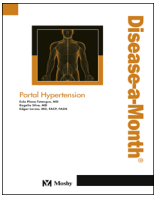
Disease-a-Month ▮ (2016) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Disease-a-Month

journal homepage: www.elsevier.com/locate/disamonth



Adverse drug reactions

Zachary Seagrave, MD, Sonya Bamba, MD

Adverse drug reactions (ADRs) are frequent and encountered in every health care setting and specialty. Hypersensitivity drug reactions are an immunologically mediated subset of ADRs that are largely unpredictable, dose independent and may potentially be life threatening.[1] Hypersensitivity reactions with mucocutaneous involvement are not uncommon as well, found in approximately 2–3% of all hospitalized patients, resulting` in morbidity, risk of mortality, and prolonged hospital admissions.[2] This represents a significant socioeconomic impact and may affect drug prescribing patterns of physicians.

Although only about 2% of adverse cutaneous reactions are severe, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are serious systemic immunologic disorders that are associated with severe morbidity and even death, with mortality rate as high as 30%.[2] Management of these conditions require timely diagnosis and treatment in the short and long-term using a multidisciplinary approach and close monitoring in an intensive care unit or burn care unit to improve the prognosis of these patients. Children and young adults are affected slightly more often but all ages may develop SJS/TEN with an estimated incidence of 5.5 cases per million populations per year.[3]

Classification

American pediatricians, Albert Mason Stevens and Frank Chambliss Johnson, first described the disease in 1922 in 2 young boys with “an extraordinary, generalized eruption with continued fever, inflamed buccal mucosa, and severe purulent conjunctivitis.” Historically, debate existed over the clinical definitions of SJS, TEN, and the similar clinical entity of erythema multiforme that was described by von Hebra in 1866. Disagreement in the literature can be found regarding the classification of these illnesses and whether they are distinct disease processes or are on a spectrum of the same disease. However, according to a consensus definition published in 1993, SJS is now generally recognized as a disease on the spectrum of TEN. SJS/TEN was separated from classification with erythema mulitforme, which itself consists of erythema minor and major forms. Both spectra of clinical disorders have similar appearing mucosal reactions but each has distinctive patterns of cutaneous lesions as well as different precipitating factors.[4] Erythema multiforme is reserved for patients with typical target appearing lesions or raised edematous papules. Erythema multiforme major is differentiated from erythema minor by the involvement of mucosa. SJS is used to characterize cases with widespread blisters on erythematous or

http://dx.doi.org/10.1016/j.disamonth.2016.09.006

purpuric maculae predominately on the face and trunk. TEN is differentiated from SJS by desquamation involving greater than 30% of body surface area while SJS is diagnosed when less than 10% of the cutaneous surface area is affected. SJS/TEN overlap is used to describe patients with 10–30% body surface involvement.[5]

Pathogenesis/etiology

SJS and TEN are severe hypersensitivity reactions involving the skin and mucous membranes leading to widespread keratinocyte death and splitting of subepidermal layers. The characteristic epidermal necrosis most frequently is the result of a drug reaction but has been associated with infectious and malignant diseases in addition to other risk factors not yet identified as well. The majority, approximately 75%, of these hypersensitivity reactions are thought to be drug induced.[6,7] Over 200 medications have been implicated in this spectrum of diseases with sulfonamides, anticonvulsants, NSAIDs, and allopurinol the most commonly associated drugs.[8] Numerous infectious diseases have been linked to SJS and TEN in the literature including several viruses, bacteria, fungi, and protozoan. Infectious causes are implicated in a higher percentage of pediatric cases although medications remain the most common etiology (Figs. 1–3).

The mechanism of SJS/TEN has yet to be fully elicited but immunologic involvement with immune complex deposition, cytotoxic reactions, and delayed hypersensitivity appears to be involved. Production of tumor necrosis factor-alpha and antigen presentation by major histocompatibility complex (MHC) class I on local tissue dendrocytes triggers inflammation in the skin and mucosa by cytotoxic T lymphocytes and natural killer cells. Keratinocyte apoptosis is activated by drug specific T lymphocytes through the release of granzyme entering the target

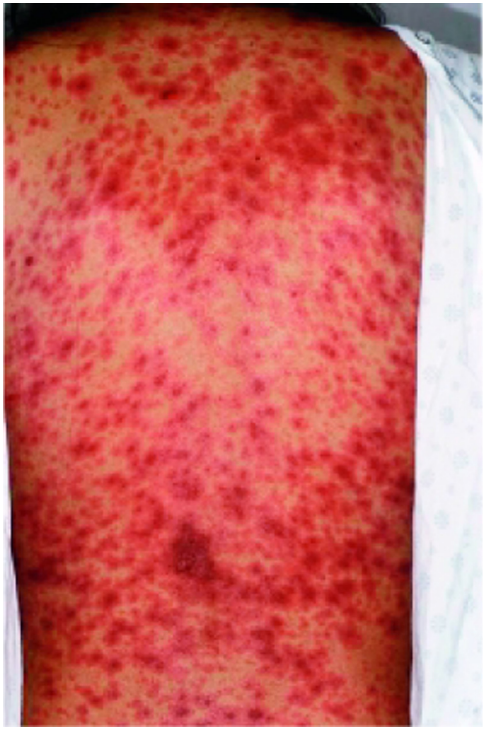


Fig. 1. Maculopapular rash seen in SJS/TEN. (Adapted with permission from Wetter DA, Camilleri MJ. Clinical, etiologic, and histopathologic features of Stevens–Johnson syndrome during an 8-year period at Mayo Clinic. *Mayo Clin Proc.* 2010 85(2):131–138. http://www-ncbi-nlm-nih-gov.proxy1.ncu.edu/pmc/articles/PMC2813820/?tool=pmcentrez).