Stevens-Johnson Syndrome Associated with Malarone Antimalarial Prophylaxis

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To the best of our knowledge, Stevens-Johnson syndrome (SJS) has not been reported previously as an adverse reaction to Malarone, which is a combination of atovaquone and proguanil hydrochloride used for antimalarial prophylaxis and therapy. We describe a 65-year-old patient who had SJS with typical clinical and histopathological findings associated with the use of Malarone prophylaxis for malaria. This report should alert physicians to this severe cutaneous reaction, and Malarone should be added to the list of drugs that can potentially cause SJS.

Cutaneous adverse events are among the most frequent complications of pharmaceutical therapy. Many pharmaceutical agents, including nonsteroidal anti-inflammatory drugs, anticonvulsants, and antimicrobials, have been implicated in such adverse events [1]. Stevens-Johnson syndrome (SJS) typically affects <10% of the skin surface, but dermal detachment may progress and overlap with the more severe and extensive form of the disease, toxic epidermal necrolysis (TEN) [2]. The incidence of SJS is 1–2 cases per million population per year, and the mortality rate associated with SJS is low; the mortality rate among patients with TEN, however, ranges from 15%–75%. The pathogenesis of both diseases involves extensive epidermal cell death caused by apoptosis, triggered by death receptors and their ligands. SJS is characterized by clinical findings of an erythematous rash with macules, and, occasionally, vesicles and bullae that may coalesce and erode and mucous membrane lesions that may involve the oral cavity, anogenital regions, and conjunctivae. Nikolsky’s sign is present, and mucosal ulcerations can result in strictures and ocular scarring. Although SJS can be confused with erythema exudativum multiforme (EEM), EEM is typically localized to the extensor surfaces of the extremities and the mucosal epithelium [3], whereas SJS is more likely to be disseminated. In addition, EEM is most commonly associated with herpes simplex virus (HSV) infections, whereas SJS is primarily caused by drugs and, less commonly, by viral and bacterial infections, neoplasms, or collagen vascular diseases. We describe a patient who had SJS with typical clinical and histopathological findings associated with the use of Malarone (GlaxoSmithKline), a combination of atovaquone and proguanil hydrochloride, as prophylaxis for malaria.

A 65-year-old tourist travelled to Namibia from 17 February to 17 March 2002. He reported no permanent or recent medication and had no history of a recent bacterial or viral infection, neoplasm, or collagen vascular disease. Two days before entering the Etoscha National Park, he began receiving Malarone once daily for antimalarial prophylaxis. One day later, he noticed painful lesions on his palate and gums. The lesions spread to the buccal mucosa and lips and then ulcerated (figure 1). During the next several days, he developed erythematous macules on his trunk and proximal extremities and erosions on the glans penis. There were no signs of conjunctivitis.

Malarone prophylaxis was discontinued after 5 days, and the patient was treated initially with 25 mg of promethazine and 60 mg of prednisone followed by a stepwise daily dose reduction. After initial improvement, the cutaneous lesions became confluent with focal areas of blistering, especially on the patient’s back (figure 2). Furthermore, the patient developed painful erosions of the scrotal skin and the perineum. On 13 March, the patient was seen by a general practitioner who suspected SJS and prescribed a combination of prednisone (60 mg) and diclofenac-hydrochloride. No new lesions developed during the next several days.

The patient returned to Europe on 17 March and was admitted to our hospital. Except for the mucocutaneous lesions and Nikolsky’s sign (figure 2), no pathologic findings were detected on physical examination. Steroid medication therapy was continued with 80 mg methylprednisolone, and antiseptics were administered topically. Laboratory testing of serum samples obtained from the patient revealed 9600 leukocytes/µL with 92% neutrophils; transaminase levels and creatinine clearance were normal, and no proteinuria was detected. ELISA for HSV IgM and HSV IgG antibodies, a direct immunofluorescence (DIF) assay for HSV type 1 and HSV type 2 antigens, and PCR for HSV DNA were performed on a cutaneous biopsy specimen;
Figure 1. Crusted ulcerations on the oral mucosa and lips of a patient with Malarone-induced Stevens-Johnson Syndrome.

Figure 2. Confluent macules and vesicles on the back of a patient with Malarone-induced Stevens-Johnson Syndrome. Note Nikolsky’s sign (arrow).

the results of these tests were all negative. In addition, direct immunoflourescence assay on lesional skin samples and indirect immunoflourescence assay on serum samples were performed to detect antinuclear antibodies and/or autoantibodies typical of autoimmune bullous skin diseases, and results were negative.

The diagnosis of SJS was supported by histopathological findings that showed epidermal regeneration with mitotic figures beneath a residual necrotic epidermis. The dermis showed a horizontally oriented lymphocytic infiltrate mixed with some pigmented macrophages surrounding the vessels of the superficial dermal plexus (figure 3) [4]. These changes were consistent with the healing of SJS lesions, which display histopathological changes that are identical to those displayed by EEM and TEN lesions, but differ in their intensity. SJS could also be differentiated by the clinical aspect of the lesions, their pattern of distribution, and the extent of skin involvement at the time the biopsy was performed. The patient was afebrile during the entire episode of the disease. All dermal and mucosal lesions healed without scarring. Since then, there have been no relapses or additional complaints.

We conclude that Malarone is the only possible cause for induction of SJS in our patient because he was not receiving any other medication at the time of the onset of the disease and the first lesions appeared within 1–28 days after receiving Malarone, which is the typical time frame in which SJS lesions appear after the intake of the causative drug [5]. At the time of presentation at our hospital, the patient’s clinical symptoms were decreasing in severity, probably as a result of early corticoid administration and prompt withdrawal of Malarone prophylaxis. To the best of our knowledge, this is the first histologically proven case of SJS induced by Malarone or its components, atovaquone and proguanil hydrochloride. Since Malarone is widely used for malaria prophylaxis and therapy, physicians should be aware of this serious side effect. Furthermore, Malarone should be added to the list of drugs that potentially can cause SJS.

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Figure 3. Epidermal regeneration with mitoses (arrow) beneath necrotic epidermis, a finding consistent with the healing of Stevens-Johnson syndrome lesions. (Hematoxylin and eosin stain; original magnification, ×200).

References