CASE REPORTS

Toxic Epidermal Necrolysis

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CASE SUMMARY

History
A 55-year-old woman was admitted because of sudden onset of generalized painful rash for 1 week. There were multiple blisters at trunk. Oral mucosal erosion was extensive. She has taken griseofulvin for nail dystrophy two weeks before the onset of skin rash. In the past, she had no history of drug allergy, and she had diabetes mellitus and nummular eczema for 10 years.

Physical examination
She had low grade fever and generalized erythema with detaching epidermis (Figure 1). Blisters were present on the trunk and oral mucosal erosion were extensive. Discrete target like lesions were found over limbs (Figure 2). Nikolsky sign was positive.

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Figure 1: Generalized epidermal detachment with bullae formation

Figure 2: Discrete Erythema Multiforme-like lesions at limbs
Investigations
A skin biopsy was done on her forearm. There was confluent necrosis of the epidermis that was partially detached from the dermis. Mild perivascular lymphocytic infiltration was present in upper dermis. The findings were consistent with toxic epidermal necrolysis.

Diagnosis
The diagnosis of griseofulvin induced toxic epidermal necrolysis was made.

Management
Basically she was managed like a burn patient. Fluid and electrolyte balance were monitored closely. Skin care included potassium permanganate soak, daily dressing and liberal emollient application. Oral and eye care included thymol gargle, solcoceryl gel and methylcellulose eye drop. Finally, she recovered completely and was discharged.

Discussion
Dermatopathologist stressed that it is difficult to distinguish erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis, solely based on the histological features. Clinico-pathological correlation was important.

Clinical manifestations
Prodromal period lasts for two to three days. It consists of malaise, fever, rhinitis and anorexia. The acute phase is of sudden onset and usually lasts for 8 to 12 days. There are persistent fever and extensive mucous membrane erosion which precedes epidermal necrolysis. Cutaneous involvement starts with generalized erythematous plaques that may progress to large flaccid bullae. The epidermis sloughs in the form of large sheets. Characteristically, there is prominent skin tenderness and the Nikolsky sign is positive. The mortality rate can be as high as 30%. Those patients who recover have gradual re-epithelialization of the skin and mucous membranes and this lasts for one to two weeks.

Clinical classification of Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome and Erythema Multiforme
There has been debate for a long time about the relationship among Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome(SJS) and Erythema Multiforme(EM). They are sometimes considered as a spectrum of diseases.

A new clinical classification was proposed by JC Roujeau et al (Table 1). The spectrum of severe bullous erythema multiforme were divided into five categories, according to the degree of epidermal detachment at most severe time, presence or absence of typical targets, atypical targets or spots. Mucous membrane involvement was not taken in account in this classification.

Target lesions are characteristic erythematous annular lesions with a raised cyanotic center, resembling a "target" and hence its name. Typical target was defined as individual well-defined round lesion of less than 3 cm in size and typically it consists of 3 different zones (2 concentric rings around a central disk). Atypical target however had poorly defined border and/or had 2 zones.
instead. It was said to be raised if it was palpable or flat if it was non-palpable. TEN with or without spots represents extensive epidermal necrosis with or without discrete EM-like lesions respectively.

The purpose of this classification was to separate EM from SJS and TEN. There was a strong and statistically significant correlation between the clinical classification and the probable cause. EM could be caused by infections or drugs whereas SJS and TEN were most likely due to drugs. Patients suffering from EM would not progress to SJS or TEN. A special category named as 'Overlap SJS-TEN' was created to better study the boundary between these two diseases.

Pathogenesis

It is believed that there is a genetic susceptibility in patient who develops TEN. HLA-B12 association was found in sulphonamide induced TEN. There is also indirect evidence to suggest that an underlying immune mediated reaction is involved, for example, type IV delayed hypersensitivity reaction. However, it cannot be explained why there is an increased frequency of TEN in patients with acquired immune deficiency syndrome as these patients have profound impairment in cell mediated immune response. Hence, metabolic predisposition to cutaneous drug reaction was suspected.

After the parent drug is administered, it is usually metabolized to reactive drug metabolites by phase I enzymes in liver, most likely to be cytochrome P450 mixed function oxidases. These reactive drug metabolites are toxic. Detoxification into non-toxic metabolites by phase II enzymes is required before they are excreted. The phase II enzymes are specific for different drugs. For examples, epoxide hydrolase is responsible to detoxify carbamazepine metabolites whereas glutathione S-transferase is responsible to detoxify sulphonamides metabolites.

Therefore, the metabolic hypothesis included several steps. There is a genetically determined disturbance of drug metabolites in the form of a generalized or organ-selective deficiency in detoxification mechanisms. Reactive intermediates are generated in the epidermis when the patient has taken the culprit drug. As these reactive intermediates are not detoxified, they act as antigens which alter the epidermal cell surface proteins, including HLA I molecules. Immune system is thus activated to generate cytotoxic CD8+ T cells which enter the epidermis to attack and damage the epidermal cells.

Moreover, the metabolic pathway is sometimes more complicated. For example, sulphonamide is metabolized by two pathways. The first pathway is acetylation by N-acetyl transferase into non-toxic metabolites. The second pathway is described in above paragraph. It was shown that majority of patients with sulphonamide-induced TEN were slow acetylators. However, 50% of the population are slow acetylators as well. Thus, slow acetylation appears to be a necessary but not a sufficient criteria for developing severe drug reaction. In slow acetylators, more sulphonamide will be channeled into the second pathway. If one has co-existent deficiency in detoxification, one is prone to develop severe drug reaction.

Prognosis

The prognostic factors include age, extent of skin loss, quality of skin care, associated medical illnesses such as diabetes mellitus and chronic renal failure, as well as presence of complications such as acute renal failure and infections.
Management

The most essential step is to discontinue the suspected drug. It is best to manage TEN patients in intensive care or burn unit with reverse isolation facilities. Nutrition, fluid and electrolytes replenishment is mandatory. Proper eye, oral, pulmonary and skin care are also important. Prophylactic antibiotics are not necessary but extensive search for infectious complications should be done regularly.

Corticosteroid administration is a controversial matter. Early administration of high dose corticosteroid is believed to stop the progression of necrolysis. However, significant morbidity and mortality can be associated with steroid use because of increased risk of sepsis, delayed wound healing and increased gastrointestinal bleeding. The course of the disease may be prolonged. Therefore, some physicians believe that the benefits of systemic steroid use is far outweighed by its risks. Cyclosporine and cyclophosphamide are used because of its immunosuppressive effect but serious infectious complications can also be induced. Plasmapheresis theoretically can remove the drug or its metabolites or an unidentified 'necrolytic factor' or 'inflammatory mediator'.

New therapies are being investigated. Intravenous N-acetylcysteine was postulated to be useful in sulphonamide induced drug reaction. N-acetylcysteine reacts with reactive oxidative intermediates and replenishes intracellular cysteine levels necessary for the production of glutathione, which is then conjugated to sulphonamide metabolites for detoxification. N-acetylcysteine has additional benefit in protecting cells from tumor necrosis factor alpha induced apoptotic cell death. Another new therapy, recombinant granulocyte colony-stimulating factor, resulted in rapid return of patient's peripheral blood white cell count to normal so that cutaneous and systemic infection could be reduced and re-epithelialization could be enhanced.

Learning Points:
There may be many pathogenic factors in TEN, including genetic, hypersensitive immune reaction and metabolic predisposition. However, metabolic predisposition alone cannot explain all cases since there are existence of non-drug induced TEN

References