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A woman in her thirties with facial swelling and necrotic lesions

EDUCATIONAL CASE REPORT

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A woman in her thirties developed multiple necrotic lesions on her face in a short space of time. A dermatologist recognised clinical features associated with a rare diagnosis, which was eventually confirmed by diagnostic workup. Known atopic eczema increased the risk of a severe course of what was initially a mild disease, and a multidisciplinary approach proved necessary.

A woman in her thirties with known atopic dermatitis was admitted via the out-of-hours primary care service to the department of medicine at her local hospital with suspected facial cellulitis. She was not taking any regular medication. She had a cat at home. She had been on holiday in southern Europe one month before the onset of symptoms. In the few days prior to admission, she had developed increasing pain, swelling, redness and warmth in the left side of her face. The day before admission, she had started to take oral phenoxymethylpenicillin 1 g four times daily after being assessed by an ear-nose-throat specialist.

On admission to the department of medicine, she was in a slightly diminished general condition. Her blood pressure was 137/77 mmHg, pulse 92 bpm, respiratory rate 19 breaths per minute, oxygen saturation 97 % and temperature 36.3 °C. She had clear swelling and diffuse redness on the left side of her face, particularly around the eye and on the cheek. Several small crusted lesions had also appeared in this area. Blood test results found CRP 70 mg/L (reference range <5) and leukocytes 5.5 × 10^9/L (4.1–9.8 × 10^9/L).

Her condition was considered to be cellulitis, with eczema as a possible portal of entry. After blood cultures had been ordered, intravenous antibiotic treatment consisting of cloxacillin 2 g four times daily was initiated.
Blood cultures were negative. Due to a lack of improvement and to improve tissue penetration, intravenous treatment with clindamycin 600 mg four times daily was added on day 5. A swab sample of wound secretion was sent for culture and sensitivity testing on day 6, which showed growth of Staphylococcus aureus. Her leukocyte count had increased to 14.9 × 10^9/L. An automated differential count was not possible, and there was an alert about potentially abnormal lymphocytes. Despite this, CRP fell from 70 mg/L to 38 mg/L.
After a few more days of clinical deterioration, oral ciprofloxacin 750 mg twice daily was also added to cover any gram-negative bacteria. A clearly enlarged gland was discovered at the corner of her left jaw, and when taken together with lymphocytosis of 10.0 × 10^9/L (1.2–3.1 × 10^9/L), this led to cutaneous manifestation of lymphoma or lymphoproliferative disease being considered. Blood smear revealed lymphocytosis with atypical cells, but findings of immunophenotyping of the blood were normal. The diagnosis of mpox (formerly known as monkeypox) was briefly discussed due to the ongoing outbreak in non-endemic countries in Europe and other parts of the world. However, since the patient was not in a known risk group, a bacterial infection was considered more likely.
Cellulitis is a common skin infection and typically involves the deeper layers of the dermis and subcutaneous fat tissue. The condition often arises as a wound complication, as suspected in our patient (1). The most common pathogens are streptococci and staphylococci, but other causative agents such as gram-negative bacteria may also be found. The diagnosis is made clinically with the support of laboratory test results. Before starting antibiotic treatment, samples should be sent for culture and sensitivity testing and blood cultures (2). Antibiotic treatment should be administered in accordance with national guidelines (3).

A dermatologist was contacted on day 9 due to the uncertain diagnosis and clinical deterioration. The review took place the same day, and the dermatologist recommended transfer to the dermatology department at a regional hospital. At the time of transfer, the patient had several large lesions with necrosis and central tissue loss located on the left cheek and temple. There were similar, but smaller, lesions on the right eyebrow and the back of the right hand. There was considerable swelling of the left side of the face, and her left eye was almost sealed shut. The lymph nodes under the corner of her left jaw were clearly enlarged (Figure 1). In the previous 24 hours, she had also developed generalised widespread maculopapular exanthem, as is seen with a drug reaction.

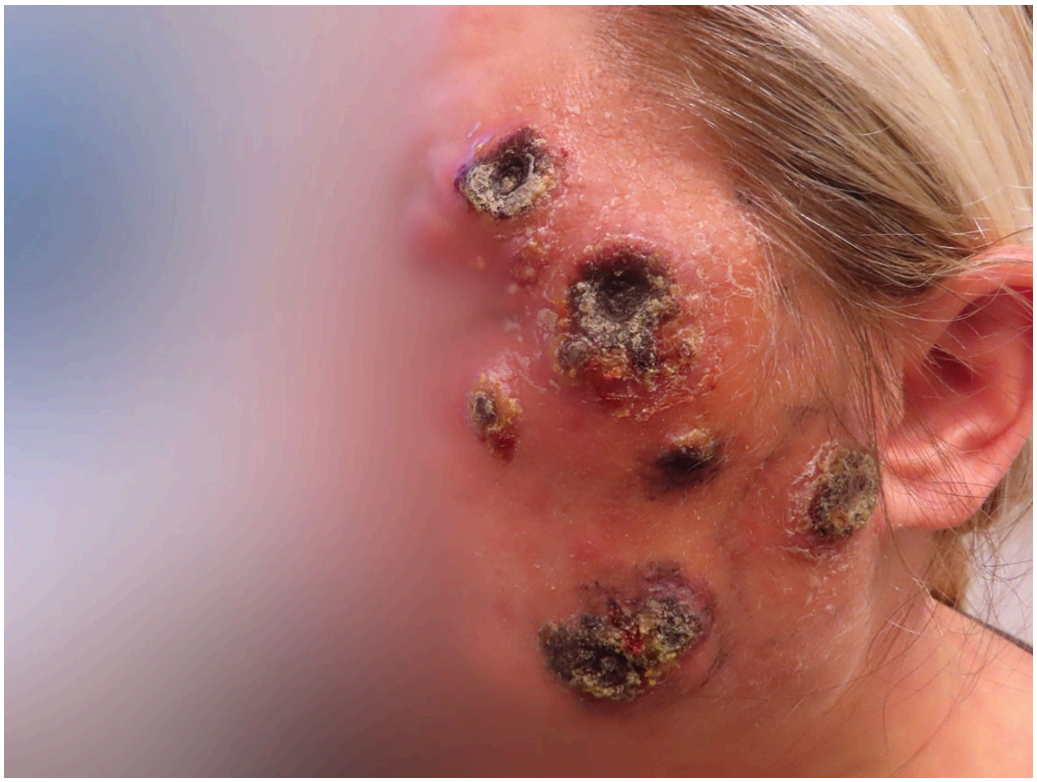

Figure 1 The patient had multiple necrotic lesions surrounded by swelling on the left side of her face.

Cloxacillin, clindamycin and ciprofloxacin were all discontinued because it was not possible to determine which medicinal product was causing the rashes. Blood test results found leukocytes 16.1 × 10^9/L (4.1–9.8 × 10^9/L), of which lymphocytes were 9.1 × 10^9 (1.2–3.1 × 10^9/L), neutrophils 5.6 × 10^9 (1.8–6.9 × 10^9), CRP 29 mg/L (<5 mg/L), alanine aminotransferase (ALT) 608 U/L (10–45), gamma-glutamyl transferase (GGT) 186 U/L (10–45) and bilirubin 6 µmol/L (> 20).

The patient's rash raised clinical suspicion of a viral skin infection, specifically cowpox. Leishmaniasis was also considered in the differential diagnosis because the patient had travelled to southern Europe. The elevated liver function tests were regarded as connected to her exanthematous drug eruption.

For diagnostic elucidation, a swab sample of wound secretion was taken on virus transport medium for polymerase-chain reaction (PCR) testing in the Department of Microbiology. A biopsy from the wound edge was placed in a sterile container with formalin and sent to the Department of Pathology at Haukeland University Hospital for haematoxylin-eosin (HE) staining. A biopsy placed in sodium chloride was sent to the National Reference Centre for Molecular Biological Parasite Diagnosis at Oslo University Hospital for leishmaniasis PCR testing.

The analysis performed at the local Department of Microbiology is real-time PCR to detect orthopoxvirus DNA, based on a method previously described (4). The method was implemented as the first part of two PCR analyses for the diagnostic workup of mpox and does not differentiate between the various orthopoxviruses. A specific PCR analysis for mpox was performed to rule out this as a cause of the patient's symptoms.

PCR analysis for orthopoxviruses was positive, while specific PCR analysis for mpox was negative. Diagnostic testing for further differentiation within the orthopox group is not available in Norway. Since we wanted to confirm the diagnosis for academic reasons, another swab sample of wound secretion was sent to the State Serum Institute in Denmark for further investigation. The sample was analysed with PCR and sequencing there, and cowpox was confirmed. Histological findings were also consistent with cowpox (Figure 2). Leishmaniasis DNA was not detected in the skin biopsy examined at the reference laboratory at Oslo University Hospital.

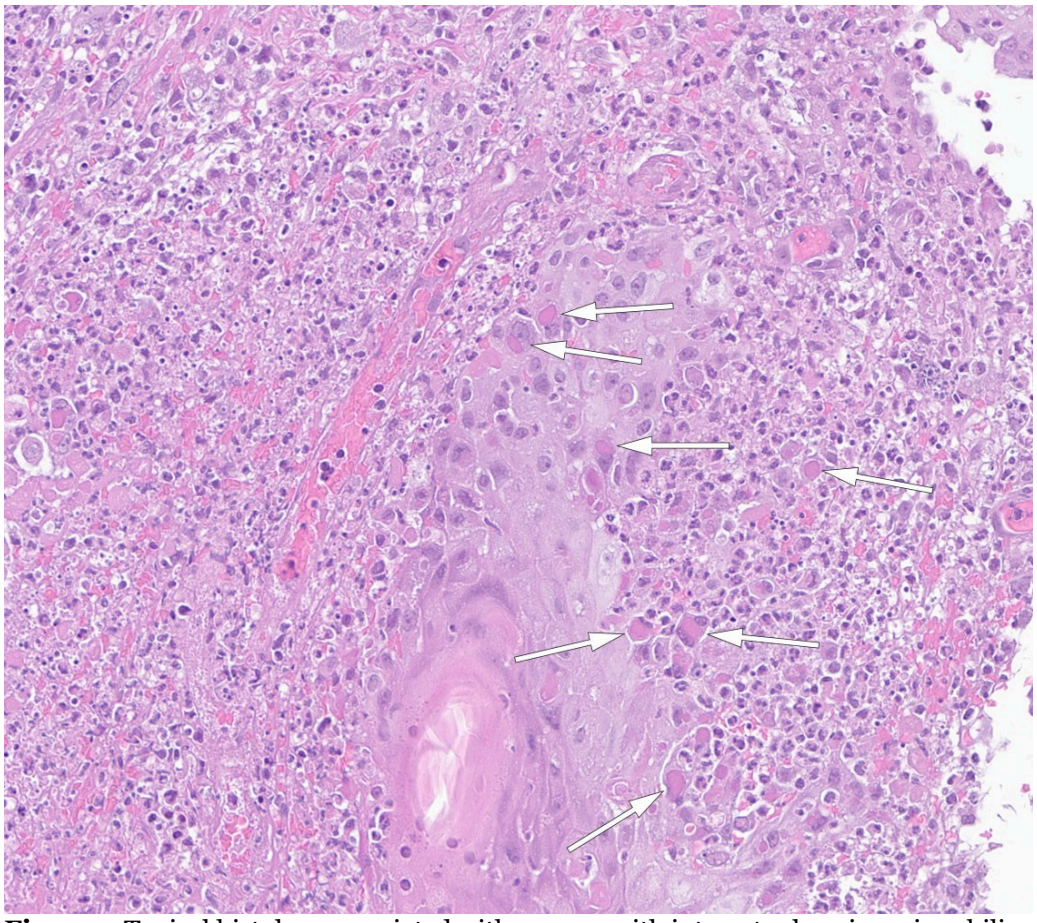

Figure 2 Typical histology associated with cowpox with intracytoplasmic eosinophilic inclusions (labelled with arrows) as well as subacute inflammation and necrosis detected in biopsy.

Cowpox is caused by the cowpox virus, which belongs to the Orthopoxvirus genus in the *Poxviridae* family. The orthopoxvirus group consists of several other species, including the mpox virus, vaccinia virus (vaccine strain) and the eradicated smallpox virus (5). Cowpox is predominantly a disease in animals. Despite the name, the virus is not endemic in cattle, but rather in rodents such as mice and rats (6, 7). In reports regarding cowpox in humans, cats are often implicated as the intermediate host, probably having been infected by rodents (8, 9). Transmission to humans is rare, but both isolated cases and small outbreaks in Europe have been published in recent decades (9–11). Cowpox cannot be transmitted between humans and is not a notifiable disease to the Norwegian Surveillance System for Communicable Diseases (MSIS) (5).

Oral prednisolone 40 mg once daily was administered, with a tapering plan, primarily for the patient's generalised drug reaction, but also to reduce the localised facial inflammation. The exanthematous drug eruption gradually

subsided over the first few days, and liver function tests returned to normal. Several attempts were made to mechanically remove the necrotic lesions on the face. Various wound dressings and antiseptic agents were used. Eventually, ultrasound of the left facial region was performed due to increasingly swollen and taut skin around the lesions on the left cheek. This examination revealed considerable inflammation and a large lymph node, which was considered to be reactive.

On day 30, the issue was discussed with a plastic surgeon, who recommended that conservative management be continued. In the following days, increasing undermining of the skin at the wound peripheries was discovered, as well as increasing deep necrosis at the wounds beyond the left lateral canthus. Repeat ultrasound revealed an incipient abscess. On day 37, another plastic surgery assessment was requested with regard to wound revision and assistance with planning further treatment. The patient was then transferred to the plastic surgery department. Surgical treatment was found to be indicated with opening of the skin and removal of fat necrosis and dead tissue. The skin defects were reconstructed with local skin flaps. Repeat samples sent for culture and sensitivity testing revealed growth of Staphylococcus aureus, and treatment with intravenous cloxacillin 2 g four times daily was initiated despite an earlier drug reaction to an unclear agent. The patient was in a good general condition and afebrile, but she had elevated CRP at 71 mg/L, while her leukocyte count was 9.1 × 10^9/L. Clinical examinations found increasing signs of localised infection, pus under the skin flaps, followed by ischaemia and ensuing necrosis of the flaps. Revision of the necrosis and wound care was performed on several occasions. During infection control and examination of clean wound surfaces, it was decided to perform reconstructive surgery with a full-thickness skin graft from a donor site on the left upper arm. One of the reasons for selecting the donor site was the patient's history of atopic eczema (Figure 3). Intravenous cloxacillin 2 g four times daily was administered for a total of nine days, before switching to oral dicloxacillin 500 mg three times daily for a total of ten days. The patient did not develop any skin reaction to antibiotics this time.

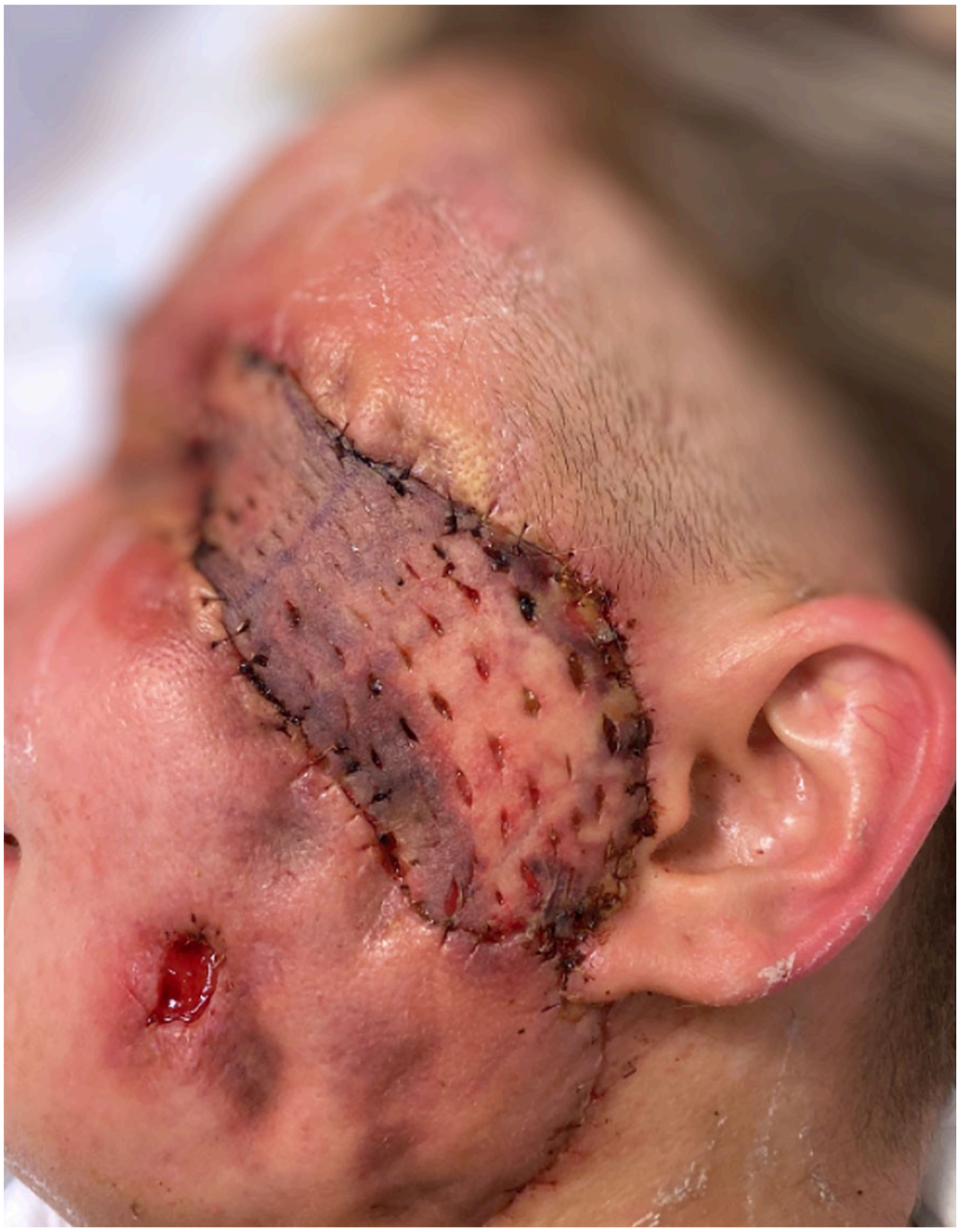

Figure 3 Full-thickness skin graft on the face was harvested from the left upper arm.

The patient was discharged home after a total of 55 days in hospital. She received follow-up with regular check-ups at the plastic surgery outpatient clinic. The graft took well, and two small residual wounds healed by secondary intention with a conservative wound care regimen.

Discussion

The history of the cowpox virus is very interesting because it gave rise to the smallpox vaccine. At the end of the 1700s, inoculation was attempted by rubbing smallpox wound material into healthy children to try to protect them from smallpox. This generally produced a milder form of the disease, and immunity, but death did occur with this method. The British doctor Edward Jenner (1749–1823) discovered that milkmaids who had close contact with

cows almost never died of smallpox. Therefore, there was a perception that cowpox could protect against smallpox. From clinical trials on patients, he eventually gained increasing support for his theory. It was later understood that protection from smallpox was due to cross-immunity between the various orthopox viruses. This laid the foundations for the smallpox vaccine, which was initially based on the cowpox virus. The word 'vaccination', which is used today for immunisation against all types of disease, originates from the word *vacca*, which is Latin for cow (12, 13). However, the virus that was used for vaccination from the 1900s was so different to the virus that causes cowpox that it was considered a separate virus, called vaccinia virus. Following intensive vaccination campaigns, reporting and isolation of patients, in May 1980 the World Health Organization was able to declare smallpox to have been eradicated, and there are now just two official stocks of the virus in the United States and Russia, under WHO supervision (5).

The incubation period of cowpox is typically 1–2 weeks, and therefore it is likely that our patient was infected by her cats in Norway after she had returned from holiday. The cats had no visible lesions. Similar skin lesions had been seen on two previous occasions in the Department of Dermatology at Haukeland University Hospital in 1994 and 2002 (14, 15). Transmission from cats was also suspected in these cases. It is worth mentioning that curiously all three patients lived in the same part of Vestland county, which might lead to the suspicion of a reservoir of the virus in rodents in the area.

In cowpox, typically one or several lesions develop with central tissue loss and necrosis. There is often surrounding erythema and oedema, as well as generalised symptoms such as fever, myalgia, headache and lymphadenopathy. In most cases, the condition is self-limiting and heals with scarring. In individuals with reduced immunity, but also those with atopy such as our patient, more serious and widespread lesions can develop, as well as more severe generalised symptoms. There have also been reports of death in such patients (16). We think that the patient's atopic eczema contributed to a large extent to the severe and prolonged clinical course, which is also known to occur with common viral infections with the herpes simplex and varicella zoster viruses (17). Initial treatment with prednisolone and discontinuation of antibiotics was likely to have made no or little contribution to the clinical deterioration. Our reasoning for this is that extensive local inflammation was already seen before these measures were implemented. Nevertheless, it cannot be entirely ruled out that prednisolone may have prolonged the course of the disease. Since the patient was born after 1980, she had not been vaccinated against smallpox. This may have contributed to the increased morbidity since a certain amount of cross-immunity is expected between vaccinia virus and cowpox (11, 18).

In the last few years, the incidence of zoonotic poxviruses, including both cowpox and mpox, seems to have been rising (16, 19). It is uncertain whether this is due to an actual rise or increased awareness and reporting of the diseases. Reduced herd immunity to zoonotic poxviruses as a result of an ever smaller proportion of the population having been vaccinated against smallpox may be a significant factor. Greater interest in pets such as cats or rodents, which can infect humans, may also be a possible cause of the increased

incidence (16, 18). Rising incidence of zoonotic viruses, along with an increasing number of older and immunosuppressed patients who either have little residual immunity from previous vaccination or are unvaccinated, may result in an increased potential for severe disease. A discussion about the reintroduction of vaccination for individual groups and a renewed focus on the development of effective and safe antiviral agents seems appropriate.

There is currently no well-documented treatment for cowpox apart from optimal wound management and prevention of bacterial superinfection. There are reports in the literature of trial treatment with the antiviral agents cidofovir, brincidofovir and tecovirimat for viruses in the orthopox group, including cowpox (20). The issue was discussed with infectious disease specialists, and no indication for such treatment was found at that time.

This case report illustrates that atopic eczema can be a predisposing factor for a severe clinical course of an initially mild infection. A multidisciplinary approach was required in this case. The diagnostic workup and treatment of this patient involved specialists in infectious diseases, dermatology, microbiology, pathology, ophthalmology and plastic surgery to ensure the best possible end result and to prevent serious complications.

The patient has consented to the publication of the article.

The article has been peer-reviewed.

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