



## Update on the Stevens-Johnson syndrome

**K**ALHAN AND DITTO<sup>1</sup> describe the anesthetic management of ocular problems in a patient with Stevens-Johnson syndrome (SJS) probably related to the phenobarbital used for febrile seizures. With the use of ketamine anesthesia, the patient's eyelid adhesions and fibrin membrane were removed over three consecutive days. By the sixth day, lid movement was much improved and the patient could open her eyes easily. On the eighth day, pressure-equalization tubes were inserted bilaterally while the patient was under halothane anesthesia. Although no data are given pertaining to the follow-up of the ocular problems, it is reasonable to assume that lysis of adhesions and removal of a fibrin membrane would diminish the destructive potential of the disease and reduce the need for subsequent surgical procedures.

■ See Kalhan and Ditto (pp 467-469)

According to Tonnesen and Soter,<sup>2</sup> the term "erythema multiforme" was first used by von Hebra in 1860 to define a spectrum of diseases represented by the hallmark of target lesions (multiple, concentric colored rings of blue, white, and red) or iris lesions (dark center). Erythema multiforme minor describes the banal development of these papular lesions, usually on the extremities. Patients with the more serious erythema multiforme major also have blisters. In 1922, Stevens and Johnson reported two pediatric patients with an erythema multiforme-like exanthem, stomatitis, and conjunctivitis. Severe involvement of mucous membranes is now considered the distinguishing characteristic of erythema multiforme major. In 1956, Lyell coined the phrase "toxic epidermal necrolysis" (TEN) to describe eruptions that he considered similar to "scalding of the skin" with widespread blistering. Goldstein et al<sup>3</sup> consider TEN to be the most severe manifestation of erythema multiforme, although this is not yet completely accepted.

Erythema multiforme therefore does represent a true spectrum of diseases from the minor varieties that feature nonbullous lesions limited to the hands and feet, to the most severe varieties such as SJS or toxic epidermal necrolysis.

Understanding of erythema multiforme has increased considerably in the past decade. Much of the most interesting information has been reported by a group of French researchers located in Créteil (a suburb of Paris). The work of Jean Revuz, Jean-Claude Roujeau and colleagues at the Hôpital Henri Mondor has made the institution France's leading center for the treatment and study of erythema multiforme, attaining international standing in the process.<sup>4-7</sup>

Most cases of erythema multiforme minor occur either after a herpes simplex virus infection or with no known cause. However, as disease severity increases through the Stevens-Johnson syndrome to toxic epidermal necrolysis, the percentage of drug-induced cases increases substantially. Guillaume et al<sup>4</sup> evaluated 87 cases of TEN and found a causative drug in 67 (77%). Sulfonamides were a common culprit, responsible for 18 cases (the combination of sulfamethoxazole and trimethoprim accounted for 12 of these cases), and anticonvulsants were implicated in seven cases. For 10-20 years, these drugs have been associated with erythema multiforme major. Of special note was the discovery that nonsteroidal anti-inflammatory drugs were also a major factor, causing 29 (33%) of the cases in their series. No other drug was responsible for more than three cases. Antibiotics such as penicillin are frequently, but incorrectly, identified as the cause of erythema multiforme major because they are often given for the prodromal symptoms of fever and pharyngitis.

Revuz et al<sup>5</sup> reviewed their clinical findings on prognostic factors in this same group of 87 patients. They noted a mortality of 25%, with infection as the most common cause of death. Factors associated with a poor prognosis were older age, extension of cutaneous necrolysis to more than 50% of total body surface area,

elevation of BUN and creatinine levels, neutropenia, lymphopenia,<sup>6</sup> and thrombocytopenia.

Persistent ocular problems developed in 15 of 30 patients who were followed for more than one year. The most common problem was the ocular sicca syndrome (in 13). One patient was nearly blind. Additionally, pigmentary abnormalities (hyperpigmentation or hypopigmentation) were seen in 20 of the 30 patients.

Probably the most significant and controversial recent development in the management of erythema multiforme major has been the growing condemnation of the use of systemic steroids for treatment of the disease.<sup>7</sup> Seven series have appeared within the last decade showing both retrospectively and prospectively that treatment with corticosteroids is associated with longer hospitalization, reduced time for healing of the injured skin, and increased mortality.<sup>8-14</sup> The Créteil group does not use corticosteroids, and the participants at an international symposium dealing with TEN also unanimously questioned their efficacy.<sup>7</sup>

Heimbach et al<sup>14</sup> have published the most recent comprehensive review of the management of TEN. The authors suggest that patients with extensive TEN are best treated in a burn unit where they undergo thorough debridement and application of porcine xenografts to all open wounds. They note that initial fluid resuscitation is not required as in patients with burns because the amount of fluid loss is usually much less. Yet, adequate fluid intake must be maintained either intravenously or through a nasogastric feeding tube. Their surgical team stresses frequent visitation by an ophthalmologist and continued removal of synechia. They believe such intensive management can reduce mortality below 20% and make long-term morbidity negligible. Even with such intensive management, three of their 19 patients died.

Despite all this new information, little is known about the exact pathophysiology involved in production of the cutaneous lesions. Immune complexes and cutaneous deposition of immunoglobulins have been noted in patients with post-herpetic erythema multiforme.<sup>14</sup> While patients with drug-induced SJS and TEN are presumed to have some allergic reaction, the exact mechanism has yet to be determined. Any explanation must take into account the fact that the skin is the primary target organ while the cardiovascular, renal, and central nervous systems, as well as the joints, are not usually involved. Roujeau et al<sup>6</sup> have noted that initial lymphopenia is common when T-lymphocytes of the T<sub>4</sub> subclass are reduced. The occurrence of TEN in patients with graft-versus-host disease also suggests that immunologically activated T-lymphocytes are an important causative factor in the disease.

Why the skin is the primary target organ is still unknown. Perhaps a drug linking with an epidermal hapten produces a potent antigen stimulating a cell-mediated type of immune response. The drug may also directly damage the epidermal keratinocytes, releasing intracellular cytokines such as interleukin I, a potent inflammatory molecule with chemoattractant properties. Neither is it known why corticosteroids have such little influence on this chain of events. It may be that they are administered too late in the course of the disease. Once the epidermis has been severely damaged, corticosteroids will do nothing to promote healing and may increase the host's susceptibility to infection.

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