Cutaneous adverse drug reactions

Idiosyncratic and potentially serious cutaneous adverse drug reactions (CADRs), although relatively rare, account for significant morbidity and mortality.

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Early recognition and withdrawal of the offending drug improves outcomes in the management of severe cutaneous adverse drug reactions (CADRs).[1] How can the diagnosis be made and what tools are useful in assigning causality? In this article I will discuss the clinical features of certain characteristic CADRs and the laboratory tests that may expedite the diagnosis.

Herbal and homeopathic products, often considered 'natural' and non-toxic, can also cause adverse drug reactions.

A detailed clinical history is crucial in establishing a diagnosis in a possible CADR. However, the history can sometimes be incomplete, imprecise or outright misleading. It is therefore important for the clinician to have the necessary insight to obtain an accurate and detailed history. It should include all prescribed medications, including those obtained from friends or relatives, over-the-counter preparations, homeopathic preparations and herbal products. Herbal and homeopathic products, often considered 'natural' and non-toxic can also cause adverse drug reactions.[2] History taking should be directed towards establishing a temporal relationship between the use of the drug(s) and the development of the adverse event(s) as well as treatment interruptions, responses to drug withdrawal and rechallenge. This information together with the known side-effect profile of the drug(s) will help in ascribing causality.[3]

A good clinical examination is clearly fundamental, as this frequently provides an accurate diagnosis. The skin reacts in a limited number of ways to different forms of insult, including infections and inflammatory conditions. It is therefore important to consider other aetiologies for the eruption when making a diagnosis. The systematic general examination should include a detailed description of the morphology and distribution of the eruption and a complete evaluation of the skin and its appendages, including all the mucous membranes.

A particular drug can cause different types of CADR, although some drugs are more likely to cause a particular type of CADR. Attributing causality on these premises should be done with caution. In establishing causality, the current gold standard is to rechallenge with the offending drug. However, rechallenge increases the risk of inducing additional and potentially fatal CADRs and is best done in a specialised centre under close monitoring. Rechallenge is only indicated if a drug essential for a patient's management is thought to be responsible for the reaction.

Some clinical features suggest severe CADR (Table I).

Table I. Danger signs in CADR

- Fever and facial oedema
- Hepatitis and eosinophilia
- Mucositis
- In cases of vasculitis, haematuria and proteinuria
- In SJS/TEN hypotension, diarrhoea, hypothermia and confusion suggest septicaemia

Morbilliform drug eruption

Morbilliform (measles-like) eruption or maculopapular exanthems are the most common presentation of a CADR, accounting for 95% of all cases.[4] The initial presentation, 7 - 14 days after first exposure to the offending drug, is erythematous macules and papules starting centrally and spreading peripherally (Fig. 1). In severe cases the lesions become confluent, leading to erythroderma.

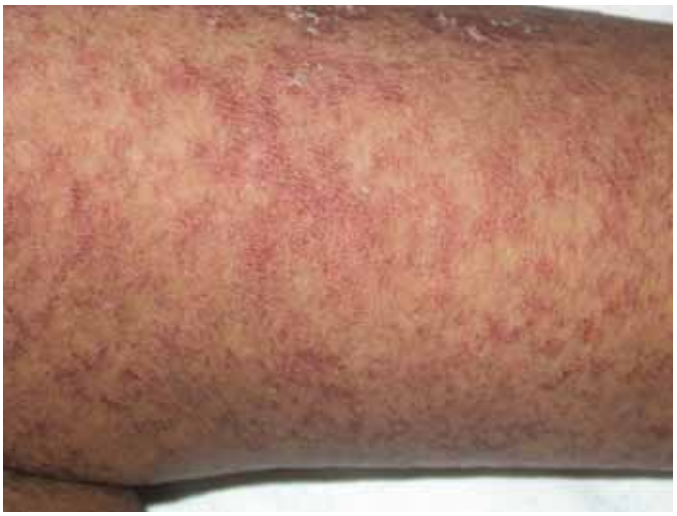

Fig.1. Morbilliform exanthem showing scaly areas that are resolving.

In a great majority of cases, morbilliform drug eruptions are self-limiting but they can be the initial presentation of more serious reactions such as Stevens-Johnson and drug hypersensitivity syndromes.[3] It is thus important for the clinician to distinguish between self-limiting morbilliform drug eruptions that resolve solely with the withdrawal of the offending drug and the life-threatening reactions.

It is important to note that in situations where there is a limited arsenal of effective drugs, e.g. antiretrovirals and antituberculous drugs, one can sometimes continue the offending drug in a case of a morbilliform drug reaction, with close monitoring to rule out progression to severe CADR. Sulphonamides, antituberculous drugs, beta lactam antibiotics, quinolones and allopurinol are commonly implicated drugs.[5-7] As the name implies, the rash resembles a viral exanthem and this, as well as other inflammatory conditions with a similar presentation, should be excluded.

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Drug hypersensitivity syndrome

Also known as drug rash with eosinophilia and systemic symptoms (DRESS), drug hypersensitivity syndrome (DHS) is a severe

disease, with a mortality of up to 8%.[8] It is characterised by a long latency period (>3 weeks), fever, oedema (particularly facial), lymphadenopathy, leukocyte abnormalities (leucocytosis, eosinophilia and/or atypical lymphocytosis) and hepatitis (Fig. 2). Less frequently nephritis, pancreatitis, pneumonitis and myocarditis may be found.[9] The eruption is often urticaria-like and maculopapular, but vesicles, pustules, cheilitis, purpura, targetoid lesions and erythroderma have been reported.[10] The severity of the rash does not necessarily reflect the extent of systemic involvement. The presence of a fever and facial oedema should increase suspicion of systemic disease.[11] Longstanding severe lesions are characterised by extensive scaling referred to as exfoliative dermatitis (Fig. 3). The clinical symptoms often persist for up to 2 weeks after withdrawal of the offending drug.

Fig. 2. Facial oedema on a background of erythema in DHS.

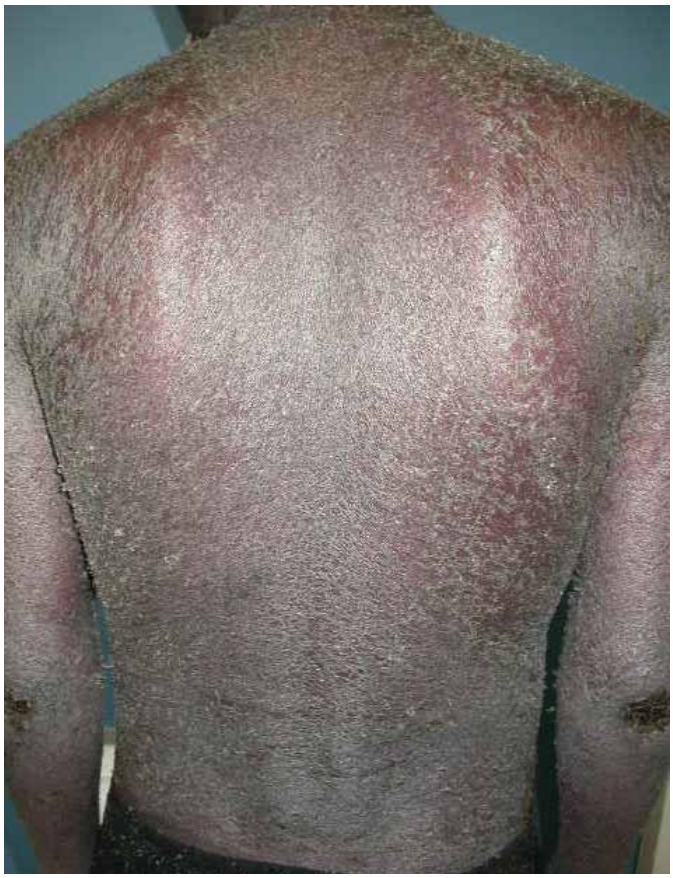

Fig. 3. Exfoliative dermatitis on a background of erythroderma.

The most common culprit drugs in our experience are sulphonamides, antituberculous drugs, antiepileptics and antiretrovirals. In the literature allopurinol is frequently implicated. DHS is generally treated with potent topical steroids but if there is systemic involvement moderate to high-dose oral corticosteroids may be required.

Stevens-Johnson syndrome and toxic epidermal necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered as a spectrum of the same disease. In SJS there is <10% of epidermal detachment and in TEN there is >30%. SJS/TEN overlap lies between these two extremes.[12] The early symptoms of fever, malaise, cough, stinging eyes and a sore throat can be confused with an upper respiratory tract infection. This rapidly progresses to an exanthem of macules and targetoid lesions, epidermal detachment and mucositis. Early painful erythema and blisters of the palms and soles are a hallmark of SJS and TEN (Figs 4 - 6).

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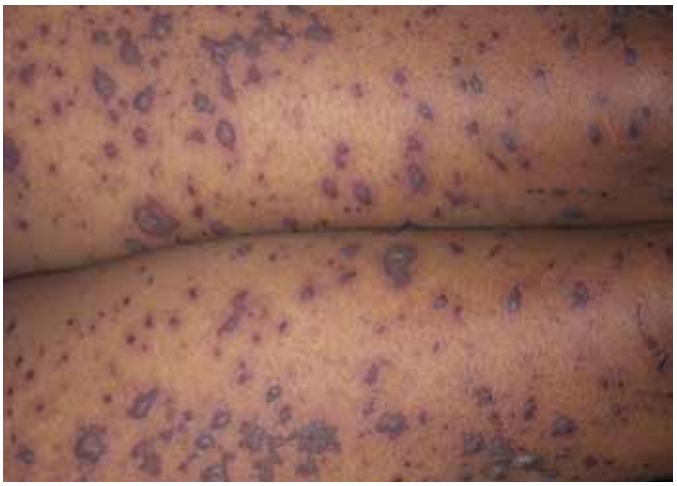

Fig. 4. Atypical targets and early blisters in SJS/TEN.

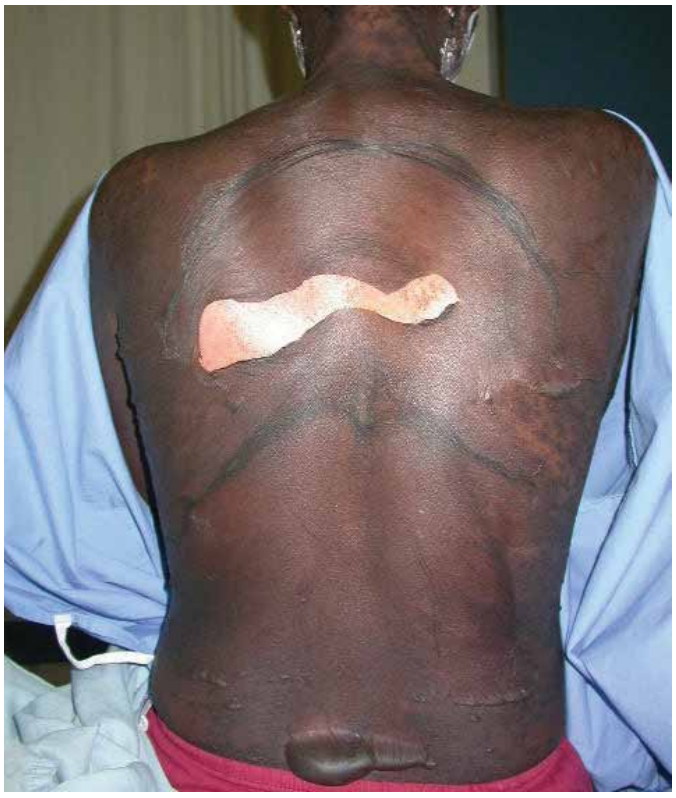

Fig. 5. TEN showing blisters and epidermal stripping.

It is important to identify and withdraw the offending drug as soon as possible. If a severe reaction is suspected the patient should be transferred to a specialised unit. SJS/TEN is a systemic disorder. A team approach, including dermatologists, ICU specialists, infectious

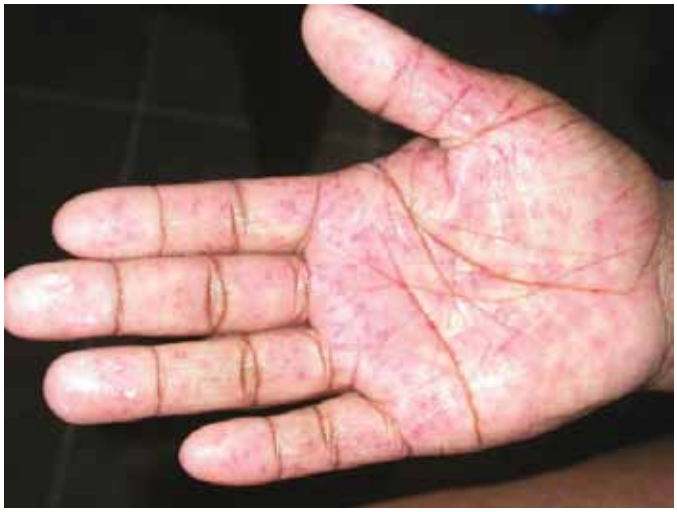

Fig. 6. Erythema of the palm in SJS/TEN.

diseases specialists, nutritionists, ophthalmologists, microbiologists, and a pain management team, centred around a good core of experienced nurses, is needed for optimal management.[13] Management of SJS/TEN is mainly supportive. Adequate nutrition, preferably soft diet to prevent oesophageal adhesions, eye care, adequate pain control, fluid balance, temperature control, protection of the exposed dermis using sterile non-adhesive dressings and daily baths are recommended. Regular monitoring for sepsis is crucial, as systemic infection is the leading cause of mortality. Regular skin swabs from denuded areas should be sent for culture and sensitivities as these guide empiric antibiotics in cases of systemic sepsis.[14] Prophylactic antibiotics are not recommended and the use of systemic steroids is controversial. Blindness, mucosal adhesions and strictures need to be anticipated and preventive measures taken. Other long-term sequelae include nail abnormalities, persistent pigmentation and sicca symptoms (Figs 7, 8).

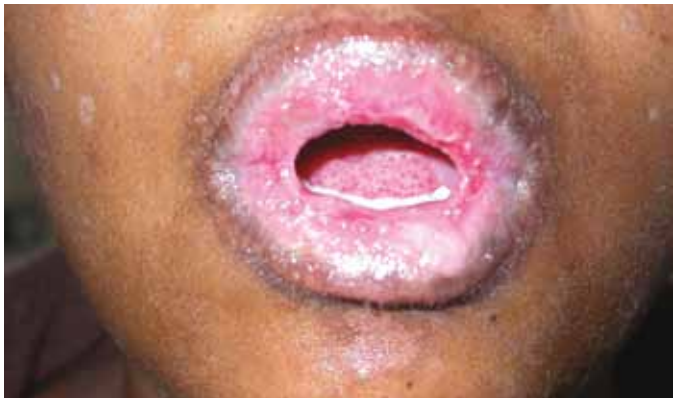

Fig. 7. Angular webbing of the mouth following SJS/TEN. The patient was not encouraged to move the lips and adhesions were not separated during the acute stage.

Fig. 8. Fibrosis of genital mucosa following SJS/TEN.

Fixed drug eruption

Fixed drug eruption usually presents as a solitary or numerous itchy, round, well-circumscribed, erythematous macules that evolve into oedematous plaques on the skin or mucosae. The lesions typically resolve with persistent hyperpigmentation (Fig. 9). They tend to recur in exactly the same sites on re-exposure to the offending drug, sometimes with new lesions erupting elsewhere. The trunk, lips, palms, soles, glans penis and groin are commonly affected. Occasionally the lesions can be extensive and bullous, resembling SJS and toxic epidermal necrolysis (Fig. 10).

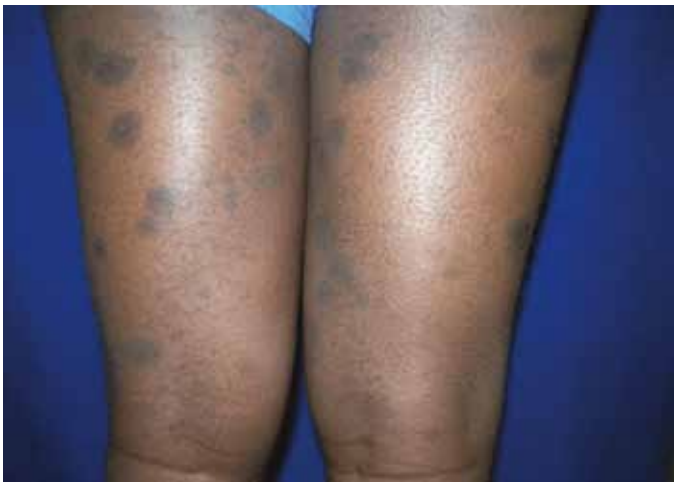

Fig. 9. Fixed drug eruption.

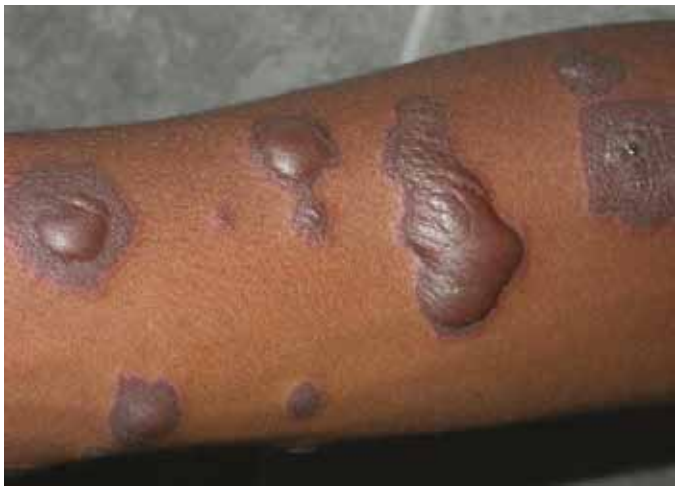

Fig. 10. Bullous fixed drug eruption.

Antibiotics, particularly sulfamethoxazole, antifungals, antipsychotics and NSAIDs, are commonly reported causes of fixed drug eruption.[15] In our setting phenolphthalein-containing laxatives and analgesic mixtures have been frequently implicated (unpublished observation). The management is withdrawal of the offending drug, education of the patient and support in severe cases.

Lichenoid drug eruptions initially present as itchy small pink macules that gradually progress to become firm violaceous, flat-topped, polygonal and scaly papules.

Lichenoid drug eruption

Lichenoid drug eruptions initially present as itchy small pink macules that gradually progress to become firm violaceous, flat-topped, polygonal and scaly papules (Fig. 11). In some cases the lesions persist as macules, only increasing in size with continuing exposure to the

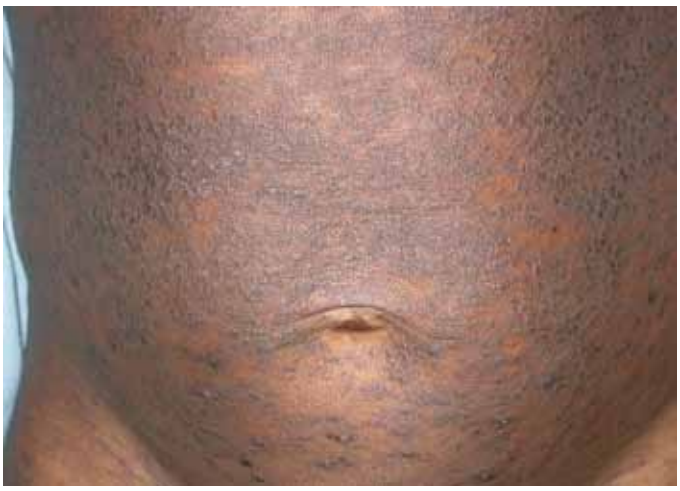

Fig. 11. Lichenoid drug reaction. Note the flat-topped polygonal papules.

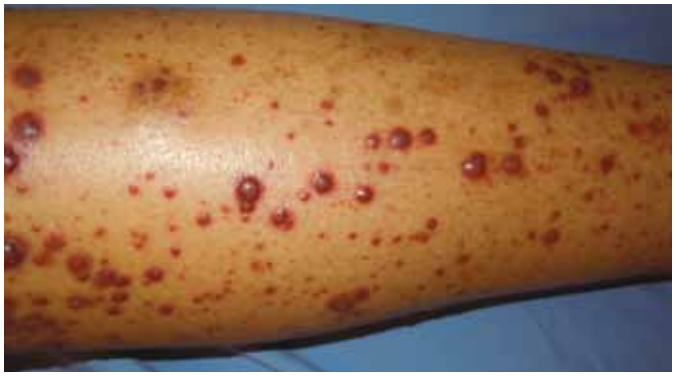

Fig. 12. Macular lichenoid drug reaction.

offending drug (Fig. 12). On the mucous membranes, buccal and genital mucosae are favoured sites with the characteristic white lace pattern called Wickham's striae. The period between initiating the drug and the development of the lesions ranges from days to several years, with most cases occurring within a few months. On withdrawal of the offending drug the lesions usually resolve spontaneously, sometimes with post-inflammatory hyperpigmentation.[16]

There are a large number of drugs that can cause photoallergic reactions, including antibiotics, ACE inhibitors, thiazides, calcium channel blockers, NSAIDs, antimalarials and cosmetics.

Drug-induced vasculitis

Vasculitis is a histological diagnosis characterised by neutrophil debris and fibrin deposition around the affected small blood vessels of the skin. The diagnosis of drug-induced cutaneous vasculitis can be suspected clinically and its hallmark is palpable purpura, most frequently on the lower limbs. Depending on severity of the reaction, the lesions can progress to become haemorrhagic blisters and ulcerate (Fig. 13).

An important variant to mention is urticarial vasculitis, which on initial presentation presents like urticaria but the lesions are non-migratory, last for more than 24 hours and resolve with post-inflammatory hyperpigmentation. As with all cutaneous vasculitides, it is imperative to exclude other causes of vasculitis as well as internal organ involvement as these can be life threatening.

In a systematic review, propylthiouracil, hydralazine, granulocyte-colony stimulating factor (G-CSF), cefaclor, minocycline, allopurinol, D-penicillamine, phenytoin, isotretinoin and methotrexate were the most frequently reported cause of drug-induced vasculitis. These data

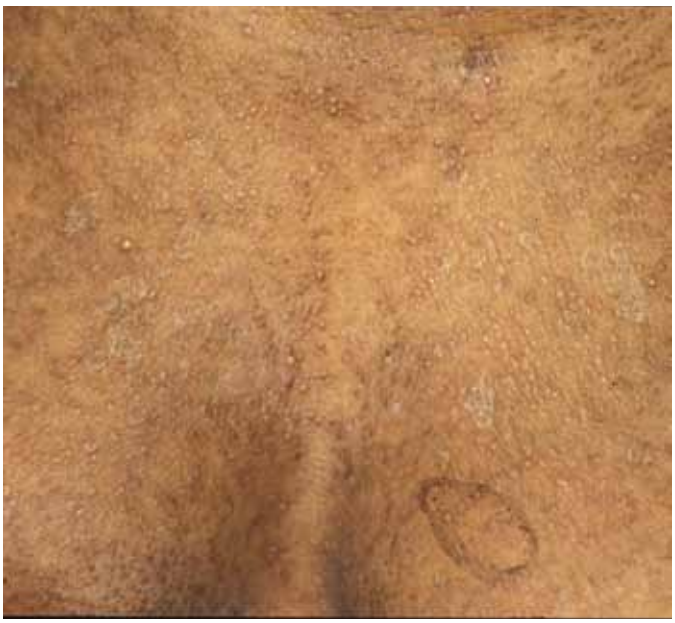

Fig. 13. Small-vessel vasculitis. Note lesions in different stages of evolution with palpable purpura and blisters.

should be interpreted with caution due to underreporting, changing prescribing patterns and local prescribing patterns.[17]

Acute generalised exanthematous pustulosis

Acute generalised exanthematous pustulosis (AGEP) is characterised by 1 - 3 mm sterile pustules on a background of generalised oedematous erythema, 12 - 24 hours after ingesting the offending drug (Fig. 14). There is usually associated fever, pruritus or burning and leucocytosis. The lesions have a predilection for body folds and the face, but may be widespread. The rash spontaneously resolves after 1 - 2 weeks with superficial desquamation. The main differential diagnoses to be excluded are bacterial infections and pustular psoriasis. Withdrawal of the offending drugs and application of topical steroids is the mainstay of management. Antibiotics, terbinafine and antimalarials are commonly implicated drug.[18]

Fig. 14. Acute generalised exanthematous pustulosis.

Urticaria typically affects the trunk and limbs. A wide variety of drugs and vaccines are implicated, with antibiotics and NSAIDs being the most common. Urticaria is managed with withdrawal of the offending drug and antihistamines.

Photoallergic drug reactions

Photoallergic drug reactions are idiosyncratic cell-mediated hypersensitivity responses, in contrast with phototoxic reactions, which clinically resemble exaggerated sunburn, and are predictable, with severity dependent on the dose of the drug and the extent of exposure to light. The allergic rash is photodistributed, eczematous and in chronic cases becomes lichenified (Fig. 15). There are photolichenoid variants. Photoallergic reactions are usually transient, resolving on withdrawal of the offending drug. Topical steroids can be used to control symptoms and speed up recovery. Photopatch tests may be useful in identifying the offending drug in cases of polypharmacy. There are a large number of drugs that can cause photoallergic reactions, including antibiotics, ACE inhibitors, thiazides, calcium channel blockers, NSAIDs, antimalarials and cosmetics.[19]

Fig. 15. Photoallergic reaction with marked lichenification and background erythema.

Patient education is critical to prevent re-exposure to the offending drug. The treating physician should also ensure that the patient obtains an Alert bracelet to be worn at all times.

Urticaria

Urticaria presents as itchy erythematous wheals that usually develop a few minutes after ingesting the offending drug. The lesions are migratory and transient, resolving without leaving behind footprints within 24 hours. Urticaria typically affects the trunk and limbs. A wide variety of drugs and vaccines are implicated, with antibiotics and NSAIDs being the most common.[20] Urticaria is managed with withdrawal of the offending drug and antihistamines.

Prevention of recurrence

Patient education is critical to prevent re-exposure to the offending drug. The treating physician should also ensure that the patient obtains an Alert bracelet to be worn at all times (Fig. 16).

Fig. 16. The importance of an Alert bracelet being explained to a patient on discharge from hospital.

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References available at www.cmej.org.za

In a nutshell

- A thorough history and a good clinical examination are critical for early recognition of CADR.
- CADR usually present days to weeks after exposure to the offending drug but can occur much later.
- Most CADRs are not serious and resolve on drug withdrawal and resolve despite continuation of the offending drug in cases where there is no alternative drug.
- Recognise the constellation of signs and symptoms, rather than diagnosing 'a rash' to identify a potentially serious CADR.
- Early withdrawal of the offending drugs saves lives.
- Rule out systemic involvement in SJS/TEN, DHS and vasculitis.
- Early referral in severe cases also saves lives.
- Prevent recurrence and arrange for an Alert bracelet.