CONTINUING MEDICAL EDUCATION

TOXIC EPIDERMAL NECROLYSIS

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Toxic epidermal necrolysis (TEN) is a rare life-threatening disorder characterized by widespread necrolysis and peeling of the skin resembling scalding, generally induced by drugs. First named as TEN by Lyell in 1956[1], controversy still persists about its definition, etio- pathogenesis and treatment.

The relation of TEN to Stevens-Johnson syndrome (SJS) is not clear. SJS was considered synonymous with EM major, but the differences in etiology and in the appearance (more erythematous) and distribution (less acral) of target like bullous lesions in SJS suggest that they can be classified separately.[2,3] TEN can be difficult to differentiate from SJS; since in severe cases SJS has extensive areas of epidermal necrolysis, and in most cases of TEN the discrete red macules typically seen with SJS occur around larger necrolytic areas. The similarities between the histopathological findings and the responsible drugs also suggest that both these conditions are part of a spectrum. [3]

Hence, it is now believed that the EM spectrum can be differentiated from the SJS/TEN spectrum. EM major and minor are hypersensitivity- related diseases (often to infectious agents), with typical target lesions, recurrence and low morbidity, whereas SJS and TEN are usually severe drug-induced reactions characterized by widespread blisters and purpuric macules, a high morbidity and poor prognosis.

Recently, a classification of severe bullous EM, SJS and TEN has been proposed to standardize the terminology by means of specific defi-

Table I Classification of severe bullous EM, SJS and TEN

Features	Bullous EM	SJS	Overlap SJS-TEN	TEN with spots	TEN without spots
Detachment	10%	10%	10%-30%	? 30%	? 10%
Typical target lesions	Yes	.....	.....	.....	.....
Atypical target lesions	Raised	Flat	Flat	Flat	.....
Erythematous or purpuric macules (with or without blisters)	.....	Yes	Yes	Yes	.....

(EM: erythema multiforme; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis)
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nitions and an atlas (Table I).[3] For accurate classification, the extent of necrolytic epidermis at the worst stage of the disease, and the nature of discrete lesions (widespread purpuric lesions or flat atypical target lesions) need to be determined. For clinicians, a simpler approach would be to diagnose TEN in the presence of mucosal involvement if blisters or sloughing constitute more than 30% of the body surface area, and SJS, if less.[4]

Aetiology

Most cases (> 95%) of TEN are drug induced. Although over 100 drugs have been implicated, the majority of cases are caused by a few drugs only (Table II).[5-13] In India, antituberculous therapy is a common cause.[9,14,15] Among drugs given on a long-term basis, the increased risk is largely confined to the first 2 months.[16] The incubation period is typically a few days to 3 weeks (mean 14 days).[17] It is less than 48 hours for a patient who has had TEN due to that drug earlier.[10]

Rare causes include food additives, fumigants, contact with chemicals, and acute graft-versus-host reaction.[18,19] Immunization, viral infections, and malignancies have been blamed, but have not been well documented.[18] Lastly, some cases have no apparent cause.

Table II. Common causes of toxic epidermal necrolysis

Antibacterials: Sulphonamides, penicillins, tetracycline
Anti-tuberculosis drugs: Thiacetazone, INH, ethambutol, rifampicin
Antiepileptic drugs: Phenobarbital, phenytoin, carbamazepine, valproic acid
NSAIDs: Phenylbutazone, oxyphenbutazone, piroxicam, diclofenac
Miscellaneous: Allopurinol, chlorpromazine, dapsone, griseofulvin.

Pathogenesis

The pathogenesis of TEN is not known, but it is believed to be immune-mediated. In the upper dermis of affected patients, CD4 lymphocytes predominate.[20] Earlier studies[21] found most cells infiltrating the epidermis to be cytotoxic CD8 T lymphocytes, but a recent study[22] found numerous monocytes-macrophages and dendrocytes. These cells could be activated early in the disease when they could act as antigen-presenting cells or by releasing cytokines, attracting inflammatory cells. As in skin graft rejection, tissue destruction in TEN could be mediated by both CD8 cytotoxic lymphocytes and monocytes-macrophages recruited by specific CD4 lymphocytes.

Perforins and other cytokines such as TNF-α released by activated mononuclear cells and keratinocytes contribute to local cell death, fever and malaise.[22] Another model suggests that proteins like FAS antigen (CD95) and other members of its supergene family (including P55 TNF-α receptor) are induced to promote apoptosis in keratinocytes.[23]

How drugs cause this immune response is also not clear. Epidermal cells modified by drug reactive metabolites could behave as haptens, but it has not been proved that such metabolites are present in the epidermis or that the cytotoxic response is directed at drug-derived antigens.[24]

Certain HLA types have been determined depending on whether the disease is induced by sulfonamides or oxicam NSAIDS.[25] A genetic defect in cell defense mechanisms could lead to a deficiency in drug metabolite

detoxification and favour the initiation of this immune reaction.[26] Slow acetylators are predominant among TEN patients.[27,28] Although most of them had not taken a drug known to be metabolized by acetylation, this mechanism could induce or inhibit other metabolic pathways.[29]

The incidence of TEN is 0.9 to 1.4 persons per million per year in various countries.[6,7,30,31] The HLA phenotype B12 is associated with a three-fold greater risk.[25] Patients with AIDS have an estimated 1000-fold higher risk because of increased exposure to sulphonamides, and an inherently greater risk of reactions.[32-34]

TEN occurs in all age groups including neonates, [9,35] but the elderly and women are more prone (perhaps because of greater use of drugs).[18,36] More than 75% of patients are over 40 years old.[29] The female/male ratio is 3:2 to 2:1.[18]

Clinical Manifestations

Prodrome

The first manifestations (fever, malaise, anorexia and rhinitis) can resemble an upper respiratory tract infection, and generally precede the mucocutaneous lesions by 1 to 3 days.

Acute phase

The acute phase lasts for about 8 to 12 days and is characterized by generalized epidermal peeling in sheets,mucosal denudations and erosions, and persistent fever.

The initial skin lesions are ill-defined, dusky or erythematous macules with darker purpuric centres that progressively coalesce.[18] They appear symmetrically on the face and upper trunk and rapidly spread, with maximal involvement within 4 days. The scalp is spared. Pain, burning and tenderness of the skin are marked. Within the area of confluent erythema, the epidermis separates in a sheet, forming raised flaccid bullae. Nikolsky's sign (i.e. dislodgement of the epidermis by lateral presssure) is positive. The detached wrinkled epidermis generally remains as a covering, except over pressure sites such as the buttocks and scapular region, where dark red oozing denuded areas are visible.[18] Rarely, extensive epidermal necrosis occurs on large areas of erythema without any discrete EM-like lesions (TEN without spots).[3]

Mucosal lesions may precede skin lesions by 1 to 3 days. The oropharynx, eyes, genitalia and anus are affected, in that order of frequency. Haemorrhagic crusts of the lips, increased salivation, impaired oral intake, photophobia, and painful micturition commonly result. Acute ocular manifestations are common (50% in a recent series) and may be sight-threatening.[5] Conjunctival lesions range from hyperemia to extensive pseudomembrane formation.[17,37] Synechia can form between eyelids and the conjunctiva. Mucopurulent conjunctivitis, keratitis and conjunctival erosions require special care because of the high risk of sequelae.

The concept of "acute skin failure" has been proposed to explain the severity and multiplicity of organ failure that results from extensive skin loss. High fever and shivering may be present even in the absence of secondary infection, and are due to impaired thermoregulation. In fact, a sudden drop in termperature

is more indicative of severe sepsis than is fever.[39] Hypoproteinaemia develops following a daily loss of 150-200 g of protein due to increased catabolism and protein loss through the skin.[40]

The lungs,liver,gut and kindneys may be involved.[41-44] In the acute phase,mucosae of the trachea, bronchi,esophagus and ileum may be eroded. Specific involvement of bronchial epithelium must be suspected in the presence of dyspnea,bronchial hypersecretion, normal chest X-ray, and marked hypoxemia during the early stages of TEN.[44] Delayed complications include pulmonary edema, bacterial pneumonitis, atelectasis and long-term pulmonary function abnormalities.[44,45]

Esophageal erosions may cause dysphagia and bleeding. Usually asymptomatic intestinal erosions can mainfest as bloody diarrhoea.[18,43] A profuse protein-rich diarrhoea may increase fluid loss and hypoalbuminemia.

Fluid,electrolyte and protein losses lead to hypovolemia that manifests as diminished urinary output and may end in acute tubular necrosis or prerenal azotemia. Proximal tubule damage occurs, possibly from necrosis of tubule cells by the same process that destroys keratinocytes. All patients in one series had increased microalbuminuria, suggesting that glomerular structures too are affected.[41]

Skin lesions are usually colonized by *Staphylococcus aureus* during the first few days and later,by *Pseudomonas aeruginosa* and other gram- negative bacilli.[17] Decreased immune responsiveness increased the likelihood of bacteremia, sepsis or pneumonia.[17] Urinary tract catheters and intravenous (especially central) lines form a significant portal of entry of bacteria.[46]

Recovery phase

The raw dermis becomes covered with dark crusts. Reepithelialization is complete in 2-4 weeks with intertriginous areas, the back, pressure areas and periorificial areas being the last to heal. Mucosal lesions can take longer.

Sequelae

Pigmentary changes, nail shedding or dystrophy, hypohidrosis, cicatricial alopecia and hypertrophic scarring are some cutaneous sequelae.[17] Mucosal sequelae include chronic xerostomia, esophageal strictures, phimosis, persistent mucosal erosions and vaginal synechia.[47] Ocular sequelae (ectropion,entropion with trichiasis, symblepharon, corneal opacities, and Sjogren-like sicca syndrome) affect about 35% of patients, and can result in persistent photophobia, burning eyes, visual impairment, and even blindness.[17]

Investigations

Histopathology

Early lesions are characterized by moderate perivascular mononuclear cell infiltration in the papillary dermis, with epidermal spongiosis, exocytosis and necrotic keratinocytes scattered along the dermoepidermal junction.[48] Close contact between dyskeratotic (necrotic) keratinocytes and sparse mononuclear cells ('satellite cell necrosis') may be seen.[18] The necrosis later extends from the basal cells to the entire epidermis which is detached from a little altered dermis, some times resulting in a subepidermal bulla. Immunofluorescence studies are negative and only help

to exclude other autoimmune bullous disorders.

Other investigations

Normocytic and normochromic anemia, lymphopenia, hypoproteinemia and electrolyte imbalances are common.[18] Elevated blood sugar levels and glycosuria are present in half the cases because of stress, infection, and possible, pancreatitis. The blood urea nitrogen and serum creatinine levels may be raised, and proteinuria and microscopic hematuria may be detected. The SGOT and SGPT are slightly elevated in half the patients, and in 10%, frank hepatitis may develop, induced by drugs, sepsis or shock.[17,18] Cultures of the blood, and of mucosal and cutaneous erosions should be obtained. An early chest X-ray may show interstitial edema.

Differential diagnoses

TEN should be differentiated from the much rarer SSSS because their treatments differ. SSSS is provoked by toxins (epidermolysins) produced by group II, phage 71 *S.aureus* that are usually present in a focal infection in the upper respiratory tract. Characteristically, there is superficial epidermal peeling, usually in a child. Mucosal involvement is rare. No target-like lesions are present, nor is there any pain. Bacterial smears and cultures are not helpful in differentiation since SSSS skin may be sterile and TEN skin is usually colonized by S.aureus.[49] Examination of frozen section of peeled skin or of a full thickness skin biopsy rapidly differentiates the two conditions: the level of the skin split in SSSS is the epidermal granular cell layer, whereas in TEN the level is subepidermal, with a full thickness necrotic epidermis.

Differentiation from SJS is based on the percentage of body surface area involved (using the rule of nines). Other differential diagnoses include pemphigus, scarlet fever, boric acid intoxication, thermal or chemical burns, toxic shock syndrome, fixed drug eruption and erythroderma.[2]

Prognosis

The mortality rate ranges from 10 to 70%.[9,10,50-52] An average of 29% was reported in 350 cases.[17] Lower rates have been reported for patients treated in burn centres.[11,12,48] Other causes are gastrointestinal bleeding, pulmonary embolism, myocardial infarction, and perforation of the gut.[17] Increased age,[8,17,36] more extensive epidermal detachment,[8,11,17] increased blood urea nitrogen concentrations,[6,17] visceral(renal, hepatic) involvement and WBC count nadir [5,11] indicate a poorer prognosis.

Treatment

Since TEN is a life-threatening disease, patients should be hospitalized.With the recognition that the clinical course is like that of extensive second degree burns, similar treatment protocols have been developed that are best carried out in a burn unit or intensive care unit .[40]

Withdrawal of the causative drug

It is often difficult to determine the causative drug because patients may be taking many drugs or may not be able to give an accurate medication history. Also , there are no safe and reliable skin or in vitro tests for this purpose. Drug challenge is not recommended because even if positive, it may be life-threatening.

All drugs, especially those introduced within 1 month of the reaction, should be considered suspect. [40] All non essential drugs should be discontinued, and those really needed, substituted with nonrelated ones where possible.[54]

General treatment

Fluid replacement , commonly with lactated Ringer's solution, is essential. Large volumes may be initially required: often 5L or more within the first 24 hours.[38] Water, electrolytes, plasma, albumin and synthetic colloids may be given. A peripheral line at a distance from the affected area can be used, but should be removed as soon as possible to avoid infection. [54] The environmental temperature should be raised to 30 to 32 C to reduce caloric losses through the skin and the resultant shivering.[29] Proper nutrition, with protein supplementation (2-3 g/kg body weight daily in adults, and 3-4 g/kg in children) is required. Nasogastric feeding with a soft tube is preferred to parenteral alimentation in alert patients.

Local treatment

Chlorhexidine (0.05%) soaks and antibacterial creams (polymyxin B sulphate or bacitracin) are recommended.[52,55] Other methods of care are petrolatum-impregnated gauze,[52] porcine xenografts,[46] synthetic skin substitutes,[56] and several newer dressings. Viscous lignocaine, topical steroids and an antiseptic mouth wash can be used for oral ulcers to minimize pain and prevent infection.[38] Opthalmological treatment is generally supportive by use of topical antibiotics and lubricants. Ocular lesions should be examined daily by an opthalmologist to prevent sequelae.

Antibiotics

An antibiotic (guided by a sensitivity test) should be given only when signs of infection are observed,e.g. increase in the number of bacteria cultured from the skin with selection of a single strain, sudden drop in fever, oliguria, or delayed gastric emptying.[18] Except for neutropenic or immunocompromised patients, prophylactic therapy is not advocated because of possible crossreactivity with the causative drug and the risk of infection with resistant organisms.[49,55]

Systemic corticosteroids

The use o systemic corticosteroids for the treatment of TEN is controversial. Earlier articles recommended their use on the presumption that an allergic drug reaction was the cause.[57,58] However, it was observed that TEN could occur in patients being treated with steroids for pre-existing diseases and that such patients had no significant survival benefit.[59] Moreover,according to a recent study, long-term steroid therapy delays the onset of TEN (24 d vs 13 d) but does not halt its progression.[60] (this, of course, does not imply that steroids are not effective when given after disease onset) Another study found that steroid-treated patients did not have any reduction in the incidence or severity of ocular complications.[5] Moreover, two other trials[52,61] concluded that steroids worsen the prognosis. This has led to recommendations that the use of steroids should be avoided considering their potential side effects (delayed epithelialization, gastrointestinal bleeding, infection and masking of septicemia), and higher mortality.[11,17,40,54,61] However both these trials have been criticised for methodologic problems.[6,29]

For example, one of them found that steroid-treated patients had a higher mortality(66% vs 33%). But, both SJS and TEN patients were included, treatment was in diffferent time periods, and there was no standardized protocol.[52]

Some articles recommend the use of steroids to reverse any active inflammatory reaction and prevent more extensive epidermal necolysis,[2,4,55,62] and a few case reports describe marked improvement.[62,63] Unfortunately, no blinded or randomized clinical trials of steroids in TEN have been performed that could settle this controversy. Nevertheless, there is agreement on one issue: that steroids are of no use once major skin loss has occurred. Consequently, if a decision is made to use steroids, a high dosage(prednisone 1-2 mg/kg per day orally[55] or dexamethasone 8- 16 mg/kg im or iv)[62] should be administered early in the reaction (preferably as soon as the diagnosis is made) in patients with limited (25% or less of the body surface area) involvement. To minimise side effects, steroids should be given only for a few days. Withdrawal should begin within 2 to 3 days and be completed within 7 to 10 days.[29,62,63]

Other therapies

Most reports of the following therapies describe small series of patients who failed to respond to some other form of therapy and in whom spread of necrolysis was promptly halted by the new agent.[4,39] Since the average duration of progression is less than 4 days in untreated patients, the results of such uncontrolled studies cannot be interpreted.[40] Moreover, because TEN progresses so rapidly, many cases fully evolve before the patients are hospitalized limiting the practical utility of such treatments.[39]

Azathioprine, cyclophosphamide,[64] hyperbaric oxygen, plasmapheresis,[64] and recombinant granulocyte colony-stimulating factor[66] have all been used in TEN. Early treatment with cyclosporine has been claimed to arrest the disease progression. It has been used in the dose of 3-10mg/kg per day for 8-25 days alone or in combination with systemic steroids or granulocyte colony- stimulating factor.[67-71] Its mechanism of action in TEN could be inhibition of primary T-cell activation and expansion of activated cytotoxic T cells. However, these reports need to be confirmed by controlled trials.

Conclusion

Toxic epidermal necrolysis is a rare, often fatal, disease characterized by extensive necrolysis and peeling of the skin resembling scalding, often with multiple organ involvement. It is generally induced by drugs. The SJS-TEN spectrum can be delineated from the erythema multiforme spectrum. Although the pathogenesis of TEN is not known, both CD8 cytotoxic lymphocytes and monocytes-macrophages recruited by specific CD4 lymphocytes are probably involved. Most recent published articles oppose the use of systemic steroids for the treatment of TEN, but some authors recommend early treatment with a high dose for a few days on theoretical grounds. Early treatment with cyclosporine has also been advocated, but no controlled trials have been published.

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