Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Review Article

Severe cutaneous adverse drug reactions

Col Rajesh Verma [a], Lt Col Biju Vasudevan [b,*], Lt Col Vijendran Pragasam [b]

[a] Professor & HOD, Department of Dermatology, Command Hospital (Southern Command), Pune 40, India
[b] Classified Specialist, Department of Dermatology, Command Hospital (Southern Command), Pune 40, India

ARTICLE INFO

Article history:
Received 3 July 2012
Accepted 1 January 2013
Available online 17 March 2013

Keywords:
Cutaneous drug reaction
Toxic epidermal necrolysis
Erythroderma
DRESS
Vasculitis

ABSTRACT

Severe cutaneous drug reactions are one of the commonest medical challenges presenting to an emergency room in any hospital. The manifestations range from maculopapular rash to severe systemic symptoms like renal failure and cardiovascular compromise. Toxic epidermal necrolysis, erythroderma, drug rash with eosinophilia and systemic symptoms, acute generalised exanthematous pustulosis and drug induced vasculitis are the common cutaneous drug reactions which can have severe morbidity and even mortality. Careful history taking of the lag period after drug intake and associated symptoms, along with detailed examination of the skin, mucosa and various systems, help in early diagnosis of these reactions. Early stoppage of the incriminating drug, specific therapy including corticosteroids, cyclosporine and intravenous immunoglobulin depending on the case along with supportive therapy and local measures help in salvaging most patients. An overview of these important cutaneous drug reactions along with their management is being reviewed in this article.

Introduction

Adverse drug reactions (ADR) are rated as the fifth leading cause of death among all diseases. Approximately 5–8% of all hospitalisation worldwide is due to ADR. Cutaneous adverse drug reactions (CADR) are the commonest ADR (30–45%) and responsible for about 2% of hospital admissions.[1] Approximately 2–7% of these may be severe.[2] In India, CADR account for 2–5% of all inpatients, while it affects 2.6% of outpatients.[3] CADRs are defined as undesirable changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug. They range from minor exanthematous skin rashes to severe, life threatening ones like Toxic epidermal necrolysis. It can affect all ages and is a global phenomenon. Female sex, increasing age, more number of drugs, immunosuppressed patients and autoimmune disorders are implicated risk factors. We herein describe the common severe cutaneous adverse drug reactions (SCAR) seen in clinical practice. It is important that all medical fraternity be aware of these adverse reactions to correctly diagnose them at an early stage and prevent complications and thereby improve morbidity and mortality due to these conditions.

Toxic epidermal necrolysis [TEN] (Lyell's syndrome)

It is a rare, severe, life threatening idiosyncratic exfoliative disease involving skin and mucosa and was first described by Lyell in 1956. It is a part of a spectrum of disorders including Stevens–Johnson syndrome (SJS). SJS is defined as epidermal

* *Corresponding author*. Tel.: +91 7798225557 (mobile).
E-mail address: biju.deepa@rediffmail.com (B. Vasudevan).
0377-1237/$ – see front matter
http://dx.doi.org/10.1016/j.mjafi.2013.01.007

detachment < 10%, while SJS/TEN overlap is epidermal detachment between 10 and 30% and TEN is defined as epidermal detachment of >30% body surface area. TEN can start denovo or by progression from SJS. The incidence varies between 0.4 and 1.2 cases/million/year worldwide with mortality varying between 14% and 70%.[4]

Aetiology

It is mostly caused by drugs (80–95%). The drugs commonly implicated are antibacterials, anticonvulsants, non-steroidal anti-inflammatory drugs and allopurinol [Table 1]. Rarely infections (especially *Mycoplasma pneumonia*), graft versus host disease (GVHD) and vaccinations have been reported to cause this condition. Risk factors include concomitant Human immunodeficiency virus (HIV) infection, radiotherapy, lymphomas, leukaemias and systemic lupus erythematosus. HIV patients are three times more prone to develop TEN compared to the normal population. Women are more affected than men for unspecified reasons (61–64%). The mean age for occurrence is 46–63 years.

Pathogenesis

It is an immune mediated, HLA class I restricted drug hypersensitivity reaction. The drugs or its toxic metabolites act as haptens providing antigenic stimulus. The stimulated cytotoxic CD8+ T-cells clonally expand and along with the help of perforins, granzyme B, granulysins and cytokines (especially TNFα) mediate the keratinocyte apoptosis leading to epidermal necrosis.[5] TNFα upregulates Fas (death receptors) on effector cells and Fas ligand (FasL) on the keratinocytes leading to their interactions: thus amplifying the apoptotic pathway. Certain specific HLA genotypes have been implicated in TEN caused by carbamazepine and allopurinol, namely HLA-B1502 (in Han Chinese/Asian population) and HLA-B5801 respectively.[6] HLA-B*5701 detected in abacavir hypersensitivity is a recent development.[7] People with altered drug metabolism, especially slow-acetylators, leading to deficient detoxification of intermediary drug metabolites may be more prone to develop TEN.

Clinical features

The lag period (period between drug administration and onset of clinical signs and symptoms) varies from 4 to 28 days usually. Rarely does it occur after 8 weeks. There is a prodromal phase (not always) of fever, cough, malaise, rhinitis and arthralgia followed 2 weeks later by the skin rash. Stinging sensation inside the eyes, conjunctivitis, oral ulcers, dysphagia or genital lesions leading to painful micturition may precede the rash by 1–2 days.

The initial skin rash may be erythematous maculopapular, urticarial, purpuric or targetoid and is specifically tender [Fig. 1a]. They usually first appear on trunk and rapidly spread over 3–4 days to involve the face, neck and extremities. The scalp is usually spared and the palms and soles unlike other drug reactions are not often involved. Later bullous lesions may develop. The lesions rapidly coalesce and lead to sheets of skin peeling off [Fig. 1b]. They leave behind erythematous, oozy, raw lesions which can easily become infected. The Nikolsky's sign is positive i.e gentle lateral pressure on the normal appearing skin adjacent to the lesions leads to epidermal separation.

Painful mucous membrane erosions can occur on the lips, tongue, oral cavity, nasal cavity, pharynx, larynx, conjunctiva, vagina, urethra, gastrointestinal tract and respiratory tract, if the process is not halted. Rarely mucous membranes may not be involved (TEN without spots).

Eye involvement occurs in 80% of patients.[8] The gastrointestinal tract (GIT) can be extensively involved. GIT bleeding and colonic perforation may occur. Upto 30% cases have respiratory involvement.[9] Marked hypoxaemia, pneumonia and sloughing of bronchial epithelium can arise. Other complications include liver function abnormalities, myocarditis, acute tubular necrosis, glomerulonephritis, acute renal failure and pulmonary oedema. Sepsis is the commonest cause of mortality and the main pathogens are *Staphylococcus aureus* and *Pseudomonas*. ARDS can also occur.

Residual effects

Once disease progression is controlled the lesions usually heal without scarring, unless there is secondary infection. Severe mucous membrane involvement can result in fibrosis and strictures of the oesophagus, urethra, vagina and anus. 35% cases have chronic residual eye problems. Dry eyes, photophobia, synechiae and scarring are the common chronic sequelae. Others include trichiasis, distichiasis, symblepharon, entropion, ankyloblepharon, lagophthalmos, corneal ulceration leading to perforation and blindness.[10] Patients may also have residual xerostomia or keratoconjunctivitis mimicking Sjögren's syndrome.

Differential diagnosis

Scalded skin syndrome, pemphigus (esp paraneoplastic) and acute GVHD.

Assessment of severity

The severity and prognosis of TEN is assessed based on the SCORTEN scale, first introduced by Bastuji, et al, in 2000.[11,12] This scale uses seven independent factors which are as given in Table 2. The assessment is done within 24 h of admission of the patient.

Table 1 – List of drugs commonly causing TEN.

Group	Drugs
Antibacterials	Sulphonamides, penicillins, cephalosporins, quinolones, vancomycin
Anticonvulsants	Phenytoin, carbamazepine, phenobarbitone, valproate, lamotrigine
NSAIDs	Phenylbutazone, piroxicam, aspirin, diclofenac
ART drugs	Nevirapine, protease inhibitors, abacavir
ATT drugs	Isoniazid, ethambutol
Anti-gout drug	Allopurinol
Anti-malarials	Chloroquine
Miscellaneous	Chlormezanone