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.

© 2013, Armed Forces Medical Services (AFMS). All rights reserved.

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 © 2013, Armed Forces Medical Services (AFMS). All rights reserved.

<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 TNF α) mediate the keratinocyte apoptosis leading to epidermal necrosis.⁵ TNF α 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

Fig. 1 – Clinical presentation in Toxic epidermal necrolysis. (a) Purpuric lesions on face. (b) Peeling off of skin on the back.

Investigations

The laboratory investigations are mostly non-specific. On histopathology, initially there may be satellite cell necrosis which later progresses to full thickness epidermal necrosis, resulting in the sub epidermal separation [Fig. 2]. There is a very sparse papillary dermal mononuclear cell infiltrate.

The definitive diagnosis is reappearance of the clinical features after rechallenge with the drug. But that should definitely not be undertaken because of the associated complications and high chances of mortality. Desensitisation is also not recommended in this situation. Patch tests are not useful. Lymphocyte transformation tests which measures proliferation of T lymphocytes in vitro, if done within a week of appearance of rash is a reliable technique to demonstrate the causative agent.¹³ The in vitro lymphocyte toxicity assay which measures activity of detoxification enzymes is a reliable test for research purposes.¹⁴

Treatment

Though several treatment protocols exist, none have been formalised by randomised controlled trials. The burns unit is the ideal set up for management and if not available, the ICU. Prompt and early diagnosis is the key to management as disease progression can be prevented and complications can be restricted. All specific treatment modalities also are successful only if started at the earliest sign of the disease. There are three cornerstones for therapy namely (1) early withdrawal/elimination of drug (2) supportive therapy and (3) specific therapy

Table 2 – SCORTEN assessment.		
Factor	Score = 0	Score = 1
Age	≤40 yrs	>40 yrs
% of BSA with epidermal detachment	≤10%	>10%
Heart rate	≤120	>120
Presence of malignancy	No	Yes
Blood urea nitrogen	≤28 mg/dl	>28 mg/dl
Blood glucose (random)	≤252 mg/dl	>252 mg/dl
Serum bicarbonate	≤20 mEq/L	>20 mEq/L
Total	0 points	7 points
Score	Mortality rate	
0–1	3%	
2	12%	
3	35%	
4	58%	
≥5	90%

Fig. 2 – Histopathology of early lesion of Toxic epidermal necrolysis revealing spongiosis, basal cell vacuolisation and satellite cell necrosis progressing to partial thickness epidermal necrosis.[H & E stain – 40×].

Table 3 – General supportive therapy in TEN.

Factor	Supportive measures
Prevent trauma to skin	1. Air fluidised beds – also prevents bed sores
Prevent hypothermia	1. Maintaining ambient temperature (30–32 °C) 2. Warmed fluids
Provide pain relief	1. Adequate analgesia, anxiolytics (morphine, diazepam)
Prevent infection	1. Repeated cultures from lesions and sites of catheters 2. Topical antibiotics and antibiotic dressings 3. Avoid invasive techniques – Use peripheral wide bore IV access and avoid central line whenever possible 4. Prophylactic antibiotics not indicated 5. Use antibiotics in culture proven sepsis, neutropenia or increase in single strain bacterial counts on swabs 6. Antibiotics given at higher doses than usual in view of large protein loss 7. Reverse isolation techniques of nursing
Nutrition	1. Early and continuous enteral nutrition reduces risk of stress ulcer 2. Albumin infusions if serum albumin is low 3. Calories – 1500 calories over first 24 h and increased gradually by 500 calories to about 3500–4000 calories/day
Fluid requirement	1. 2/3rd of that of burns patients 2. 4–6 L/day in the first few days when >35–40% BSA is affected. 0.5% NaCl is the fluid of choice

1. Elimination of drug – Prompt drug withdrawal is the most important factor in limiting damage caused by the drug. Studies claim a reduction of mortality from 26% to 5% in drugs with short half-life (<24 h), if drug is withdrawn on first appearance of skin lesions.¹⁵ Removal of both drug and inducing cytokines by plasmapheresis is another method of restricting progression of disease. Other filtration methods like dialysis and other extracorporeal blood purification techniques are useful especially in long acting drugs. Another important mortality predictor is the time interval between initial skin rash and admission to a specialised centre. It has been seen that 100% patients admitted within 5 days of onset of symptoms survive, but mortality increases with every passing day of delay.¹⁶

2. Supportive care

a. Dressings – Bland dressings like petrolatum gauze are usually preferred. Biobrane, a temporary semi-synthetic skin substitute dressing is associated with reduced pain, decreased fluid loss and faster re-epithelialisation.¹⁷ Biologic dressings like porcine xenografts or human skin allografts can also be used. Silver nitrate impregnated gauzes along with topical antibiotics have been found to cover wounds without risk of immune reactions and found to

maintain the moist wound environment, speeding up re-epithelialisation and decreasing chance of infection. White petrolatum is ideal for lips while chlorhexidine mouth washes help in maintaining good oral hygiene and preventing secondary infection. It is recommended that all intravenous and other invasive lines be sutured at site without applying adhesive tapes to prevent further skin damage.

b. Rest of the supportive therapy is as given in [Tables 3 and 4](#).

3. Specific therapy – As the process is mainly considered to be immunological, immunosuppressants are the specific treatments available.

a. Corticosteroids – Nothing is more controversial than the use of systemic corticosteroids in TEN.¹⁸ Few reports have shown improvement with steroid use¹⁹; however, others show better prognosis in patients treated without steroids compared to those treated with steroids.²⁰ Steroids have beneficial immunosuppressive, anti-inflammatory and antiapoptotic effects. Their use is however risky due to increased chances of severe infections, GI ulcers, prolonged wound healing and masking of early signs of sepsis. If at all they are to be used, they have to be started within first 48 h of

Table 4 – Systemic support therapy in TEN.

Factor	Protective measures
Care of the eye	1. Use of glass rods daily for sweeping the fornices to break the forming adhesions 2. Lubricants, topical antibiotics and steroids should be used judiciously 3. Topical preparation similar pharmacologically to the incriminated drug should not be given 4. Amniotic membrane transplants- for damaged surfaces 5. Topical bevacizumab (humanised IgG monoclonal antibody) which binds to vascular endothelial growth factor – for preventing chronic sequelae 6. Soft contact lenses – for persistent corneal defects
Respiratory system	1. Use of aerosols and physiotherapy to prevent pneumonitis 2. If trachea and bronchi get involved – intubation and finally mechanical ventilation
GI tract	Antacids – reduce chances of GI bleeding

appearance of rash and withdrawn in a total of 3–5 days.²¹ Short term supra-pharmacological doses of steroids like Dexamethasone 1.5–2 mg/kg IV for 3 consecutive days and methylprednisolone are better than prolonged dose of oral corticosteroids.

- b. Cyclosporine – It is presently the drug found to have maximum benefits in treatment of TEN. It's strong immunosuppressive action by blocking T cell activation and tumour necrosis factor alpha (TNF α), as also the antiapoptotic effect are probably the reason for its increased benefits. The time taken to arrest disease progression is 24–36 h and complete re-epithelialisation is also found to be faster.²² Doses of 3–5 mg/kg daily IV or oral for a duration of 8–24 days (till re-epithelialisation) followed by weaning off the dose in another 2 weeks is recommended.²³
- c. Intravenous immunoglobulin (IVIg) – It blocks Fas–FasL interactions between effector cells and keratinocytes and prevents apoptosis of keratinocytes. There are studies which report reduced mortality with use of IVIg,²⁴ but also reports which say that they do not improve outcome.²⁵ Despite these conflicting reports, many clinicians worldwide are still using IVIg as a first line treatment based on clinical and laboratory evidence and also because of the good safety profile. In patients where the disease is progressing, it is advocated to use IVIg for halting progression and to speed up re-epithelialisation. Doses of 0.2–0.75 g/kg daily for 4 days is recommended, with the higher doses being preferred nowadays. They should be avoided in cases of renal insufficiency, cardiac abnormalities, patients with risk of thromboembolism and in IgA deficiency. They are the drugs of choice when TEN occurs in HIV patients.
- d. Other therapies – Cyclophosphamide, Infliximab,²⁶ N acetyl cysteine, Pentoxifylline, Oral Zinc, Granulocyte colony stimulating factor (G-CSF) and many other drugs have been tried in various studies, though no concrete evidence for their use has been proposed.

Drug induced erythroderma

It is characterised by widespread, generalised erythema and desquamation extending to >90% of BSA. Compared to other causes of erythroderma, the drug induced cases are sudden in onset, rapidly progressive, and resolve faster.²⁷ Drugs commonly incriminated are sulphonamides, penicillin, isoniazid, antimalarials, allopurinol, phenytoin, omeprazole, captopril and vancomycin. Drug induced erythroderma is seen twice more often in males than in females and is definitely more common among elderly.

The complex interaction between cytokines and cellular adhesion molecules results in highly increased epidermal turnover leading to reduced transit time of keratinocytes through epidermis causing loss of cellular material from the surface.

Lag period is 1–2 weeks. It begins as erythema and exudation in the flexures and progresses to generalised scaling

[Fig. 3]. Pruritus, lymphadenopathy, hepatosplenomegaly, pedal and facial oedema, hypothermia, pneumonia, fluid, protein and electrolyte loss and infection can occur. Basal metabolic rate is usually high with increased catabolism. The excessive protein loss by means of scaling and leakage through skin, increased plasma volume causing haemodilution and hypermetabolism, all contribute towards hypoalbuminemia and therefore severe oedema. Increased cutaneous blood flow leading to high output cardiac failure is a dreaded complication. The nails may be thick, dry, lustreless, and show ridging. The rash takes 4–6 weeks to resolve even after withdrawal of drug.

Common lab abnormalities are anaemia, leucocytosis with eosinophilia, increased erythrocyte sedimentation rate, decreased serum albumin levels and increased uric acid levels. Increased IgE levels may be there. Biopsy reports are nonspecific including hyperkeratosis, parakeratosis, acanthosis along with a chronic mainly perivascular inflammatory infiltrate with few eosinophils [Fig. 4].

Emollients, maintenance of fluid and electrolyte balance, nutritious protein-rich diet, and antihistamines for pruritus are advised. Local skin care measures such as starch baths and wet dressings for crusted sites followed by the application of bland emollients and low-potency corticosteroids are in order. Secondary infections should be treated with antibiotics. The patient should be placed in a regulated environmental temperature to avoid cooling and overheating. Systemic steroids are required when conservative therapy is ineffective.

Fig. 3 – Extensive exfoliation of the skin in erythroderma.

Fig. 4 – Histopathology of drug induced erythroderma revealing parakeratosis, hyperkeratosis and perivascular dermal infiltrate. [H & E stain – 10×].

Drug rash with eosinophilia and systemic symptoms (DRESS)

Also called Drug hypersensitivity syndrome (DHS) or drug induced delayed multiorgan hypersensitivity syndrome (DIDMOHS), it is another severe idiosyncratic drug reaction associated with multiorgan involvement. Incidence of DHS is 1/1000–1/10,000 drug exposures. The commonest cause is anti- convulsants.²⁸ Here cross reaction can occur between all the aromatic anti- convulsants namely phenytoin, phenobarbitone, carbamazepine and lamotrigine. Other drugs incriminated include dapsone, sulphonamides, allopurinol, minocycline, terbinafine, azathioprine, captopril, nevirapine, abacavir and sulfasalazine.²⁹

Pathogenesis

The main pathogenesis in the anticonvulsant hypersensitivity syndrome is the inability to detoxify intermediate drug metabolites and this is genetically determined. However there may be other immune mechanisms in play which are not yet fully determined. Reactivation of herpesvirus-6 may occur during the course of the disease.³⁰

Clinical features

A characteristic triad of fever, rash and internal organ involvement is considered diagnostic. The symptoms develop 2–6 weeks after intake of drug, much later than other drug reactions. However Dapsone can cause early reactions. When re-exposed to same drug, the reaction can occur as early as within 24 h.

The sequence is usually fever followed by skin rash, then lymphadenopathy, pharyngitis and finally systemic involvement. Fever is high grade, ranging from 38 to 40 °C and is persistent. The skin lesions are in the form of maculopapular

rashes. However they may develop features of erythroderma or blistering. Initially the face, upper extremities and upper trunk are involved which generalisation in later stages. Facial oedema is prominent. Lymphadenopathy is tender with initial involvement of cervical nodes followed by generalised lymphadenopathy. Hepatitis is present in about 50% cases. The involvement can present as mild transaminitis to fulminant hepatic necrosis. It is a high risk factor for mortality. Kidney (interstitial nephritis) and lungs (pneumonitis) are involved in 10% cases each. 10% cases also develop hypothyroidism after reaction settles. Severe rhabdomyolysis, myopathy and pancreatitis have also been reported. Mortality is about 10%.³¹ The skin rashes and systemic involvement can last very long.

Differential diagnosis other than lymphomas includes viral exanthems, hypereosinophilic syndrome and pseudolymphomas.

Investigations- Eosinophilia is a prominent diagnostic feature. Atypical lymphocytes present in the peripheral blood smear create a diagnostic confusion with lymphomas. Neutropenia, thrombocytopaenia, agranulocytosis and haemolytic anaemia can occur. Histopathology is nonspecific with a dense lymphocytic infiltrate in the superficial dermis associated with dermal oedema. The lymphocyte toxicity assay is probably the only specific test available for diagnosis.

There are mainly two diagnostic criteria for DHS, the RegiSCAR and the Japanese. In the RegiSCAR, three out of 5 criteria are required [Table 5] while in the Japanese scale, if all seven criteria are present, it is a classical DHS and if at least 5 criteria are present, it is an atypical DHS [Table 6].³²

Treatment

Oral Prednisolone in a dose of 1–2 mg/kg is drug of choice, but it is to be continued for a prolonged period of 2–3 months. Valproic acid, benzodiazepine and gabapentin are ideal replacement for drugs causing anticonvulsant hypersensitivity syndrome. Haematological, hepatic and renal parameters must be monitored. Supportive care with accurate fluid and electrolyte balance is a must. Topical steroids are helpful for cutaneous manifestations as are antihistamines. Patient should not be prescribed the same or related drug. First degree relatives should be counselled about increased risk. A lymphocyte toxicity assay can be done for relatives to confirm increased susceptibility.

Table 5 – RegiSCAR criteria for DRESS absolute criteria – 1. hospitalisation 2. reaction suspected to be drug related.

Sr no	Feature
1	Acute skin rash
2	Atleast one internal organ involvement
3	Lymph node enlargement of atleast 2 sites
4	One of the following blood count abnormalities <ul style="list-style-type: none"> a. Lymphocytosis/lymphopenia b. Eosinophilia c. Thrombocytopaenia
5	Fever > 38 °C

Table 6 – Diagnostic features of DRESS: Japanese scale.

Sr no	Feature
1	Maculopapular rash atleast 3 weeks after starting drug
2	Clinical symptoms lasting atleast 2 weeks after discontinuation of drug
3	Fever > 38 °C
4	Raised LFT (Serum ALT > 100 IU/L)
5	Abnormal blood counts, atleast one of: <ol style="list-style-type: none"> WBC count > 11,000/mm³ Atypical lymphocytes > 5% Eosinophilia > 1500/mm³
6	Lymphadenopathy
7	HHV-6/EBV/CMV reactivation

Acute generalised exanthematous pustulosis (AGEP)

First described in 1968 by Baker and Ryan, it is characterised by an acute febrile illness with a rapidly progressive generalised pustular skin eruption. The most striking feature of AGEP is the short interval between the drug administration and the onset of the disease.³³ The presence of eosinophils in the inflammatory infiltrate is a helpful pointer to a drug cause. Incidence is 1–5 cases/million/year. The main pathogenesis is a hypersensitivity reaction. It is postulated that initial vesiculation may be mediated by keratinolytic cytokines like perforins, granzymes and FasL, all produced by the drug specific CD4+ T-cells infiltrating epidermis. These cells further express IL-8, which leads to subsequent infiltration by neutrophils and causes pustule formation. Activation of protein kinases also induces keratinocyte apoptosis and inflammation through independent signalling pathways. Certain viral infections like parvovirus are also implicated.³⁴ The drugs causing AGEP are aminopenicillins, macrolides, quinolones, terbinafine, carbamazepine, diltiazem and antimalarials.³⁵ The characteristic features of AGEP are:

- Skin rash- Small non follicular pustules on background of erythema appearing mainly in folds namely neck, axilla and groin and also trunk and upper extremities. There is associated burning sensation and generalised oedema, especially on face.
- Fever > 38° appearing on same day of rash
- Increased neutrophil count
- Histopathology shows subcorneal pustules, papillary dermal oedema and perivascular polymorphic infiltrate [Fig. 5].
- Spontaneous resolution in <15 days

The lag period is less than 48 h. The disease is usually self-limiting with fever and pustules lasting 7–10 days, followed later by desquamation. Mucosal involvement is reported in only 20% cases and is usually restricted to a single mucosa. Leucocytosis and neutrophilia are present in 90% patients. Transient renal failure, hepatitis, eosinophilia and hypocalcemia can occur. Patch testing is more informative in AGEP than in other severe cutaneous reactions. Topical steroids and

Fig. 5 – Histopathology of drug induced AGEP lesion revealing loss of stratum corneum and subcorneal necrotic material along with neutrophils. [H & E stain – 40×].

oral antihistaminics are the drugs of choice in mild cases. Systemic corticosteroids and Methotrexate are the preferred drugs of choice for treatment of severe cases.

Drug induced angioedema

It is a type I hypersensitivity reaction characterised by dermal and subcutaneous oedema due to increased vascular permeability and fluid leakage secondary to vascular reaction. It can be accompanied by urticaria. Face (esp eyelids and lips), oral mucosa, pharynx, larynx and genitalia can also be affected. When submucosa is also involved, it can be dangerous. Involvement of the respiratory tract can cause acute respiratory distress and airway obstruction, sometimes even death. NSAIDs, ACE inhibitors, angiotensin receptor blockers and penicillins are the commonest drugs implicated.³⁶ It is seen in various studies that angioedema occurs in approximately 2–10 of every 10,000 naive ACE inhibitor users. The reaction occurs mostly during first week of therapy, usually within hours of initial dose, but late reactions can also occur. Pathogenesis is due increased release of bradykinin. H1 antihistaminics are the drugs of choice. However when severe, Oral or IV corticosteroids along with IM Adrenaline may have to be administered.

Drug induced vasculitis

Approximately 10% cases of cutaneous vasculitis are drug induced. It is probably a type III hypersensitivity reaction (immune complex deposition) of post capillary blood vessels. In this condition antibodies which are formed against the

drugs (haptens), act on the vascular endothelium and vascular wall leading to vasculitis. Palpable purpura in lower extremities, hemorrhagic blisters, ulcers, Raynaud's and digital necrosis may all occur. Drug induced cutaneous necrotising vasculitis may also involve internal organs, including the heart, liver, joints and kidneys with fatal results. It usually occurs 1–3 weeks after drug intake. The main drugs implicated are NSAIDs, thiazides, aspirin, allopurinol, penicillin, cephalosporins, propylthiouracil, quinolones and sulphonamides. Most of the cutaneous vasculitis induced by drugs are leukocytoclastic in morphology. Other forms of vasculitis which can also be caused by drugs are Henoch–Schönlein purpura, polyarteritis nodosa, Wegener's granulomatosis and Churg–Strauss vasculitis. There exists no significant difference in either the clinical presentation or serologic abnormalities or pathologic findings between drug induced and idiopathic forms of these vasculitides. Drug induced vasculitis patients show a higher rate of ANCA, ACLA, ANA and antihistone antibodies with low C4 values as compared to idiopathic. Histologically endothelial cell swelling, fibrinoid necrosis, a neutrophilic infiltrate in and around blood vessels along with nuclear dust is found [Fig. 6]. Direct immunofluorescence reveals deposits of IgM, C3 and fibrin within and around capillaries.

Withdrawal of drug is therapeutic in most cases. Antihistamines along with non-steroidal anti-inflammatory drugs generally reduce the arthralgias and myalgias. Only severe disease warrant oral corticosteroids.

Approach to a patient with SCAR

The first aspect is to have suspicion of possibility of drug reaction. Any new skin rash in patients with no history of skin disorders should raise a suspicion. The offending drug has to be identified quickly. When a patient is on multiple drugs, careful history taking can usually identify the drug causing reaction. Prior similar reactions give definitive clues. The incriminating drug should ideally be identified before

Fig. 6 – Histopathology of drug induced vasculitis revealing infiltration and destruction of vessel walls. [H & E stain – 40×].

Table 7 – Assessment of drug causality.

Sr no	Factors
1	Duration between beginning of drug usage and onset of the adverse reaction
2	Was drug present in the body before the onset of adverse reaction? Factors considered: <ol style="list-style-type: none"> Drug's half-life Patient's liver and kidney function
3	Results of prechallenge/rechallenge and dechallenge
4	Relative risk of drug in causing reactions (updated literature review of drug reactions to specific drugs)
5	Other causes for the reaction ruled out

instituting any specific therapy. Other similar looking skin conditions have to be ruled out. Stop the offending drug and institute other measures as explained. Patient and first degree relatives should be counselled to avoid causative and related drugs. Patients should be advised to carry a card hung around their necks or in their wallets identifying their drug allergies and reactions. The causality of adverse drug reaction to a particular drug can be assessed by mainly two scales: World Health Organization's ADR probability scale,³⁷ and Naranjo's scale.³⁸ An algorithm to assess drug causality has been devised which helps in identifying the responsible drug [Table 7].³⁹

Conclusion

In conclusion, prompt diagnosis, immediate withdrawal of incriminated drug, early referral to a specialised centre, aggressive management, good supportive care with fluid and nutritional support, multidisciplinary team work, and control of infection are crucial in minimising the morbidity and rate of mortality.

Conflicts of interest

All authors have none to declare.

REFERENCES

- Valeyrie-Allanore L, Sassolas B, Roujeau JC. Drug-induced skin, nail and hair disorders. *Drug Saf.* 2007;30:1011–1030.
- Ajayi FO, Sun H, Perry J. Adverse drug reactions: a review of relevant factors. *J Clin Pharmacol.* 2000;40:1093–1101.
- Chatterjee S, Ghosh AP, Barbhuiya J, Dey SK. Adverse cutaneous drug reactions: a one year survey at a dermatology outpatient clinic of a tertiary care hospital. *Indian J Pharmacol.* 2006;38:429–431.
- Trent J, Halem M, French LE, Kerdell F. Toxic epidermal necrolysis and intravenous immunoglobulin: a review. *Semin Cutan Med Surg.* 2006;25:91–93.
- Chung WH, Hung SI, Yang JY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens–Johnson syndrome and toxic epidermal necrolysis. *Nat Med.* 2008;14:1343–1350.

6. Chan HL. Observations on drug-induced toxic epidermal necrolysis in Singapore. *J Am Acad Dermatol*. 1984;10:973–978.
7. Kaniwa N, Saito Y, Aihara M, et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens–Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics*. 2008;9:1617–1622.
8. Power WJ, Ghoraiishi M, Merayo-Llones J, Neves RA, Foster CS. Analysis of the acute ophthalmic manifestations of the erythema multiforme/Stevens–Johnson syndrome/toxic epidermal necrolysis disease spectrum. *Ophthalmology*. 1995;102:1669–1676.
9. Sugimoto Y, Mizutani H, Sato T, et al. Toxic epidermal necrolysis with severe gastrointestinal mucosal cell death: a patient who excreted long tubes of dead intestinal epithelium. *J Dermatol*. 1998;25:533–538.
10. Haber J, Hopman W, Gomez M, Cartotto R. Late outcomes in adult survivors of toxic epidermal necrolysis after treatment in a burn center. *J Burn Care Rehabil*. 2005;26:33–41.
11. Yip LW, Thong BY, Lim J, et al. Ocular manifestations and complications of Stevens–Johnson syndrome and toxic epidermal necrolysis: an Asian series. *Allergy*. 2007;62:527–531.
12. Carrotto R, Mayich M, Nickerson D, Gomez M. SCORTEN accurately predicts mortality among toxic epidermal necrolysis patients treated in a burn center. *J Burn Care Res*. 2008;29:141–146.
13. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*. 2000;115:149–153.
14. Kano Y, Hirahara K, Mitsuyama Y, Takahashi R, Shiohara T. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. *Allergy*. 2007;62:1439–1444.
15. Neuman MG, Malkiewicz IM, Shear NH. A novel lymphocyte toxicity assay to assess drug hypersensitivity syndromes. *Clin Biochem*. 2000;33:517–524.
16. Garcia-Doval I, LeCleach L, Bocquet H, et al. Toxic epidermal necrolysis and Stevens–Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol*. 2000;136:323–327.
17. Endorf FW, Cancio LC, Gibran NS. Toxic epidermal necrolysis clinical guidelines. *J Burn Care Res*. 2008;29:706–712.
18. Worswick S, Cotliar J. Stevens–Johnson syndrome and toxic epidermal necrolysis: a review of treatment options. *Dermatol Ther*. 2011;24:207–218.
19. Lehrer-Bell KA, Kirsner RS, Tallman PG, et al. Treatment of the cutaneous involvement in Stevens–Johnson syndrome and toxic epidermal necrolysis with silver nitrate impregnated dressings. *Arch Dermatol*. 1998;134:877–879.
20. Tripathi A, Ditto AM, Grammer LC, et al. Corticosteroid therapy in an additional 13 cases of Stevens–Johnson syndrome: a total series of 67 cases. *Allergy Asthma Proc*. 2000;21:101–105.
21. Halebian PH, Corder VJ, Madden MR, Finklestein JL, Shires GT. Improved burn centre survival of patients with toxic epidermal necrolysis managed without corticosteroids. *Ann Surg*. 1986;204:503–512.
22. Chave TA, Mortimer NJ, Sladden MJ, Hall AP, Hutchinson PE. Toxic epidermal necrolysis: current evidence, practical management and future directions. *Br J Dermatol*. 2005;153:241–253.
23. Arevalo JM, Lorente JA, Gonzalez-Herrada C, Jimenez-Reyes J. Management of toxic epidermal necrolysis with cyclosporin A. *J Trauma*. 2000;48:473–478.
24. Mockenhaupt M, Viboud C, Dunant A, et al. Stevens–Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR study. *J Invest Dermatol*. 2008;128:35–44.
25. French LE, Trent JT, Kerdel FA. Use of intravenous immunoglobulin in toxic epidermal necrolysis and Stevens–Johnson syndrome: our current understanding. *Int Immunopharmacol*. 2006;6:543–549.
26. Prins C, Gelfand EW, French LE. Intravenous immunoglobulin: properties, mode of action and practical use in dermatology. *Acta Derm Venereol*. 2007;87:206–218.
27. Khaled A, Sellami A, Fazaa B, Kharfi M, Zeglaoui F, Kamoun MR. Acquired erythroderma in adults: a clinical and prognostic study. *J Eur Acad Dermatol Venereol*. 2010;24:781–788.
28. Knowles SR, Shear NH. Recognition and management of severe cutaneous drug reactions. *Dermatol Clin*. 2007;25:245–253.
29. Kumari R, Timshina DK, Thappa DM. Drug hypersensitivity syndrome. *Indian J Dermatol Venereol Leprol*. 2011;77:7–15.
30. Shiohara T, Iijima M, Ikezawa Z, et al. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. *Br J Dermatol*. 2007;156:1083–1084.
31. Walsh SA, Creamer D. Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking. *Clin Exp Dermatol*. 2011;36:6–11.
32. Tohyama M, Hashimoto K, Yasukawa M, et al. Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome. *Br J Dermatol*. 2007;157:934–940.
33. Sidoroff A, Dunant A, Viboud C, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)- results of a multinational case-control study (EuroSCAR). *Br J Dermatol*. 2007;157:989–996.
34. Ofuji S, Yamamoto O. Acute generalized exanthematous pustulosis associated with a human parvovirus B19 infection. *J Dermatol*. 2007;34:121–123.
35. Taberner R, Puig L, Gilaberte M, et al. Acute generalized exanthematous pustulosis induced by terbinafine. *Eur J Dermatol*. 2003;13:313–314.
36. Femiano F, Lanza A, Buonaiuto C, et al. Oral manifestations of adverse drug reactions: guidelines. *J Eur Acad Dermatol Venereol*. 2008;22:681–691.
37. Hedner T, Samuelsson O, Lunde H, et al. Angio-oedema in relation to treatment with angiotensin converting enzyme inhibitors. *BMJ*. 1992;304:941–946.
38. World Health Organization. *Technical Report Series 498*. Geneva: World Health Organization; 1972.
39. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239–245.