What is Going on in Erythema multiforme?

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One hundred and thirty years after the original description of von Hebra, erythema multiforme (EM) is still giving rise to many controversies on all the aspects which constitute a disease as an entity. Clinical definition and nosology, pathology, etiology, physiopathology and treatment remain the subjects of often confuse debates.

Nosology

In the last 30 years it became widely accepted that EM minor, EM major, ectodermosis erosiva pluriorificialis, Stevens-Johnson syndrome (SJS) and toxic epidermal necroly-sis (TEN) were all part of a single 'EM spectrum'. That unifying concept, prevalent in major textbooks of dermatology, has probably contributed to the current confusion.

In fact there is little resemblance between the two ends of the spectrum. It was recently proposed to split again the EM spectrum and to come back as close as possible to the original clinical descriptions [1]. The denomination of EM should be restricted to acrally distributed typical targets or raised edematous papules fitting the original descriptions (erythema iris, erythema papulatum). Depending on the presence or absence of mucous membrane erosions the cases could be classified as EM major or EM minor. In keeping with the original description, the denomination of SJS should be used for a syndrome characterized by mucous membrane erosions and widespread blisters, often predominant on the chest, arising on erythematous or pur-puric macules, clinically quite different from targets.

A retrospective reclassification of 63 cases of 'EM major/SJS' according to the above-mentioned criteria supported the validity of that separation by showing different etiologies. EM major was mainly related to herpes simplex virus (HSV) infection and SJS to drug reactions [unpubl. data]. In my mind SJS and TEN are probably severity variants of the same drug-induced process.

Anyhow until this has been demonstrated on the basis of common etiology and physiopathology, it seems preferable to keep the two denominations (1) for analytic purposes and (2) as the severity of SJS and TEN is very different. Because the extent of necrolysis is a major prognosis factor, we proposed the limits of 10 and 30% of the body surface area involved by epidermal detachment as arbitrary boundaries between SJS, 'overlap SJS/TEN' and TEN [1].

Whether all the categories proposed represent distinct etiopathologic entities will require further clinical, epidem-iologic and laboratory investigations. Anyhow that 'splitting' attitude is a prerequisite to such studies by creating more homogeneous subgroups.

Physiopathology

The pathogenetic mechanisms responsible for EM remain unknown in spite of many recent advances. In HSV-associated cases, herpes simplex antigens and DNA are frequently detected in skin lesions of EM [2]. Isolation of infective HSV is usually negative, and pathology does not show cytopathogenic effects. It is therefore postulated that the lesions are not directly caused by

the virus itself but rather by some 'immunological' reaction to viral antigen (or to other triggering agents in cases secondary to e.g. *Mycoplasma pneumoniae* or drugs). Ten to fifteen years ago, several studies mainly dealing with HSV-associated cases provided several pieces of evidence for an antibody-mediated process.

Cryoglobulinemia, circulating immune complexes containing HSV antigen and deposits of C3 and IgM in superficial vessels of the dermis supported the concept of immune-complex-related vasculitis [3, 4].

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Actually true vasculitis is not a pathologic feature of EM, and more recent studies focused on cell-mediated immune response. In this issue of *Dermatology*, Sayama et al. [5] present the result of a study showing deposits of perform in the lesional skin of 3/7 cases of EM. Because perform is the molecular weapon of cytotoxic T cells, this finding is another clue to the cell-mediated hypothesis. Recently other authors have also demonstrated that in EM (1) keratinocytes expressed adhesion molecules (ICAM-1) allowing binding of T cells [6], (2) most infiltrating cells into the epidermis were CD8+ T cells [7] and (3) blood mono-nuclear cells had increased adherence to keratinocytes [8].

All the above findings, strongly suggesting a cell-mediated cytotoxic reaction, have been obtained in patients suffering from 'drug-induced EM' (clinically not described). It remains to show whether HSV-associated cases result or not from the same mechanisms. Further studies should also address the respective role of specific, i.e. antigen-driven, versus nonspecific cell interactions. The putative antigens, viral proteins and drug-reactive metabolites being usually known, rapid progress can be expected. To be more meaningful future studies should include clear clinical descriptions of patients and/or reference to classification criteria.

Treatment

Recent advances in the pathophysiology of EM should not be used as a rationale for hazardous therapies. Even if immunologically mediated, EM, SJS and TEN are self-limited disorders. One may wonder whether any therapeutic intervention can be early enough to shorten the process.

The answer will not come from theoretical considerations but only from carefully controlled therapeutic trials. The long-lasting controversy about corticosteroid [9] is fading away while supporters of immunosuppressive therapies are turning toward more fashionable drugs [10, 11], still of unproven usefulness. To date the only treatment of proven value is acyclovir, when used before the beginning of EM in HSV-related recurrent cases [12]. Up to one third of recurrences are suppressed when acyclovir, 200 mg five times daily for 5 days is taken from the first symptom of HSV infection [13]. About two thirds of HSV-related recurrences are suppressed by continuous oral acyclovir, 400 mg twice daily [12, 13].

Patients with frequent recurrences of unknown etiology and those with continuous condition may benefit from thalidomide [14] or azathioprine [13].

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Editorial