Critical inflammatory dermatoses

Asok Biswas

Abstract

Although relatively uncommon, there exists a group of potentially life threatening inflammatory skin disorders where early diagnosis and treatment is of paramount importance. Clinically, such critical inflammatory dermatoses can fall under the categories of adverse drug reactions, infections or primary skin conditions. The latter may sometimes involve a paraneoplastic dermatosis which can either precede an occult underlying malignancy or signal possible tumour recurrence. Using the standard pattern-based approach to inflammatory skin disorders, this review offers a clinicopathological overview of select examples which are sufficiently distinctive for recognition under the microscope. The importance of clinicopathological correlation in these conditions is perhaps more crucial than anywhere else in dermatopathological practice due to the management implications of many of these diagnoses.

Keywords adverse drug reactions; cutaneous infections; dermatological emergencies; inflammatory skin diseases; paraneoplastic dermatoses

Introduction

It is often erroneously believed that the practice of dermatology no longer involves dealing with life threatening conditions. The worldwide trend of reduction in the number of dermatology inpatient beds and an on-going shift from medical to surgical/cosmetic dermatology in recent years has anything but reinforced this misconception. By association, this conjecture extends to inflammatory dermatopathology where there needs to be a better awareness amongst pathologists of clinicopathological scenarios which can make a difference between loosing and saving a patient's life.

Fortunately, such situations are relatively uncommon in routine practice but are nevertheless critical given their seriousness. This review is largely structured from the viewpoint of the reader potentially approaching a new case of critical inflammatory dermatoses under the microscope and follows the traditional pattern-based approach to inflammatory skin disorders. Only select entities with significant morbidity which tend to get biopsied and are specific enough for clinical and/or pathological recognition will be considered here.

Inflammatory dermatopathology cannot be practiced within a microscopic vacuum and therefore particular emphasis is given to clinicopathological correlation of these entities. As part of the diagnostic exercise, it is useful for the pathologist to have an understanding of the clinical dilemmas which had prompted a skin biopsy in the first place and whether there are potential microscopic pitfalls which one needs to be careful about. From a clinical perspective, critical inflammatory dermatoses can also be divided into three main categories: *allergic reactions*, *infections* and *primary skin disorders*. Such a scheme is followed in the clinicopathological summary presented in Table 1

Asok Biswas *MD FRCPath DipRCPath is a Consultant Dermatopathologist at Western General Hospital, Edinburgh, UK. Conflicts of interest: none declared.*

Interface reactions

Acute graft-versus-host disease

Acute graft-versus-host disease (GvHD) has been defined as the onset of GvHD signs and symptoms in the first 100 days following transplantation. Since skin changes precede other manifestations, dermatologists are often faced with an urgency to establish a diagnosis of acute GvHD in such settings. Severe acute GvHD can profoundly reduce survival and early detection is therefore critical. Clinically, acute GvHD presents as erythematous macules and patches often starting acrally with a tendency to become increasingly generalized.[1]

Histologically, acute GvHD is characterized by basal cell vacuolization, intraepidermal lymphocytosis, keratinocytic necrosis and a mild superficial dermal lymphohistiocytic infiltrate (Figure 1). Additionally, satellite cell necrosis and dyskeratosis involving adnexal epithelium signify target cell injury phenomenon and are useful diagnostic clues. The histopathological spectrum of acute GvHD is reflected by a grading system whereby cases are divided into four groups of increasing severity ranging from only basal vacuolization (grade I) to full thickness epidermal necrosis (grade IV).[2]

Clinicopathological correlation of acute GvHD is poor and there is significant histological overlap with other conditions which present as a skin rash in the post-transplantation period. Superficial dyskeratotic cells, basal vacuolization and sweat gland necrosis without significant dermal inflammation are features of *chemotherapy induced reactions*. *Sub-acute radiation dermatitis* also lacks significant dermal inflammation. *Adverse drug reactions* produce similar changes with the additional presence of superficial apoptotic keratinocytes and dermal eosinophils. The presence of a few dermal eosinophils however does not rule out acute GvHD. *Viral exanthems* tend to show basal vacuolization, scant dyskeratotic keratinocytes, sparse superficial perivascular lymphohistiocytic infiltrate often with extravasation of erythrocytes. *Erythema multiforme* shows histological overlap with acute GvHD but can be readily distinguished clinically. Non-specific changes like rare dyskeratotic keratinocytes, spongiosis, perivascular inflammation and vasodilation are seen in *cutaneous eruption of lymphocyte recovery*.

Given the difficulty in distinguishing early acute GvHD from its clinicopathological mimics, the following minimum criteria have been proposed: basal vacuolization, keratinocyte necrosis (at least four necrotic keratinocytes per linear millimetre of the epidermis) and a mononuclear dermal inflammatory infiltrate associated with lymphocytic exocytosis.[3] Studies have shown that these features are rarely seen during the very early stages (<3 weeks) following transplantation and therefore the value of a skin biopsy to establish a diagnosis of acute GvHD in this period is limited.[2]

Toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN) is an acute life threatening, usually drug-induced mucocutaneous disorder with a mortality rate of 30%. The relationship between TEN, erythema multiforme (EM) and Steven Johnson syndrome (SJS) continues to be

Summary of clinicopathological features of selected critical inflammatory dermatoses

Disease	Clinicopathological issues
Primary dermatoses	
Acute GvHD	One of the many causes of post-transplantation rash. Vacuolar interface dermatitis but clinical correlation is poor.
NME	Association with pancreatic glucagonoma. Superficial epidermal pallor in classical cases.
Early BP/PV	Urticated lesions often predate blisters. Look for eosinophilic spongiosis and recommend IF studies.
Calciphylaxis	Painful necrotic lesions in patients with end-stage renal failure. Small and medium vessel intravascular calcification.
PNP	Associated with haematolymphoid neoplasms. Mix of interface and suprabasal acantholysis but variable and often elusive.
NXG	Association with monoclonal gammopathies. Broad areas of necrobiosis and palisading granulomas.
Sweet's syndrome	May be harbinger of occult malignancy. Diffuse neutrophilic dermatosis with papillary dermal oedema.
Pancreatic panniculitis	Associated with pancreatitis and pancreatic carcinoma. Lobular panniculitis with distinctive enzymatic fat necrosis.
Allergic	
TEN	Early onset drug-induced severe mucocutaneous disorder. Full thickness epidermal necrosis with sparse inflammation.
DRESS	Delayed onset severe drug reaction with systemic symptoms. Histology variable but helpful in excluding TEN.
AGEP	Self-limiting, most commonly triggered by drugs. Subcorneal/intraepidermal pustular dermatitis.
Infective	
SSSS	Often clinically confused with TEN. Subcorneal subtle acantholysis, "absent stratum corneum" clue.
NF	Deep biopsies are needed for diagnosis. Be cautious in cases with myonecrosis and lack of demonstrable bacteria.

AGEP: Acute generalized exanthematous pustulosis; BP: Bullous pemphigoid; DRESS: Drug eruption with eosinophilia and systemic symptoms syndrome; GvHD: Graft-versus-host disease; NME: Necrolytic migratory erythema; NF: Necrotizing fasciitis; NXG: Necrobiotic xanthogranuloma; PNP: Paraneoplastic pemphigus; PV: Pemphigus vulgaris; SSSS: Staphylococcal scalded skin syndrome; TEN: Toxic epidermal necrolysis.

Table 1

a subject of controversy. It is now generally accepted that EM is a separate self-limiting disease and there is also an increasing trend to consider TEN and SJS as variants of the same entity. TEN manifests as generalized tender erythema which rapidly progresses to blistering and extensive sloughing involving more than 30% of the body surface area, mucosal ulceration and multiorgan dysfunction.[4]

Histopathologically, there is overlap between TEN, SJS and EM major with early cases showing a sparse perivascular lymphohistiocytic infiltrate, basal vacuolization and necrotic keratinocytes. Fully developed lesions of TEN show full thickness epidermal necrosis surfaced by a normal stratum corneum and a cell-poor subepidermal blister (Figure 2).[5]

As already mentioned, TEN and *EM* show overlapping histological features although EM tends to show lesser degrees of epidermal necrosis and more dermal inflammation. Some forms of acute cutaneous lupus erythematosus (*LE*) can clinically and histologically mimic TEN. The acronym "ASAP" (*a*cute *s*yndrome of *a*poptotic *p*an-epidermolysis) has been coined for such cases presenting with life threatening hyperacute epidermal injury.[6] Cases reported in the literature as *Rowell's syndrome* probably represent a mild form of the same disease. Histological

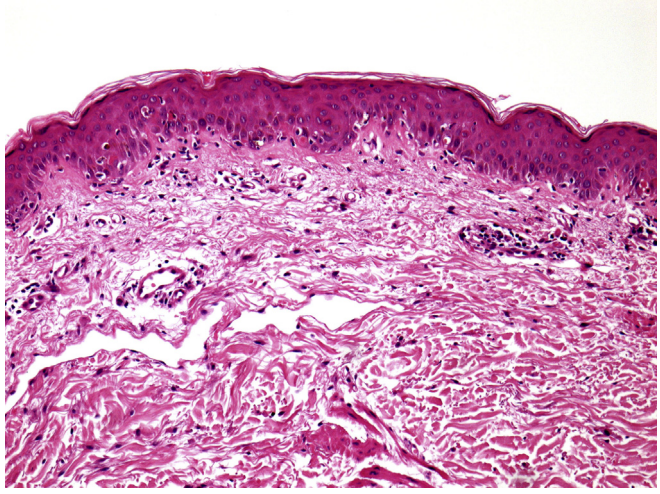

Figure 1 Acute GvHD: mild basal layer vacuolization associated with scattered necrotic keratinocytes some of which are tagged by intraepidermal lymphocytes (Grade 2 changes).

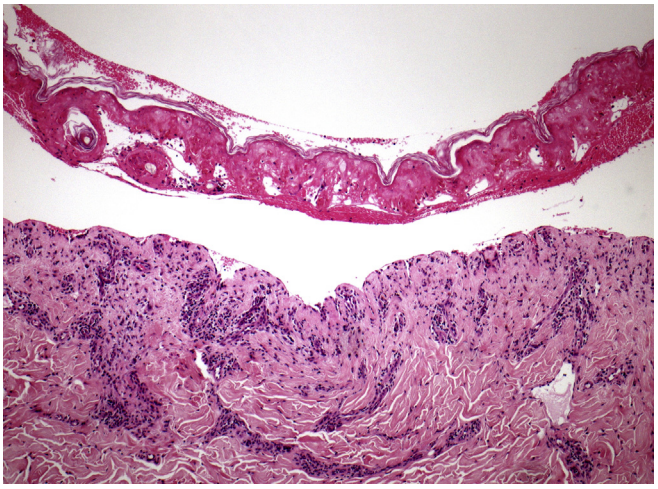

Figure 2 TEN: full thickness epidermal necrosis with dermal-epidermal separation. Note the paucity of dermal inflammation and preservation of the "basket-weave" architecture of the stratum corneum.