Disseminated herpes simplex virus: a case of eczema herpeticum causing viral encephalitis

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Abstract

Eczema herpeticum is a dermatological emergency causing a mortality of up to 10% if untreated. It frequently presents in a localised form and rarely disseminates via haematogenous spread with pulmonary, hepatic, ocular and neurological manifestations. Although it commonly appears on a background of atopic dermatitis, many other dermatological conditions have been described preceding this disease. Eczema herpeticum can be easily mistaken for folliculitis and is often treated accordingly with antibacterial drugs; therefore patients will often deteriorate before a diagnosis of eczema herpeticum has been considered.

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Background

Eczema herpeticum (EH) was initially described by Moriz Kaposi in 1887 and is also known as Kaposi varicelliform eruption.[1] It can be a dermatological emergency manifesting as a generalised vesicular eruption in a toxic patient with high morbidity and mortality. It is often associated with a pre-existing eczema diagnosis and for this reason it has a higher incidence rate in children; however, it is also common in the second and third decades of life.[2–4] It affects all ages with an equal incidence in males and females.[5] Some predisposing factors associated between atopic eczema and EH include an earlier onset of atopic eczema, a low level of natural killer cells, high level of immunoglobulin E and *Malassezia sympodialis* antibodies.[5]

Prompt treatment with antiviral medication is needed due to dissemination internally. If this occurs, and depending on the site of infection, the patient may present with pulmonary, hepatic, ocular and neurological symptoms. With the process of dissemination comes viraemia and scepticaemia.[1]

Case presentation

A 36-year-old male presented to accident and emergency with a 4-day history of rash, fever, headaches and generally feeling unwell. The rash was painful, with areas of blisters and punched out erythematous lesions approximately 0.5 cm in diameter, which were non-blanching in nature. The lesions started on the left side of the neck and progressed over the mandible area onto the face, the right side of the neck, the top of the chest and back and eventually to all four limbs. In places the rash produced serous and yellow fluids.

On admission the patient was being treated with oral flucloxacillin and amoxicillin for folliculitis, after initial presentation in the community. After being admitted this was changed to intravenous flucloxacillin, intravenous benzylpenicillin and topical fusidic acid for presumed folliculitis unresponsive to oral antibiotics. The patient also complained of a stiff neck, dry 'gritty' eyes, nausea, fever and a headache. The headache was initially a stabbing pain in the occipital region and progressed to be a holocephalic, constant ache. There was no photophobia or vomiting, no change in pain with position or time of day. Due to the ocular symptoms, topical chloramphenicol was also commenced.

Examination on admission

The patient looked generally unwell, but was alert and orientated with a GCS of 15/15. Temperature was 38°C, respiratory rate 15 breaths/min, and oxygen saturation was 100% on room air. His chest was clear to auscultation with no changes on percussion. Heart rate was 67 bpm, blood pressure 100/65 mmHg, and heart sounds were normal. There were eruptions of vesico-pustules on a pink base, with some punched out lesions that were well demarcated and approximately 0.5 cm in diameter. The rash was widespread on the face, arms, trunk, back and backs of upper leg (Figures 1–3). The patient had a normal range of movement of the neck in all directions.

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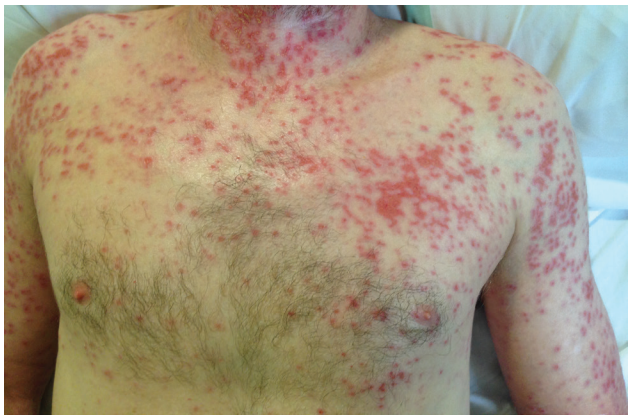
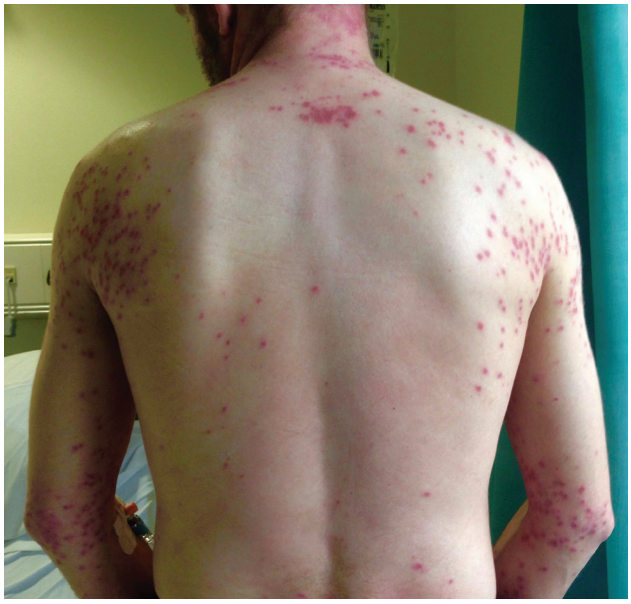
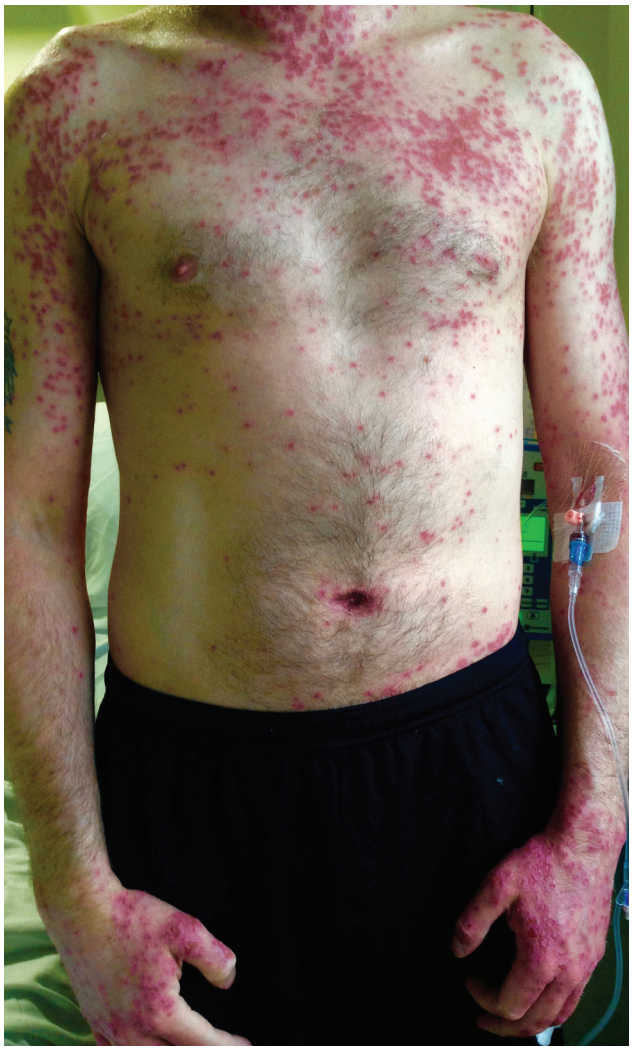
Figures 1–3 A 36-year-old male with widespread eczema herpeticum.







Vesicles were present on the right eyelid. Cranial nerve examination was normal. There was mild reduction in power in all four limbs but sensation, tone and coordination were normal. His abdomen was soft, non-tender, with no organomegaly and no masses.

Past medical history

The patient had been diagnosed with eczema in 2002; it was usually well controlled with regular emollients (Diprobase) and occasional Eumovate for any flares. He had previously been treated with tacrolimus 0.1% ointment between 2005 and 2010 and Oilatum cream and Plus Bath between 2002 and 2008. He had received no blood transfusions, no history of intravenous drug use and no known drug allergies. He was a non-smoker, and consumed 24 units of alcohol at the weekend.

Clinical progress

After admission, a lumbar puncture was undertaken due to the possibility of meningitis. This was considered because of the headache, stiff neck and rash. Ceftriaxone and aciclovir were administered to cover for bacterial and viral infection until the cerebrospinal fluid (CSF) results were returned.

A differential diagnosis of EH was considered when, on further history taking, it was noted that the patient's wife had suffered from oral herpes 2 weeks prior to the patient's admission. Dermatology input on the same night confirmed the diagnosis of EH and the patient was advised to continue antiviral treatment: intravenous aciclovir 10 mg/kg, every 8 h for 10 days to 2 weeks. The patient started to clinically improve within 24 h of treatment.

On day 3 of admission the patient presented feeling 'spaced out' and at times confused. He described blurring of his vision that had started in the past 12 h. His headache and neck stiffness had been persistent since admission with no improvement. The patient felt feverish; his temperature at this time was 37°C while on regular paracetamol. Neurological examination showed a decreased GCS of 14/15 (E4 V4 M6), diplopia and decreased visual acuity. All other cranial nerves remained intact and gross ocular examination still showed the vesicles on the right eyelid, which had been present on admission. Upper and lower motor examination showed no changes from admission. Neck examination showed slightly decreased range of movements in both flexion and lateral flexion. A clinical diagnosis of viral encephalitis secondary to the EH was made.

Table 1 Blood test results

	On admission	Day 3
WCC	10.59	8.46
Neutrophils	9.14	7.02
Haemoglobin	146	132
MCV	92.4	91.5
Platelets	212	192
Sodium	134	133
Potassium	3.7	3.8
Creatinine	82	72
Urea	2.9	3.1
Bilirubin	20	15
AST	26	23
ALT	24	21
ALP	73	64
GGT	36	33
CRP	9.1	17.1

Ophthalmologic review confirmed right upper lid involvement, with no evidence of corneal infection and no changes to the optic discs. These findings were thought to be consistent with herpes zoster ophthalmicus; aciclovir eye drops were advised for 10 days. Visual changes improved after day 4 of admission.

The patient described a tingling of his left little finger and half of the ring finger, which persisted intermittently over 48 h. On examination of the upper limbs there was no change in power, no deficit in sensation and no change in tone, coordination or reflexes. The patient was treated with gabapentin for ulnar nerve involvement, which settled the symptoms.

On day 7 the patient started to feel systemically improved. The headache took 10 days to resolve. He received 2 weeks of intravenous aciclovir, and during this time the number of vesicles decreased, others crusted over and became less erythematous. There were remaining patches of vesicles over the wrists that had coalesced but showed signs of healing. The patient was discharged with ophthalmology and dermatology outpatient follow up.

Investigations

Investigations undertaken included bloods tests (Table 1) that showed neutrophilia and raised C-reactive protein, with these settling on day 3 of admission. HIV testing, hepatitis screen and blood cultures on admission were negative. Facial vesicle swabs and a throat swab revealed normal flora. No group A/C/G haemolytic streptococci were seen on throat swab.

The CSF fluid was clear and colourless. Gram staining showed no organisms. White cell count was < 5/cu mm; red cell count 16/cu mm. CSF protein was 0.36 g/L (normal), CSF glucose 3.5 mmol/L with serum glucose being 5.3 mmol/L. On day 4 of admission, the polymerase chain reaction (PCR) result was positive for herpes simplex virus (HSV)1. Computed tomography of the head showed no changes in the parenchyma, ventricles and skull. There was no evidence of space occupying lesions or acute haemorrhage.

Treatment

While in hospital, this patient received intravenous 10 mg/kg aciclovir 8 hourly for 14 days, 4 mg chlorphenamine 4 times a day to aid pruritus, a 5 day tapering course of prednisolone starting at 30 mg, 3.75 mg zopiclone once daily in the evening to support sleep, 300 mg gabapentin twice daily to settle the ulnar nerve involvement and 1 g paracetamol 4 times a day to aid with pain. Long term medications prior to admissions were continued. These included Balneum Plus oil used once a morning in the bath, Diprobase applied twice per day and Eumovate used in acute flare-ups of eczema.

Medication that had been discontinued during inpatient admission included chloramphenicol 4 times a day for 5 days and antibiotic medication (1 g intravenous flucloxacillin 4 times a day and 1.2 g benzylpenicillin 4 times a day).

Discussion

EH is caused by a viral infection usually on a background of a previous dermatological condition. Mortality from EH can be 6–10% if untreated[1] and is therefore regarded as an emergency. HSV1 and 2 are the common pathogens but others include coxsackie virus A16, smallpox and vaccinia.[1]

The majority of cases are in patients with pre-existing atopic eczema, but it can occur with other conditions such as pemphigus, seborrheic dermatitis, lupus erythematous, psoriasis, Darier's disease and after thermal burns.[2–4] EH can occur in all cases of atopic eczema but is often worse in more severe cases.[5] There is no seasonal variation.

Atopic eczema is due to underlying genetic and inflammatory changes as well as filaggrin gene mutations. Compromised innate immunity leads to an increased vulnerability to infections via a decrease in antimicrobial peptides such as cathelicidin LL-37, β-defensin 2 and β-defensin 3.[5] The most common bacterial infection is due to *Staphylococcus aureus* and most common viral infections include HSV1 and 2, coxsackievirus and pox virus.[5]

Many mechanisms in the pathogenesis of EH have been identified. It is thought that pre-existing dermatological conditions decrease the efficacy of both humeral and cell-mediated immunity, especially in immune pathways intertwined with the skin.[3] Beck et al. found that patients with atopic dermatitis and a history of EH had an increased rate of skin infections, which is thought to be related to these patients having a higher level of Th-2 cytokine.[6] Excoriation and scrubbing of the epithelium by patients with underlying dermatological conditions is thought to cause a disruption of the stratum corneum which can also play a role in the pathological mechanism.[1,7] Low levels of LL-37, an antimicrobial peptide cathelicidin, is linked to a decrease in

dermal innate immunity.[5] Dissemination of EH in more severe cases is thought to be via haematogenous spread.[5]

The rash, which can be described as clusters of itchy blisters or punched-out erosions, usually arises during the primary infection of herpes, 5–12 days after contact with an infected individual. It affects both areas with previous involvement with another pathology, and skin not formerly involved. It is commonly a localised rash, but, rarely, continues to disseminate over 7–10 days to distant dermal sites and internal structures.[2] Each lesion appears akin to the next and may be described as 'monomorphic'.[1,2] The blisters themselves may be filled with clear/yellow serous, purulent or blood-stained fluid. New blisters often have a central umbilication, discharging fluid and go on to crust over, forming erosions that can take between 2–6 weeks to heal.[1,2] A secondary bacterial infection can occur with *Staphylococcus* or *Streptococcus*[2] and should be treated accordingly.

The patient may feel generally unwell and have signs and symptoms such as fever and lymphadenopathy. In the case of disseminated disease involving organs such as the eyes, brain, lungs and liver, [1,2] each gives rise to its own set of signs and symptoms. Investigations into the cause can include scrapings of the blister for viral culture, direct fluorescent antibody stain, PCR sequencing or Tankz smear.[2] Bacterial swabs should also be taken to differentiate the cause of the rash.[2]

Antivirals such as oral or intravenous aciclovir should be started immediately on considering the diagnosis.[2] Topical steroids are only indicated to treat flares of eczema. An ophthalmologist should be involved if there is indication of eye or eyelid involvement.[2] EH can recur and therefore patients with a history of EH should avoid contact with active HSV.[5] In the case described here, it was close contact with active HSV which was the triggering event.

Viral encephalitis

Since the introduction of aciclovir, the mortality rate of HSV encephalitis has dropped from 70% to 20%; this may be lower if treatment is started within 48 h of admission.[8]
A large number of viruses have been implicated in viral encephalitis, although in many cases a definite diagnosis in not attained. The most common agents belong to the herpes virus family: HSV1 and 2, varicella zoster virus and Epstein-Barr virus.[9] HSV1 is thought to be the causative organism for 42% of all encephalitis cases.[10,11]

A wide variety of neurological symptoms have been described, including confusion, behavioural change, agitation, and focal or generalised seizures. Many more symptoms based on the site of infection can be produced, including upper and lower motor neurone symptoms and cranial nerve deficits.[9]

CSF PCR has become the primary investigation in suspected HSV encephalitis; it has a sensitivity of 96% and specificity of 99%.[9] However, an initial CSF PCR may be negative and if there is a high index of suspicion then antiviral therapy should not be delayed, and a second lumbar puncture carried out to confirm the diagnosis at the earliest opportunity.[8] CSF may show a lymphocytosis with a small rise in protein (< 150 g/dL); typically glucose is within normal limits.[9,12] HSV can cause haemorrhagic encephalitis and in these case red cells may be present in an atraumatic lumbar puncture.[9]

MRI reveals focal temporal lobe changes in 80% of HSV encephalitis, 10% in extra-temporal regions and 10% will have a normal MRI in those with CSF PCR positive for HSV.9 EEG findings consistent with HSV encephalitis include general low amplitude with occasional temporal lobe spikes.[9] Other investigations include culture of the CSF to exclude bacterial or fungal causes, and, rarely, brain biopsy.[13] Treatment with 10 mg/kg aciclovir 3 times a day for 14–21 days is the current recommendation.[10,14]

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