A syndromic rash in patients attending methadone clinics in New South Wales

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We report an outbreak of a "rash" syndrome in patients attending methadone clinics in New South Wales. It presents with a pruritic, exanthematous or purpuric rash involving the trunk, limbs, palms and soles, which develops over a week and proceeds in most patients to desquamation (mainly of palms and soles) persisting for 3–4 weeks. Mucosae are not involved, and patients are generally systemically well. To date, the rash has affected 22% of 316 patients attending one methadone clinic in western Sydney, as well as patients in clinics elsewhere in Sydney and rural NSW. The aetiology is as yet unknown.
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We report an outbreak of a "rash" syndrome in patients attending a number of methadone clinics across New South Wales during October and November 2004. The syndrome first came to our attention when, over a week, two patients presented to a methadone clinic in western Sydney and three to the Westmead Hospital emergency department with a distinctive rash. Subsequent enquiries and patient surveillance revealed that 70 of 316 patients (22%) at the methadone clinic had developed a similar "rash" syndrome in October and November. All were prescribed methadone syrup. Clusters of patients have also been increasingly reported at other methadone clinics across metropolitan Sydney and some regional and rural areas in NSW. To date, informal communication with interstate methadone clinics has identified small numbers of patients with the "rash" syndrome outside NSW. In the first western Sydney case reliably identified by history, symptoms developed in August 2004.

The principal features of the "rash" syndrome are a pruritic, exanthematous or purpuric rash that typically develops over 2 to 4 days on the hands, feet, trunk and lower limbs and persists for up to 7 days. It is usually followed by a desquamative phase that particularly involves the hands and feet and lasts up to 3 to 4 weeks. Some patients develop only the desquamative phase. The condition appears relatively benign, with few, if any, systemic symptoms, although the palms and soles of the feet can become painful with pressure after desquamation. In several patients, the rapidly developing purpuric nature of the presenting rash raised initial concern about meningococcal disease or a systemic vasculitic syndrome sufficient to warrant referral for specialist assessment.

We describe four illustrative cases.

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Clinical records

Patient 1

A man aged in his 30s presented to a hospital emergency department with a 3-day history of a petechial and purpuric rash. He was an intravenous drug user who had been in a methadone treatment program for 7 years. He intermittently injected his oral methadone intravenously, most recently 24 hours before onset of the rash. This initially involved the lower limbs, but spread over 24 hours to affect the buttocks, lower back and abdomen. Associated but relatively mild symptoms included malaise and nausea for a week before rash onset, followed by sore throat, myalgia, ankle arthralgia, abdominal and chest pain and vomiting.

At presentation, the patient was afebrile. Blood pressure was 120/60 mmHg, and pulse 70 bpm. A sparse petechial and purpuric rash was present on lower limbs, feet, buttocks and lower abdomen. There was no pedal oedema, joint effusion or tenderness. There were no abnormalities on respiratory and cardiovascular examination, no clinical evidence of endocarditis, no lymphadenopathy, and mucosae were normal. The right upper abdominal quadrant was tender, but the liver and spleen were not enlarged, and no renal masses were palpable. Investigations were uninformative (Box 1).

Inpatient progress was unremarkable, and, 10 days after presentation, all symptoms had resolved, despite ongoing oral and intravenous methadone use.

Patient 2

A middle-aged man presented with a 2-day history of an erythematous, pruritic rash over his trunk and limbs which was now beginning to desquamate. He was also an intravenous drug user in a methadone treatment program. In addition to taking prescribed oral methadone, he intermittently injected both methadone and stimulants, such as amphetamine, intravenously. There was no history of fever, oropharyngeal, genital, eye or systemic symptoms. On examination, he was afebrile, looked well and had a general-

ised exanthem, with erythema and significant desquamation of soles and palms (Box 2, A and B). There were no oral, mucosal or eye signs, and no lymphadenopathy or hepatosplenomegaly. Results of investigations were unremarkable (Box 1).

He was treated for 2 days with oral prednisolone and an antihistamine, and then discharged. The rash settled over a week, although he continued to have desquamation of the soles and palms 2 weeks later.

Patient 3

A young man who was an intravenous drug user in a methadone treatment program presented to the same hospital with a 2-day history of a purpuric lower-limb rash. In addition to taking prescribed oral methadone, he intermittently injected both heroin and methadone intravenously. Five days before presentation, he developed bilateral calf pain and generalised myalgia. He was initially seen at another hospital, where he was treated with broad-spectrum intravenous antibiotics for presumed sepsis. He discharged himself after 24 hours and was admitted to our hospital about 12 hours later because of his concern about the rash.

On admission, he was afebrile, with blood pressure of 115/65 mmHg and pulse of 75 bpm. He had a prominent purpuric rash involving both lower limbs (Box 2C), with sparse lesions on both forearms. Mucosae were normal, and there was no meningism, lymphadenopathy, hepatosplenomegaly, joint swelling or tenderness, no abnormalities on respiratory and cardiac examination, and no stigmata of endocarditis. Results of investigations were once again unremarkable (Box 1). The patient remained well despite the rash and was discharged from hospital 24 hours after admission.

Patient 4

A young woman who was an intravenous drug user in a methadone treatment program presented to the methadone clinic with a 4-day history of an erythematous, pruritic rash over her trunk, limbs and hands. Other than oral methadone, she was taking no

1 Results of investigations in four patients with rash

Investigations	Reference range	Patient 1	Patient 2	Patient 3	Patient 4
Full blood count and film		Normal; platelet aggregates on film	Normal apart from WBC 10.8×10^9/L; occasional reactive lymphocytes	Normal	Normal, apart from Hb 107 g/L
Haemoglobin (Hb) (g/L)	115–161				
White blood cell count (WBC) ($\times 10^9$/L)	3.7–9.5				
ESR (mm/h)	0–15	4	11	5	38
C-reactive protein (mg/L)	0–11	20	27	22	15
Liver function tests		Normal	Abnormal	Abnormal	Normal
_γ-Glutamyltransferase (U/L)	8–43		47	48	
_Alanine aminotransferase (U/L)	10–47		88	157	
_Aspartate aminotransferase (U/L)	12–45		104	154	
ANA, ANCA, ENAs, rheumatoid factor, complement C3 and C4		Normal	nd	Normal	nd
Cryoglobulins		Absent	nd	Detected	nd
Prothrombin time (s)	11–18	Normal	Normal	Normal	nd
APTT (s)	25–36	Normal	39	Normal	nd
Hepatitis C virus		IgG-positive; undetectable viral load (< 600 IU/mL)	IgG-positive; viral load not assessed	IgG-positive; viral load > 850 000 IU/mL	IgG-positive; refused viral load assay
HIV antibody		Negative	nd	nd	nd
Urinalysis		Trace protein (39 mg/24 h); no casts/red cells	Normal	Normal	nd
Blood culture		Negative	Negative	Negative	nd
Throat swab		Nd	Normal flora	nd	nd
Electrocardiogram		Normal	nd	nd	nd
Chest x-ray		Normal	Normal	Normal	nd
Echocardiogram		Transthoracic normal; transoesophageal not tolerated by patient	nd	nd	nd

ESR = erythrocyte sedimentation rate. nd = not done. ANA = antinuclear antibody. ANCA = antineutrophil cytoplasmic antibody. ENAs = extractable nuclear antigen antibodies. APTT = activated partial thromboplastin time.

drugs and was otherwise well. Examination revealed an extensive exanthem over her trunk, hands and legs. She had no fever, and blood pressure was normal. She was reviewed a week later and still had an extensive generalised erythematous exanthem, as well as finger and palm desquamation (Box 2, D and E). Results of investigations were unremarkable (Box 1).

Discussion

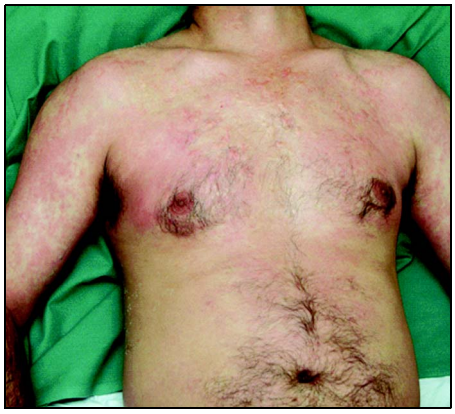
The aetiology of this "rash" syndrome is yet to be elucidated. Currently, it appears to be restricted to people using methadone syrup, with no reports of rash in over 100 patients in western Sydney prescribed buprenorphine for treatment of opioid dependence, nor among non-methadone-using family members of patients with the rash, nor among healthcare workers in contact with these patients. To date, all patients with the "rash" syndrome who have been assessed for hepatitis C exposure are seropositive, but not all are viraemic. Some patients with the "rash" syndrome smoke cannabis and intermittently inject methadone or other drugs. However, these characteristics are not universal among affected patients, nor more frequent than in unaffected patients on the methadone program, among whom they are also common. Similarly, the use of prescription or complementary medicines does not seem to be associated with the "rash" syndrome.

Similar rashes and associated desquamation are common in staphylococcal and streptococcal toxin-induced illnesses, such as toxic shock syndrome and scalded skin syndrome,[1-3] and in some viral illnesses, such as parvovirus infection and measles.[4] However, the patients in the current outbreak did not give a history of bacterial or viral illness, and family members not taking methadone do not appear to have developed the syndrome. HIV antibody testing has been performed in some affected patients and has been negative. Throat swabs taken in some patients have grown only normal respiratory flora. Markers of streptococcal infection, such as antideoxyribonuclease B antibodies and anti-streptolysin O titre, are positive in some but not all patients.

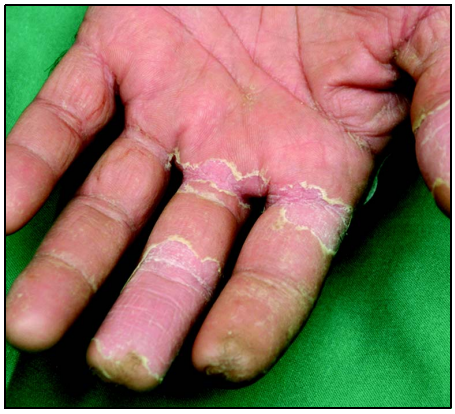
Skin biopsy performed in a number of patients has failed to help define the aetiology of the rash. Histological examination often shows focal and mild spongiosis with superficial perivascular chronic inflammation, while direct immunofluorescence examination shows deposition of IgM and complement 3 in dermal capillaries. These findings are consistent with an immunological reaction in the skin, but do not clarify whether it is the primary cause of the rash or a secondary phenomenon. A hypersensitivity reaction to a contaminant in the methadone syrup could present with such a picture.

The fact that, to date, all the patients identified in western Sydney had been taking methadone syrup from a single manufacturer raises the possibility of batch contamination; however, batches are distributed nationally, so more widespread involvement would probably be expected if this was the basis of the syndrome. In addition, examination of the methadone syrup has failed to detect any contamination. The possibility of alternative sources of contamination, such as methadone storage or delivery devices, remains to be explored.

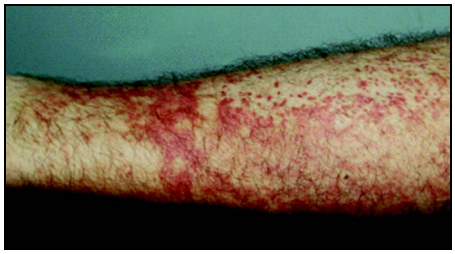
2 Features of the rash in four patients



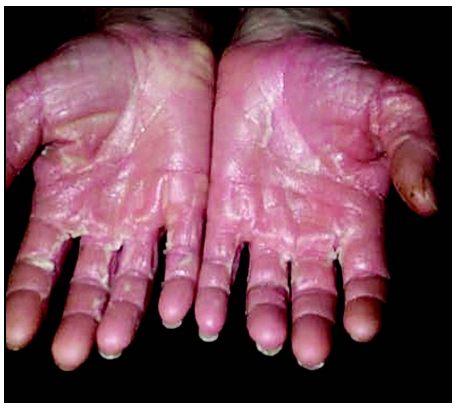
↑*A. Generalised exanthem on trunk and limbs in Patient 2.*



↑*B. Palm desquamation in Patient 2.*

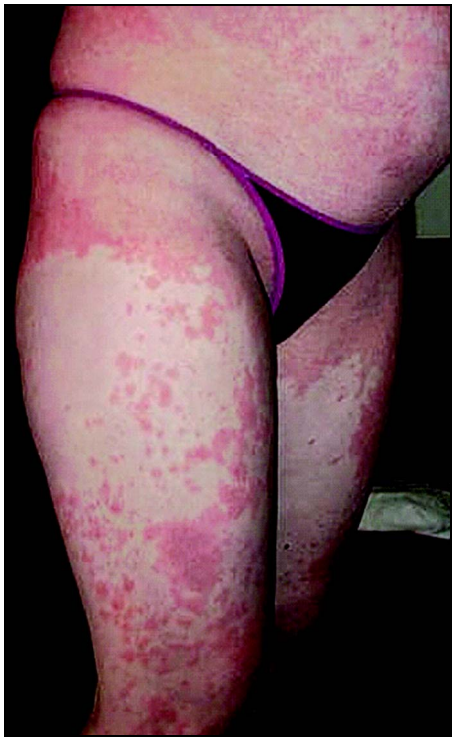


↑*C. Purpuric rash involving lower limbs, with areas of confluence on the lower calf in Patient 3.*



↑*E. Palm desquamation in Patient 4.*

↓*D. Extensive erythematous exanthem over trunk and limbs in Patient 4.*



We believe it is important for physicians to be aware of this newly emerging syndrome, both to assist with more accurate delineation of its epidemiology and pathogenesis, and to permit more effective investigation and treatment of affected patients. State public health units and the Therapeutic Goods Administration are investigating this outbreak to try to determine the cause of this new syndrome.

Competing interests

None identified.

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