Serious cutaneous adverse reactions to traditional Chinese medicines

Y L Lim, T Thirumoorthy

ABSTRACT

Introduction: Serious cutaneous adverse reactions to traditional medicines are not well described or reported in the literature, despite growing use of these medicines.

Methods: This is a case series of four patients who were found to have various serious cutaneous adverse reactions to the traditional Chinese medicines that they had taken.

Results: In this series, there was a patient with toxic epidermal necrolysis from traditional Chinese medicine, another with acute generalised exanthematous pustulosis from piroxicam and salicylate-contaminated traditional Chinese medicine, and two patients with drug hypersensitivity syndrome – one from traditional Chinese medicine and the other from phenylbutazone-adulterated traditional Chinese medicine.

Conclusion: The series illustrates that serious cutaneous adverse reactions do occur with traditional medicines and emphasises the importance of being aware of such reactions.

Keywords: adverse reaction, cutaneous reaction, drug reaction, traditional Chinese medicine

Singapore Med J 2005; 46(12):714-717

INTRODUCTION

Serious cutaneous adverse reactions to conventional (allopathic) medicines are well-recognised, but those to traditional medicines are not well-described or reported in the literature. This is in spite of a rapidly growing popularity and worldwide increase in the use of traditional medicine[1]. To many of the traditional medicine users, these medicines are generally regarded as "natural", therefore innocuous, without major side effects and at worst, ineffective. 12 out of 49 cases of cutaneous adverse drug reactions referred to our Dermatology Unit in Singapore General Hospital from July to October 2004 were serious cutaneous adverse drug reactions (SCADR). Of these 12 cases, four were SCADR-related to traditional medicines. These four cases illustrate a myriad of morphologies of serious cutaneous adverse reactions to traditional medicines and their contaminants. It is important for clinicians to be aware of traditional medicine-induced adverse cutaneous reactions.

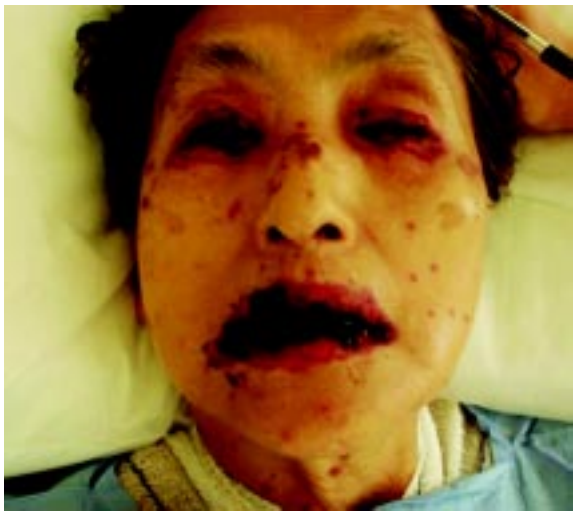

Fig.1 Photograph of patient 1 shows severe conjunctivitis, erosive cheilitis and eroded skin.

CASE SERIES

Case One

Patient 1 was a 70-year-old woman with pancreatic carcinoma diagnosed four years ago, for which she had undergone a Whipple's operation. She also had total knee replacement for osteoarthritis of both knees and thyroidectomy 15 years ago. She gave a history of skin rash to propantheline bromide. She has otherwise no previous skin problem.

She was admitted for complaints of sore eyes and mouth for one week and generalised rash for two days. She had visited a general practitioner (GP) on the third day of her symptoms and was given augmentin, diclofenac and paracetamol. The GP confirmed that the patient had severe conjunctivitis and severe oral ulceration, but had no rash then. Two days after the visit to the GP, a rash broke out

Dermatology Unit
Singapore General Hospital
Outram Road
Singapore 169608

Y L Lim, MBBS, MRCP
Registrar

T Thirumoorthy, FRCP
Senior Consultant

Correspondence to:
Dr Lim Yen Loo
National Skin Centre
1 Mandalay Road
Singapore 308205
Tel: (65) 6253 4455
Fax: (65) 6253 3225
Email: yllim@nsc.gov.sg

on the patient's body. Apart from L-thyroxine and medicines given by the GP, she denied vehemently ingestion of other medication.

On admission, this patient had a fever of 39.4ºC. She had painful erosive cheilitis, buccal erosions, severe conjunctivitis, multiple bullae and necrolytic changes on her skin, as well as skin denudation (Fig. 1). About 40% of her body surface area was affected. Her total leukocyte count was normal. There was no peripheral eosinophilia or elevated transaminases. Her serum albumin was 29g/L.

A diagnosis of toxic epidermal necrolysis (TEN) was made. The patient was given intravenous immunoglobulin after a skin biopsy. She was also empirically started on intravenous ciprofloxacin for possible sepsis. To ensure adequate nutrition, nasogastric feeding was commenced, in addition to an intravenous dextrose-saline infusion. Swab from the mouth for *Herpes simplex* virus antigen immunoflorescence was negative. Blood and urine cultures showed no growth and her Ca 19-9 was 6.1 (normal range 3-50). The skin biopsy confirmed TEN.

The cause of the TEN remained uncertain initially, as the medications given by the GP was taken only after the mucosal erosions and ulcerations had occurred. With repeated interview of the patient and her family, the patient eventually admitted to taking a white-coloured traditional Chinese medicine powder in the prior one week. She added, though, that she had been intermittently taking the same white powder for the past ten years as a tonic. This white powder was never recovered for analysis as the patient's family had already discarded it and the traditional Chinese medical hall where she bought the powder has since closed, as reported by the patient.

The patient recovered well, after meticulous skin and eye care. She was discharged after 17 days of hospitalisation. In the follow-up review, she was noted to have post-inflammatory hyper- and hypopigmentation of her skin, associated with dysaesthesia. Her eyes had recovered well.

Case Two

Patient 2 was a 19-year-old man with no past illness or known drug allergy. He saw a sinseh (Chinese traditional medicine practitioner) after he sprained his left ankle. He was given local massage with traditional liniment as well as traditional Chinese oral medications, which consisted of yellow tablets and an unlabelled bottle of brown solution. Four days into taking these medicines, he developed a generalised, non-pruritic rash. He denied taking any other medication.

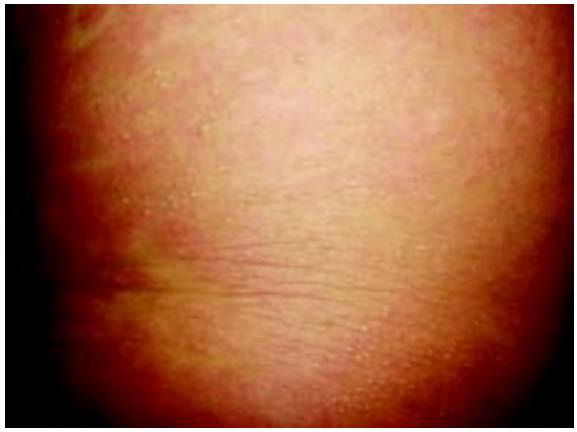

Fig. 2 Photograph shows tiny postules and confluent erythematous maculopapular rash on the trunk of patient 2.

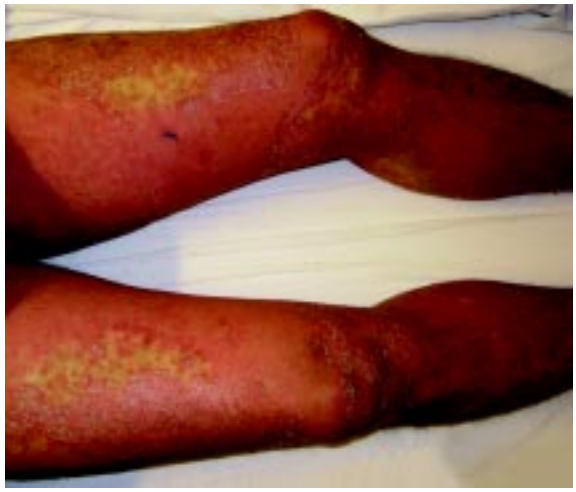

Fig.3 Photograph of the lower limbs of patient 3 shows psoriasis and drug hypersensitivity syndrome.

On examination, he was afebrile and had a generalised, confluent erythematous, papular exanthem with tiny pustules mainly on his trunk (Fig. 2). There were oral erosions in the buccal mucosa and a small sublingual ulcer. There was no eye or genitalia involvement. His left ankle was red, oedematous and had a large bulla with clear fluid within it. His full blood count and his liver enzymes were normal.

The clinical diagnoses of acute generalised exanthematous pustulosis (AGEP) and contact dermatitis on the left ankle were made. A skin biopsy taken from the patient's back showing subcorneal pustules, superficial perivascular dermatitis with inflammatory infiltrate composed of lymphocytes and plasma cells, and occasional intravascular eosinophils, consistent with the diagnosis of AGEP.

His rash improved with four days of oral prednisolone and he was discharged after eight days of hospitalisation. Upon follow-up, he was well. The brown solution and the remaining four yellow tablets were sent for analysis at the Health Science Authority. It was reported that the former specimen

contained in a white-capped plastic bottle was "found to contain the following: coumarin, piroxicam and salicylates." The laboratory did not measure the concentration of these drugs. The yellow tablets were not found to have any of the common western adulterants tested by the laboratory.

Case Three

Patient 3 was a 31-year-old man who had psoriasis and psoriatic arthropathy for the past ten years. He was on follow-up with a rheumatologist, and was taking methotrexate until six months ago when he discontinued his medications. His previous known drug allergy consisted of angioedema on taking non-steroidal anti-inflammatory drugs and a maculopapular rash on taking cotrimoxazole.

He was admitted with a six-day history of fever, a new pruritic rash on his trunk and limbs, and worsening of his pre-existing chronic plaque psoriasis. He started traditional Chinese medicine tablets (three types) given by a friend for relief of his neck pain, and had been taking them for two weeks till admission. He denied any other medication ingestion.

His temperature was 39ºC on admission. He had a generalised exanthem on areas of his skin not involved by psoriasis, including his palms (Fig. 3). His eyes and oral mucosa are not involved. His face looked flushed and oedematous, and there were multiple enlarged lymph nodes in the cervical, axillary and inguinal region. Clinically, he was not jaundiced. His blood investigations revealed atypical monocytosis (leukocytes 4.43 x 10^9, lymphocytes 10%, monocytes 12%, eosinophils 8% and atypical monocytes 14%), and hepatitis (ALT 107 U/L and AST 146 U/L). A skin biopsy taken from his thigh showed interface dermatitis with occasional necrotic keratinocytes and perivascular lymphocytic infiltrate.

Despite stopping the traditional Chinese medications and switching the empirical intravenous ceftriaxone to aztreonam and vancomycin, the patient continued to be febrile. Chest radiograph was normal. Blood and urine cultures showed no bacterial growth and Epstein-Barr viral-capsid antigen (EBV VCA) IgM to exclude infectious mononucleosis was negative. Intravenous hydrocortisone was started after serious infections were considered unlikely and clinical findings attributed to drug hypersensitivity syndrome. With this treatment, his fever plummeted within 48 hours and he was discharged after ten days of hospitalisation. The patient went home with oral prednisolone 1 mg/kg/day for a week.

Analysis showed that the orange sugar-coated tablets contained phenylbutazone and the white tablets contained dexamethasone. The red sugar-coated tablets were adulterant-free. His psoriasis flared up subsequently, likely to be secondary to the decreasing dose of steriods and koebnerisation of the uninvolved skin, and he had to be started on cyclosporin.

Case Four

Patient 4 was a 34-year-old woman with a history of ectopic pregnancy two years ago for which she underwent right salpingectomy. She is otherwise well without past history of skin problem or drug allergy. She presented with an intensely pruritic rash, involving her face, trunk and limbs of two days duration, associated with high fever. On careful questioning, she admitted to taking an herbal mixture from a traditional Chinese medical practitioner for the past one week. The herbal mixture was packed in 200ml airtight bags without label of the active ingredients. It was recommended to be effective in the prevention of ectopic pregnancy.

On admission, she had a fever of 38.7ºC and a generalised, confluent erythematous eruption on her trunk. The primary lesion looked targetoid on the lower limbs. Her total white count was raised at 15.57 x 10^9 with 12.2% eosinophils. The transaminases were also elevated (ALT 198 U/L, AST 52 U/L).

A clinical diagnosis of drug hypersensivity syndrome was made and skin biopsy done showed perivascular inflammation with predominant lymphocytes. Oral prednisolone was started and continued for ten days with eventual resolution of her rash and fever. Analysis of the herbal mixture did not detect any common western adulterants.

DISCUSSION

An adverse drug reaction is defined as "a response to a drug, which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiologic function"[2]. SCADR to drugs are such responses leading to changes in the structure or function of the skin, its appendages or mucous membrane, which result in "patient outcomes such as death, life-threatening events, hospitalisation, disability or interventions to prevent permanent impairment or damage"[3]. Commonly-recognised SCADR to drugs include angioedema or anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), generalised exfoliative dermatitis, drug hypersensitivity syndrome and acute generalised exanthematous pustulosis[4].

An extensive literature search for SCADR to traditional medicines yielded few reports[5,6]. The paucity of data may be due to under-reporting of

traditional medicine use by patients and doctors in general, and more specifically, under-recognition of the causal relationship between rash and traditional medicine. These in turn may be due to a lack of familiarity of the medicinal materials found in traditional medicine, its sheer diversity[7] and its non-drug status. Comparatively, more have been reported on traditional medicine causing adverse reactions involving other organs. These reports, together with studies of traditional Chinese herbal medicines on atopic eczema in-vivo and in-vitro[8,9]. suggest that the naturally-occurring substances in these medicines are not inert and are therefore capable of causing adverse effects.

SCADR to traditional medicine can thus be a reaction to naturally-occurring medicinal compounds, natural toxins, or to contaminants or adulterants in these medicines. Determining which of these components are responsible for a particular drug eruption can be difficult as illustrated by the scenarios involving patients 2 and 3. Adulterants in the traditional medicines in these two cases can neither be incriminated nor disregarded as the cause of the SCADR. Thus, patients should, nevertheless, be informed of these findings and advised on avoidance of these specific drugs in the future. The problem of adulteration is significant. The prevalence of adulteration was reported as 23.7% in one Taiwanese study involving Chinese herbal medicines associated with reports of adverse effects and poisoning[10]. In Singapore, no such data has been collated yet, but in the period between 1990 and 1997, samples of Chinese proprietary medicine obtained via both routine sampling and tip-offs by the public showed a prevalence of about 4.5% on such adulteration[11].

Establishing the causal connection between agent and disease is important in any suspected adverse drug reaction, including SCADR to traditional medicines. The causal link can be established through the time relationship between the medicine use and the onset of rash, and exclusion of other offending drugs or non-drug agents as the cause of the rash. This may be challenging in the case of SCADR to traditional medicine. Firstly, the doctors may not even be suspecting such a causal link because of a lack of awareness. Secondly, patients may not always be candid with their doctors about the use of such medicines and thirdly, patients may be concurrently taking other coventional (allopathic) medicines, which cannot be totally excluded as the cause of the rash. Finally, there is lack of data regarding the possible interval between ingestion of the various traditional medicine and onset of cutaneous reactions.

Other aspects to establishing a causal link include a response to dechallenge (as in withdrawal of the offending agent) and a response to rechallenge. The latter may again be impractical either because the traditional medicine in question is not available (as depicted by patient 1), or there are differences in the medicinal content due to lack of standardisation of these products. More importantly, the risk of re-exposing the patient to the same medicinal compound is not justifiable. Like in any other adverse events, the strength of causal association that an event (in this case a reaction) is linked to a drug can be graded as certain, probable/likely, possible or unlikely[12]. Unless a thorough history is taken, determining this would otherwise be difficult.

The problem of SCADR to traditional medicine will become more significant as the use of traditional medicine becomes more widespread and of increasing healthcare and economic importance. Already, in many parts of the world, expenditure on traditional medicine is growing rapidly. Therefore, it is important that the public, traditional practitioners and qualified doctors be cognizant of potential adverse reactions of traditional medicines. Awareness will help in dispensing the appropriate advice and therapy, which will in turn prevent unnecessary complications or even fatalities, reduce unwanted readmissions, prolonged hospital stays or inappropriate labelling of drug allergy to other medicines.

REFERENCES

1. WHO Traditional Medicine Strategy 2002-2005. Geneva: World Health Organisation, 2002: 1,12.
2. International drug monitoring: the role of national centres. Report of a WHO meeting. World Health Organ Tech Rep Ser 1972; 498:1-25.
3. U.S. Food and Drug Adminstration MedWatch. What is a serious adverse event? Available at: www.fda.gov/medwatch/report/DESK/advevnt.htm. Accessed April 14, 2005.
4. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994; 331:1272-85.
5. Ernst E. Adverse effects of herbal drugs in dermatology. Br J Dermatol 2000; 143:923-9.
6. Chowdhury AD, Oda M, Markus AF, et al. Herbal medicine induced Stevens-Johnson syndrome: a case report. Int J Paediatr Dent 2004; 14:204-7.
7. What is traditional medicine? Towards a working definition. In: WHO Traditional Medicine Strategy 2002-2005. Geneva: Wolrd Health Organisation, 2002: 7.
8. Sheehan MP, Atherton DJ. A controlled trial of traditional Chinese medicinal plants in widespread non-exudative atopic eczema. Br J Dermatol 1992; 126:179-84.
9. Latchman Y, Bungy GA, Atherton DJ, et al. Efficacy of traditional Chinese herbal therapy in vitro. A model system for atopic eczema: inhibition of CD23 expression on blood monocytes. Br J Dermatol 1995; 132:592-8.
10. Huang WF, Wen KC, Hsiao ML. Adulteration by synthetic therapeutic substances of traditional Chinese medicines in Taiwan. J Clin Pharmacol 1997; 37:344-50.
11. Koh HL, Woo SO. Chinese proprietary medicine in Singapore: regulatory control of toxic heavy metals and undeclared drugs. Drug Saf 2000; 23:351-62.
12. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356:1255-9.