EM/SJS/TEN: overview – human perspective

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Introduction

Erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are a group of mucocutaneous diseases characterized by varying degrees of skin and mucosal involvement. The latter two conditions associated with high morbidity and mortality.

The classification and terminology of these diseases has been constantly evolving, and new classification systems are being proposed every few years. Erythema exsudativum multiforme, as first described by von Hebra in 1866\(^1\), was later classified as either EM minor or major, the latter having mucous membrane involvement. The terms EM Major and SJS were used interchangeably, which was quite confusing, even though the first cases reported by Stevens and Johnson in 1922 differed in many aspects. The term TEN was introduced by Lyell in 1956\(^4\), and he agreed in a later paper that SJS and TEN are part of the same spectrum. It was previously thought that all these diseases were part of a single spectrum of disease; however, recent reports show that EM is now considered separate from SJS, SJS/TEN overlap, and TEN, in terms of aetiology and clinical features\(^6,7\). A consensus classification was introduced in 1993 by Bastuji-Garin et al., who proposed five categories: bullous EM, SJS, SJS/TEN overlap, TEN with spots, and TEN without spots\(^8\).

Erythema multiforme

Erythema multiforme (EM), as originally described by von Hebra in 1866, is a self-limited condition characterized by the abrupt onset of red papules which evolve into target lesions, with a tendency to recur. EM is classified into “EM minor” and “EM major” in an attempt to separate the classical, mild disease described by von Hebra (EM minor) which is most often associated with herpes simplex virus (HSV) infection in almost 50% of cases, and the more severe form with mucosal involvement usually attributed to Mycoplasma pneumoniae infections and drugs\(^9,10\).

EM may experience burning or itching at the site of the eruption, which usually appears symmetrically on the distal extremities, gradually progressing proximally. The involvement of the extensor surfaces of the extremities is common, as is involvement of the palms and soles. The individual lesions may start off as erythematous macules that later evolve into papules, plaques, and finally target lesions, which are only seen several days after the onset\(^10\). There are usually lesions of varying morphology coexisting, hence the term erythema “multiforme”. Target lesions have three distinct zones, a dusky area of central necrosis, a middle zone of pale oedema, and an outer zone of erythema\(^10\).

As EM is generally self-limiting, management rarely requires hospital admission. EM usually resolves spontaneously in three to five weeks, but has a tendency to recur\(^10\). This is usually the case when it is found in association with HSV infection. In these cases, there is a role for acyclovir prophylaxis.

Stevens-Johnson Syndrome

SJS is one of the rare, severe adverse cutaneous reactions to drugs, although a small proportion may be attributed to infection (i.e. HSV and Mycoplasma pneumoniae). As indicated in the criteria, SJS is characterized by erythematous or purpuric macules, widespread blisters predominantly on the chest, and involvement of at least 2 mucosal surfaces and less than 10% detachment\(^7,8\). Upon commencing treatment and withdrawal of the offending drug, re-epithelialization occurs, and there may be resulting post-inflammatory hyperpigmentation and scaling, with the average course of the disease lasting 2-3 weeks. Reported mortality is around 5%, and there are reports that prompt withdrawal of the offending drug reduces the risk of death by 30% per day, although this is generally in the case of drugs with short half-lives\(^11\). The management involves general supportive care measures, and referral to the ophthalmologist to prevent serious complications\(^12\).
**Toxic Epidermal Necrolysis**

TEN is a severe life-threatening disease characterised by mucosal involvement and greater than 30% epidermal detachment. Almost all cases are due to drugs, with allopurinol and carbamazepine being the most common causes in adults, and antibiotics and anticonvulsants in children. Similar to SJS, there is a prodrome of fever, malaise and mucositis followed by the onset of tender, purpuric target lesions and the extensive epidermal detachment that ensues within 24 hours, but most erupt over a period of two to fifteen days. The skin is usually quite painful to touch. Laboratory abnormalities include anemia and lymphopaenia, with neutropaenia having a worse prognosis. There is also inflammation of internal mucosal surfaces such as the gastrointestinal and respiratory tracts due to the massive release of proinflammatory cytokines into the systemic circulation. This can lead to metabolic imbalance, multiorgan failure, pulmonary embolism, and gastrointestinal haemorrhage.

Due to the high mortality associated with TEN (30-50%), management of these cases usually require admission to burns or intensive care units, and prompt installation of supportive treatment and possibly IVIG or corticosteroids. The offending drug must be discontinued immediately, and supportive treatment must be initiated early to have the best outcome. Referral to the ophthalmologists paramount in order to prevent serious complications such as permanent visual loss due to corneal scarring or vascularisation.

**Overview of Management**

The cornerstone of treatment of EM, SJS, and TEN is meticulous skin care, fluid management, nutritional support, and surveillance as well as treatment of infections. When the precipitant is identifiable, treat the underlying cause, i.e. oral acyclovir in HSV-induced EM, or a macrolide in Mycoplasma-induced illness. In the case of drug-induced disease, the offending drug should be ceased. General measures should be done, including increasing the room temperature to 30°C to 32°C to reduce caloric loss through the skin, giving anticoagulation with subcutaneous heparin or low molecular weight heparin to prevent deep vein thrombosis in immobile patients for the duration of their hospital stay. Pulmonary care is instituted via the use of aerosols, bronchial aspiration, and physical therapy. Various biologic dressings, as well as silver dressings due to their inherent antimicrobial properties have also been used.

There is really no established standard treatment for SJS and TEN. There have been numerous small studies and reviews suggesting that various treatments, in particular corticosteroids, are either beneficial or harmful. Data on therapy was retrospectively collected from patients in France and Germany enrolled in EuroSCAR, a case-control study looking at risk factors. It was found that neither IVIG nor corticosteroids had any significant effect on mortality in comparison with supportive care only, although a trend for beneficial effect of corticosteroids was noted. Currently, it is acceptable to use high dose systemic corticosteroids over a short period of time in SJS and TEN, and in addition, IVIG may be instituted early in TEN as small studies still show benefit.

**References**