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ENDGAMES

PICTURE QUIZ

Erythroderma in the emergency department

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A 29 year old man was referred to the dermatology department by the accident and emergency department because of a "maculopapular rash." He had a four day history of an upper respiratory tract infection. Within half an hour of ingesting an over-the-counter flu remedy he developed redness and itching of his skin and a burning sensation in his groins and axillae. An hour later he felt systemically unwell with a painful skin.

He had a history of infantile eczema, did not take regular medications or recreational drugs, and had no known drug allergies. He reported previous use of cold and flu remedies without ill effect, had no history of recent travel, but admitted to a single episode of unprotected intercourse a month earlier with a female sex worker.

On examination, he was diaphoretic with cool peripheries, had a temperature of 38°C, his pulse rate was 120 beats/min, and his blood pressure was 110/56 mm Hg. Confluent erythema covered his entire body, with petechiae and oedema of his lower legs (figs 1 and 2). There were no palpable epidermal changes, there was no mucosal involvement, and Nikolsky's sign was negative. He had cervical, axillary, and inguinal lymphadenopathy. Systemic examination was otherwise unremarkable. Bloods tests showed leucocytosis with a neutrophilic shift, eosinophilia, and raised inflammatory markers (table 1⇓).

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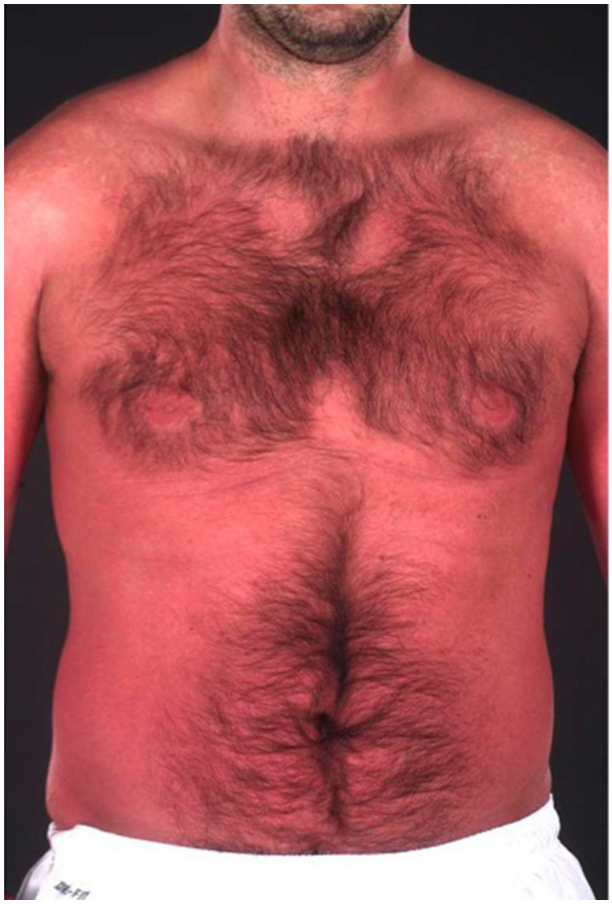

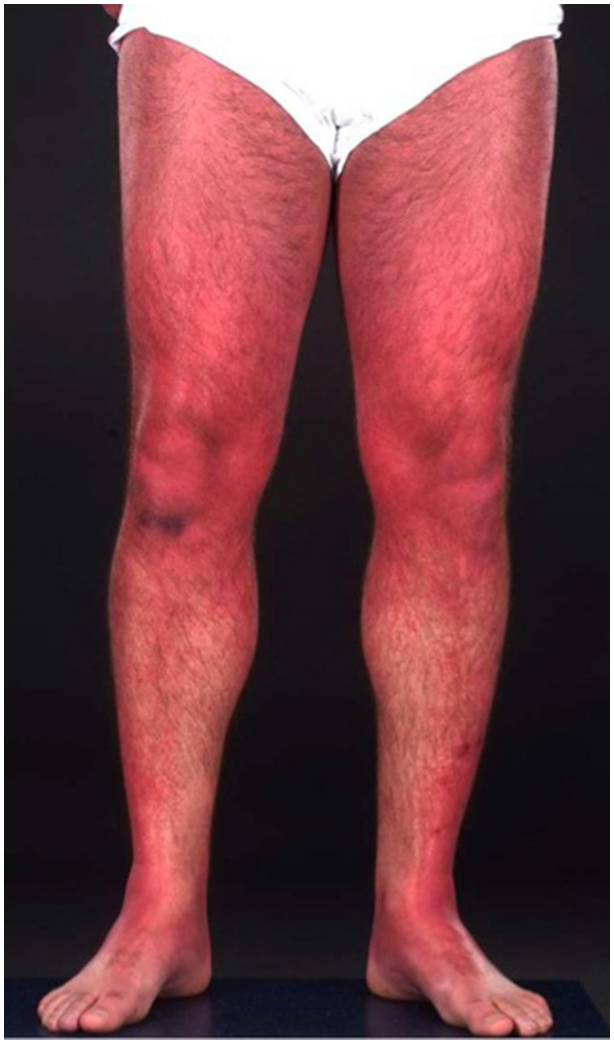

Questions

1 What is the differential diagnosis of erythroderma in this patient?

2 How would you manage this patient initially?

3 What initial investigations are needed?

4 How might the causative agent of this eruption be identified?

5 How would you diagnose this condition?

Answers

1 What is the differential diagnosis of erythroderma in this patient?

Short answer

Toxic erythema, an adverse drug eruption, HIV seroconversion, secondary syphilis, pityriasis rubra pilaris, acute eczema or psoriasis, or cutaneous T cell lymphoma.

Long answer

Erythroderma is erythema that covers at least 90% of the body surface area; it has many causes (box 1). Because of the patient's recent history of an upper respiratory tract infection, the rash might be a consequence of the infective organism (a toxic erythema) or related to its treatment. Although erythroderma caused by an adverse drug reaction is often preceded by a

morbilliform (measles-like) eruption, absent in this case, the temporal association between administration of the flu remedy and symptoms suggest that an adverse drug reaction is a possibility.

2 How would you manage this patient initially?

Short answer

Dermatological review; skin biopsy and admission; stop possible causative drugs; monitor fluid balance, pulse, blood pressure, and temperature; and frequent application of greasy emollients.

Long answer

The rapid onset of redness and itching of the skin, accompanied by systemic symptoms, suggests a severe, complex, unstable reaction, possibly progressive. The cause of erythroderma should be rapid identified, all unnecessary drugs stopped, and the patient monitored for consequences of failure of the skin barrier. The skin's functions are supported by the use of emollients—as well as relieving cutaneous discomfort, greasy emollients improve barrier function and reduce transepidermal loss of fluid and heat.

Although antihistamines are often prescribed, topical super potent steroid ointments are more effective at reducing pruritus and can halt progression of the skin eruption. Because this patient had systemic features of inflammation, he was also given systemic steroids; this would not be necessary if the adverse drug reaction was limited to the skin.[1] It is important to distinguish erythroderma due to psoriasis from other causes because administration of corticosteroids in patients with psoriasis may precipitate a flare—occasionally life threatening pustular psoriasis.

3 What initial investigations are needed?

Short answer

Blood tests (full blood count; urea and electrolytes; liver function tests; C reactive protein; erythrocyte sedimentation rate; IgE titre; serology for HIV, cytomegalovirus, Epstein-Barr virus, rubella, parvovirus, and mycoplasma; and blood cultures) plus skin biopsy help identify the cause of this patient's erythroderma (box 1).

Long answer

Blood tests can rule out infective causes and provide evidence of a systemic process. Raised C reactive protein and marked leucocytosis would support the possibility of an acute lymphoma, a neutrophilic shift infection, or an acute phase response. Eosinophilia can be a helpful indicator of a drug eruption, such as drug eruption with eosinophils and systemic symptoms (DRESS), otherwise known as drug hypersensitivity syndrome (DHS), which is accompanied by lymphocytosis in 30% of cases.[2] The systemic effects may be caused by myositis, hepatitis, nephritis, or pneumonitis.[3]

A skin biopsy (fig 3) would distinguish between the primary and some secondary causes of erythroderma by allowing histopathological correlation with the clinical findings Direct immunofluorescence would identify autoantibodies attacking the skin in prebullous pemphigoid.

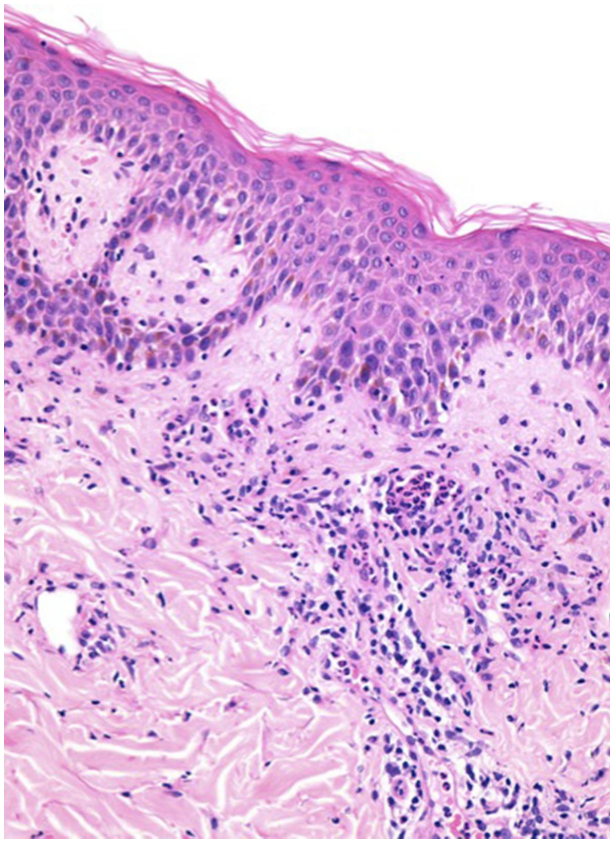

Fig 3 Skin biopsy obtained on day 1 of admission (haematoxylin and eosin stain) showing an acanthotic and focally parakeratotic epidermis with mild spongiosis and moderate upper dermal oedema. Apoptotic keratinocytes and colloid bodies are not seen but there are small numbers of lymphocytes, neutrophils, and eosinophils within the dermis and a mild perivascular lymphohistiocytic infiltrate

Inflammatory markers, white cells counts, and liver and kidney function tests are helpful in monitoring progress after admission. In drug hypersensitivity syndrome, a reduction in eosinophilia can indicate that the patient's condition is improving before this becomes clinically evident and can reassure the clinician that the agent responsible has been withdrawn.

4 How might the causative agent of this eruption be identified?

Short answer

By taking a comprehensive history of temporal associations between prescribed and over-the-counter drugs and the onset of rash.

Long answer

The temporal association between the patient taking the flu remedy and the onset of clinical signs, together with the blood and skin biopsy results, suggests a type B (bizarre) adverse drug eruption.[4] Because the tablets were a compound preparation (containing paracetamol, caffeine, phenylephrine, maize starch, croscarmellose sodium, sodium laurel sulphate, magnesium stearate, talc plus quinoline yellow, titanium dioxide, patent blue V, and erythrosine) the causative agent was not immediately obvious.

Delayed-type cell mediated drug reactions (formerly Gell-Coombs type IV reactions; table 2⇓) may be reproduced

Box 1 Causes of erythroderma in adulthood

Primary (cutaneous)

- Eczema
- Psoriasis
- Pre-bullous pemphigoid
- Cutaneous T cell lymphoma
- Pityriasis rubra pilaris

Secondary

- Adverse drug eruptions
- Secondary syphilis
- Other infections (toxic erythema)
- HIV seroconversion
- Graft versus host disease
- Cancer (haematological and internal)

by patch testing the skin with the drug mixed with white soft paraffin or by intradermal testing.[5] However, positive responses are found in only 30-50% of cutaneous adverse drug eruptions, usually in patients with allergy to aromatic anticonvulsants and certain antibiotics.[5] For this reason, and because of the risk of provoking a dangerous reaction, patch testing, skin prick testing, and intradermal testing with drugs is not standard practice.

Because the constituents of the tablets were common and any re-exposure would probably be more severe, it was important to identify the cause of the reaction. After discharge, our patient underwent skin prick and intradermal testing to patent blue V 2.5%, erythrosine, a titanium based sunscreen, and phenylephrine 1% because these were thought to be the most likely culprits.

5 How would you diagnose this condition?

Short answer

Drug hypersensitivity syndrome can be diagnosed by identification of at least three of the seven diagnostic criteria defined by the European registry of severe cutaneous adverse reactions to drugs and collection of biological samples.

Long answer

The European Registry Of Severe Cutaneous Adverse Reactions To Drugs And Collection Of Biological Samples has produced diagnostic criteria to aid the diagnosis of drug hypersensitivity syndrome (box 2).[6]

Our patient met all seven of the criteria for this diagnosis, which has an estimated 8% mortality rate.[7] The pathophysiology of drug hypersensitivity syndrome is unknown, but a genetic predisposition,[8] slow acetylator status,[2] defective detoxification of reactive oxidative metabolites,[2] and co-infection with human herpesvirus 6[9] have all been implicated. The most common causative agents are anticonvulsants, sulfonamides, allopurinol, minocycline, and lamotrigine, with onset usually 15-40 days after initiation of the drug.

Patient outcome

Our patient improved over seven days, with normalisation of his blood tests and complete recovery of his skin. He had a positive intradermal response to phenylephedrine, a constituent of the cold and flu tablets, and was diagnosed with a type IV reaction manifesting as drug hypersensitivity syndrome, a previously unreported reaction to this drug. Although unusual, severe cutaneous and systemic reactions to over-the-counter flu remedies have been reported.[10-14] We reported this adverse drug reaction via the *British National Formulary* yellow card system.

Florence Deroide, consultant histopathologist and Nisha Patel, pharmacist, at the Royal Free Hospital contributed to this patient's care.

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Patient consent obtained.

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Box 2 Diagnostic criteria for drug hypersensitivity syndrome[6]

- Hospital admission
- Reaction thought to be drug related
- Acute skin rash
- Temperature around 38°C
- Enlarged lymph nodes at two sites
- At least one internal organ affected

Tables

Table 1| **Table 1 Our patient's sequential blood results**

Parameter	Reference range	Day 1	Day 2	Day 4	Day 5	Day 21
White blood cell count (cells/L)	$3.5\text{-}11\times10^9$	28.84	33.14	16.23	13.44	6.54
Neutrophil count (cells/L)	$1.7\text{-}8.0\times10^9$	25.84	31.34	12.45	10.13	3.94
Lymphocyte count (cells/L)	$1.0\text{-}4.0\times10^9$	1.38	0.76	2.34	2.35	1.89
Monocyte count (cells/L)	$0.1\text{-}1.0\times10^9$	1.33	1.06	0.89	0.65	0.49
Eosinophil count (cells/L)	$0.0\text{-}0.46\times10^9$	0.14	0.30	0.90	0.26	0.20
C reactive protein (mg/L)*	0-5	332	212	77	44	2
Alanine aminotransferase (U/L)	<37	45	31	NA	NA	39
Bilirubin (μmol/L)†	<17	26	8	NA	NA	11

Table 2| **Table 2 Immunologically mediated drug reactions**

Type of drug reaction	Gell-Coombes classification	Clinical examples
IgE dependent	I	Urticaria, angio-oedema, anaphylaxis
Cytotoxic	II	Petechiae secondary to drug induced thrombocytopenia, haemolytic anaemia, transfusion reactions
Immune complex dependent	III	Vasculitis, serum sickness, some types of urticarial glomerulonephritis
Delayed-type cell mediated	IV	Exanthematous, fixed, and lichenoid drug eruptions; drug hypersensitivity syndrome; Sjögren's syndrome; toxic epidermal necrolysis