.

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