INVESTIGATIVE REPORT

The Munich Outbreak of Cutaneous Cowpox Infection: Transmission by Infected Pet Rats

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Cowpox virus infection of humans is an uncommon, potentially fatal, skin disease. It is largely confined to Europe, but is not found in Eire, or in the USA, Australasia, or the Middle or Far East. Patients having contact with infected cows, cats, or small rodents sporadically contract the disease from these animals. We report here clinical aspects of 8 patients from the Munich area who had purchased infected pet rats from a local supplier. Pet rats are a novel potential source of local outbreaks. The morphologically distinctive skin lesions are mostly restricted to the patients' necks, reflecting the infected animals' contact pattern. Individual lesions vaguely resemble orf or Milker's nodule, but show marked surrounding erythema, firm induration and local adenopathy. Older lesions develop eschar, leaving slow-healing, deep ulcerative defects after eschar separation. Severe flu-like illness may be present in the acute phase. Smallpox-vaccinated patients tend to develop less severe reactions and heal more quickly. The differential diagnosis may include other localized orthopoxvirus infections, herpes simplex, bacterial infection, anthrax, foreign body granuloma, and primary tuberculosis. Dermatologists should be aware of the diagnostic and therapeutic algorithms for handling this disease. Key words: orthopoxvirus; cowpox; rat; human; infection.

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Cowpox virus infection of humans is a clinically distinct, but relatively uncommon, skin disease. It is confined to Europe and the adjacent former USSR, and has potentially serious consequences. It is not found in Eire, USA, Australasia, or the Middle or Far East. Prior to 2009, more than 50, mostly sporadic, cases have been reported (1). Small rodents are believed to be the current reservoir of cowpox virus (2), whereas cats and cows are most relevant in transmitting the orthopoxvirus to humans. Clusters of patients who acquired monkeypox virus,

another type of orthopoxvirus, from infected pet prairie dogs have recently been described in the USA, making the medical community aware of the risk of transmission of pox viruses from pets (3).

Seven of 8 exposed patients living in the Munich area contracted cowpox virus infection from an unusual source: rats infected with cowpox virus bought from local pet shops and reputedly from the same supplier caused a clinically distinctive pattern of infection, which was mostly restricted to the patients' neck and trunk. We report here dermatologically relevant aspects of our patients in order to alert the medical community to the possible risk of a zoonotic orthopoxvirus outbreak in people handling rats, discuss patient diagnosis and management, and highlight some clinically unique features in this case series.

CASE REPORTS

We report here 4 patient clusters with a total of eight patients. Clinical data and selected aspects of our patients are summarized in Table SI (available from: http://www.medicaljournals.se/acta/content/?doi=10.2 340/00015555-1227).

Patient 1

A 16-year-old, non-atopic school student was the index patient of the first cluster. She had developed 8 cutaneous seropapules on her neck, ranging from 3 to 12 mm in size, and a single 8-mm lesion on her scalp. Her first lesions appeared 5 days after purchasing a pet rat. Severe lymphadenitis and oedema of the neck region (Fig. 1) interfered with her daily activities. Subsequently, all lesions became necrotic, transformed into an eschar and ulcers persisted for the following 3 months. Five months after her infection, all lesions healed, but left extensive, disfiguring scars. When a veterinary dermatologist examined the rat, rodent orthopoxvirus infection was suspected immediately. The diagnosis was confirmed as cowpox by polymerase chain reaction (PCR) analysis of crusts. Subsequent PCR and gene sequencing confirmed an identical strain of cowpox virus in the patient. Patient 1 had never been vaccinated against smallpox.



Fig. 1. Necrotic lesion and lymphangitis due to cowpox virus infection (patient 1).

Patient 2

The 40-year-old mother of patient 1 developed a single, 8-mm diameter, round seropapule on her neck 12 days after purchase of the rat. There were no signs of lymphadenitis. She had been vaccinated against smallpox 28 years previously and did not have a history of atopic diseases. Her superficial lesion became crusted and healed rapidly within 6 weeks.

Patient 3

The 60-year-old grandmother of patient 1 also developed 2 distinct, 1-cm diameter, round seropapules on her neck approximately 14 days after the rat was purchased. Her papules became crusted and healed uneventfully. She had been vaccinated against smallpox 48 years previously and did not have an atopic background. She had been on oral medication with diclofenac and low-dose (5–10 mg/day) prednisolone for rheumatoid arthritis for years. Upon diagnosis of cowpox infection in her granddaughter, prednisolone was discontinued for safety reasons for 3 weeks without a relapse of arthritis. Patient 3 showed a prolonged course of healing, but no signs of lymphadenitis.

Patient 4

A 16-year-old girl was the index patient of cluster 2. She presented with a 2-day history of 3 small (5-mm), oedematous papules on her neck, chest and abdomen, accompanied by enlarged axillary lymph nodes, fever, sore throat, coughing, headache, malaise and loss of appetite. Though diagnostic examinations were scheduled for the next day, she returned after 8 days with erythematous nodules up to 20 mm in diameter showing central necrosis. The cervical nodule developed a small satellite pustule. Swelling and tenderness of regional lymph nodes were also present. Pulmonary involvement

was excluded by chest radiograph. The abdominal lesion was excised for diagnostic purposes. Histology showed ulceration with multinucleated giant cells, eosinophilic intracytoplasmic inclusion bodies inside the keratinocytes, and ballooning keratinocyte degeneration on the ulcer's edge. PCR analysis and gene sequencing, as well as an orthopoxvirus specific serum antibody titre of 1:640, confirmed the infection. Anti-inflammatory treatment was initiated with glucocorticosteroid cream under occlusive dressings and oral methylprednisolone 24 mg/day (0.6 mg/kg body weight). Clindamycin 600 mg twice daily was administered for 7 days to prevent bacterial superinfection. Since the lymphangitis progressed after 3 days, the corticosteroid dose was increased to 40 mg/day for 7 days and tapered off within a further 9 days. The lesions regressed significantly, and healed in 6 weeks, leaving scars. The girl had not been vaccinated with vaccinia virus. There was no history of atopic dermatitis. A new pet rat had been purchased 4 days prior to the first symptoms from the same local pet dealer and died 9 days after its purchase. Three of 5 other rats, which had already been kept at the family's house, subsequently developed skin lesions compatible with rodent cowpox infection, but none of these died.

Patient 5

The 42-year-old mother of patient 4 presented with ten, up to 35-mm diameter, confluent plaques with central erosions (Fig. 2). The plaques showed central necrotic crusts 5 days later. The regional lymph nodes were tender and enlarged, but there were no other systemic findings. The lesions had appeared 11 days after the purchase of the new rat. An orthopoxvirus specific serum antibody titre of 1:2560 confirmed the diagnosis. Topical corticosteroids and antibiotics were started on admission to hospital without any visible improvement. The lesions started to regress only upon initiation of oral methylprednisolone 24 mg/day (0.5 mg/kg body weight), which was subsequently tapered



Fig. 2. Early lesion of cowpox virus inoculation (patient 5).

off and administered for a total of 17 days. In addition, glucocorticoid cream had been applied under occlusion. Pulmonary involvement was excluded by chest radiograph. Complete resolution took 4 weeks. Smallpox vaccination had been performed in her childhood. There was no history of atopic dermatitis.

Patient 6

A 22-year-old woman was the index patient of cluster 3. She presented with an 8-mm diameter, dark eschar surrounded by a raised, erythematous border in her right clavicular region, which had developed over the past 12 days, influenza-like symptoms, myalgia, pronounced local lymphadenopathy, and fatigue. Oral clindamycin 600 mg 3 times a day was administered for 10 days to prevent bacterial superinfection. Four weeks later, the necrotic tissue fell off. Healing by secondary intention continued for several weeks and left a scar. The patient had purchased 2 pet rats 9 days prior to the development of the skin lesion. One of the animals developed a cutaneous lesion on its leg. A skin biopsy taken from patient 5 showed central necrotic ulcerations, vacuolated keratinocytes with eosinophilic intracytoplasmic inclusion bodies, and multinucleated giant cells. She had allergic rhinoconjunctivitis and had never been vaccinated with vaccinia virus.

Patient 7

The 20-year-old boyfriend of patient 6, who had observed a small vesicle on his right shoulder 5 days previously, presented with an erythematous, raised, crusted papule of 5-mm diameter. He denied pain or tenderness and did not have lymphadenopathy or fever. Three days later the lesion changed into a necrotic, painful ulcer with concomitant lymphangitis, regional lymphadenopathy, fever and night sweats. He received topical fusidic acid and betamethasone valerate cream for 6 days and oral clindamycin 600 mg t.i.d. for 10 days. Skin biopsy was similar to patient 6. He also had allergic rhinoconjunctivitis and had never been vaccinated with vaccinia virus.

Patient 8

Patient 8 was a single 33-year-old patient with kidney transplant. She had been on oral ciclosporin and mycophenolate mofetil for 3 years. She had already owned three rats and had purchased two new rats from the same local pet dealer as patient 1. After a few days, one of the new rats died, and the surviving rat was moved into the cage of the other rats. Approximately a month after the date of purchase, the woman was bitten on the tip of the finger by one of her older animals. When she was informed of the orthopoxvirus outbreak by the local health authorities, she avoided all direct contact with her rats,

and presented to her physician. Clinical examination of patient 8 performed 10 days after the bite showed no cutaneous signs of viral inoculation. However, an elevated specific IgM orthopoxvirus titre was found. The dead new rat was confirmed to have died from orthopoxvirus infection, and 3 of the 4 living rats had typical rodent cowpox lesions (Fig. 3). The rat which had bitten her was pregnant and many of the baby rats showed signs of early orthopoxvirus infection. All rats were sacrificed for safety reasons. Orthopoxvirus PCR was positive in all the animals' blood, but negative in the animals' saliva. A cat living in the house without direct access to the rats did not contract the infection.

DISCUSSION

This local outbreak of cowpox infection occurred in a group of patients who contracted the disease directly from infected pet rats. The rats were all purchased within a short period of time from a variety of pet shops within Munich. All patients except patient 8 repeatedly handled their rats. The close contact and the preference of rats for sitting in the supraclavicular region appear to be important epidemiological factors in both the severity and characteristic clinical localization of the lesions.

Some of the clinical features were in common with Milker's nodule and cowpox transmitted by cats. The localization, however, is different, as the rats like to sit on the owners' shoulders and tiny scratches may occur at the neck and pectoral girdles. The number of lesions was low (a maximum of 10 in patient 5), and the incubation period ranged from 4 to 16 days. Although most lesions resolved within the expected 6-week time-frame, in patient 1 the disease took a very protracted course of up to several months. Extensive residual scarring occurred in 4 patients, and there was marked and painful local lymphadenopathy in five of the seven patients with clinical lesions.

Orthopoxvirus

The cowpox virus belongs to the *Poxviridae* family and the *Chordopoxvirinae* subfamily, a diverse subfamily



Fig. 3. Close-up of a pet rat infected with cowpox virus.

of extremely large virions (Table SII; available from: http://www.medicaljournals.se/acta/content/?doi=10.2 340/00015555-1227). The orthopoxvirus genus is one member of this subfamily, and includes more than ten distinct species, such as the closely related vaccinia, cowpox, and smallpox viruses. The cowpox virus exhibits low infectivity for humans and is transmitted only by direct contact with skin lesions of infected animals. Despite widespread disease in domestic and wild animals (2, 4–7), human infections are very rare and are commonly acquired from pet cats. No human case has been reported in anyone caring for a sick pet after the diagnosis had been made (8). Person-to-person transmission of cowpox has not been reported, although autoinoculation may rarely occur (8).

Rats as popular pets

Pet rats are popular domestic animals in Germany. These rats like to sit on the owners' neck and shoulders or hide under shirts and jumpers. Their claws may produce tiny, often unnoticed, scratches and punctures, and inoculate the cowpox virus, especially in the neck region. The infected rats themselves most frequently had ulcers on the legs, toes, footpads, faces, and ears in our series.

In contrast, cat-associated cowpox has been reported to occur mostly on the hands and the face (9), thus reflecting the different handling and contact behaviour regarding this species. Ulceration of lymph nodes and secondary bacterial infections have been reported, but were not observed in our case series. Although the human infection usually remains localized and self-limited, disseminated disease may occur (10). Even a fatal outcome due to secondary complications has been reported in an immunocompromised patient (11).

Reservoir of cowpox

Cowpox has long been regarded as a cow's disease transmissible to humans, manifesting as ulcers on cow's teats and milker's hands. Wild rodents are the reservoir, not cows (2). With the exception of some endemic areas in Russia, the occurrence of cowpox in a cow or farmer is uncommon today. In Great Britain and, more recently, in Germany, cowpox infection of cats has been recognized as a seasonal disease with a peak incidence in the autumn (12). Skin lesions in cats are usually multiple and consist of papules, vesicles, pustules, and finally crusts, predominantly on the face. In severe cases, the animals may develop anorexia, pneumonia, conjunctivitis, diarrhoea, and, rarely, may die of the disease (2).

Cowpox infections following transmission by rodents have been described repeatedly in captive exotic animals living in zoos and circuses (8, 13, 14). Human cowpox infection in recent years has been described most fre-

quently after contact with infected domestic cats. Prior to 2009, only 4 isolated cases of rat-associated human cowpox infections had been recorded in the literature. One of them was, in fact, a transmission from a rat to an elephant and subsequently to a human (15–18). In 2009, two additional outbreaks of mini-epidemics were reported in Germany and France (8, 16, 18–22).

Path of infection

All our patients apparently contracted cowpox infection by direct inoculation from affected rats. In all cases, at least one of the rats had typical clinical lesions, and all patients reported repeated and close contact with the pets in the affected body regions. In contrast, two adult men living in the household of patient 1, one adult man and one child in the household of patient 4, and the husband of patient 8 did not have direct contact with the rats, and did not develop any clinical signs. The tiny, but sharp, claws of an infected rat may easily penetrate the skin barrier of humans, thereby inoculating the orthopoxvirus. This mechanism closely resembles skin lesions caused by auto- and hetero-inoculation of vaccinia virus in children (23). The incubation period of 4–14 days in our patients parallels that of Milker's nodule. None of the rat owners reported noticeable skin wounds prior to the development of the lesions.

Cross-reaction between cowpox and vaccinia virus

Smallpox vaccination with vaccinia virus is suggested to attenuate cowpox infection through cross-immunity with orthopoxviruses, but the clinical reality may be different. First, the protective effect of smallpox vaccination decreases within decades, and an adult vaccinated more than 30 years ago may be as susceptible to smallpox and cowpox virus infection as an unvaccinated person (24). Secondly, even a recent vaccinia vaccination does not fully protect against cowpox (8). Cowpox virus may induce clinical lesions in spite of pre-existing immunity. Therefore, vaccination is not performed in individuals working with cowpox virus (8, 25).

Infectivity and lethality of cowpox virus

Cowpox infection in immunocompetent individuals is a self-limiting disease, but 4 cases with severe, generalized infection have been reported (8, 11, 26). One patient with a fatal outcome suffered from severe atopic dermatitis and was concurrently being treated with systemic glucocorticosteroids (8, 11).

Two of our patients were on current immunosuppressive therapy. Patient 8 was a renal transplant patient and patient 3 was treated for rheumatoid arthritis. Patient 8 was bitten on her finger by a rat with confirmed viraemia. As salivary swabs for cowpox virus DNA were PCR-negative at the time of a positive blood test,

it seems probable that its saliva would also have been negative at the time of the bite. Patient 3 developed only one lesion, which healed within the anticipated period of 6 weeks. In addition, the younger sister of patient 4 also had direct contact with the new rat, but she remained healthy. These observations underline the role of chance and the complexity of immune response in the disease development.

Although there is no risk of airborne infection, infectious particles may be spread by accidental inoculation following contact of contaminated matter with skin. Thus all cowpox lesions should be covered with non-occlusive dressings, as recommended for vaccination sites.

Atopic dermatitis as a risk factor

Patients with atopic dermatitis may develop eczema herpeticum and vaccinatum. Similarly, generalized eruptions due to cowpox virus infection may occur (10). These potentially lethal, disseminated viral infections are associated with an impaired innate and adaptive immune response (27). They are the consequence of the patients' atopic background, and do not require the presence of clinically visible lesions (23). The low numbers of plasmacytoid dendritic cells in atopic dermatitis lesions and low levels of the antiviral peptide LL-37 may contribute to this phenomenon (28, 29).

As vaccinia virus resembles cowpox virus in most aspects, some authors believe that it has originated from wild type cowpox virus strains (23), whereas others favour an origin from horsepox (30). The biological response of humans to cowpox infection may follow the reaction pattern of vaccinia virus and vaccination. For instance, a case of almost fatal eczema vaccinatum in a child with atopic dermatitis caused by heteroinoculation of vaccinia virus from a vaccinated parent has recently been described in the USA (31).

Differential diagnosis and diagnostic approach

The differential diagnosis of cowpox infection involves other localized orthopoxvirus infections, such as orf, Milker's nodule, vaccinia, monkeypox, and tanapox infections. Herpes simplex, impetigo contagiosa, ecthyma, staphylococcal abscess, sporotrichosis, anthrax (32), foreign body granuloma, and primary tuberculosis should also be considered.

Cowpox virus infection can be suspected on clinical grounds, but the diagnosis must be confirmed. The direct ultrastructural detection of a brick-shaped virus using tungstic acid-stained native material is most useful to quickly confirm the diagnosis of an orthopoxvirus. Serology can also be helpful. Histopathological examination of crusts or infected epidermis may identify pox virus inclusions. The identification of species and subspecies requires specific molecular biological methods. For the clinician, PCR is the easiest and fastest specific test method.

Vesicles, pustules, crust material, or even dry swabs from the edges of the crusts may be all that is needed. Specific determination of virus type and gene sequencing requires the help of an experienced reference laboratory, such as in our case the German National Poxvirus Reference Laboratory, the Robert-Koch-Institute in Berlin, or the Bavarian Health and Food Safety Agency.

Treatment options

The immune response against cowpox virus may cause collateral damage to healthy tissue. Thus, slight therapeutic immune response attenuation may reduce skin necrosis and tender, persisting lymphadenopathy. Although oral glucocorticoids and other immunosuppressive drugs are relatively contraindicated in cowpox infection (11), they may in fact be beneficial in later disease stages when an established immune response is confirmed by serology. Disease resolution depends, among other factors, on a delayed-type hypersensitivity response. Analogously, low-dose oral glucocorticoids are administered in carefully selected, severe cases of mononucleosis, herpes zoster, or eczema herpeticum. Short courses of anti-inflammatory glucocorticoid doses (such as prednisolone 0.2-0.8 mg/kg body weight/day for 1–2 weeks) may be considered only in selected, well-monitored cases of cowpox infection, depending on the clinical presentation. This restrictive recommendation is due to the reported fatal case of a patient treated with systemic steroids (11). As there is no licensed antiviral chemotherapy for cowpox infection, and the whole spectrum of antivirals for herpes simplex virus is ineffective in orthopoxvirus infection, a delay of effective therapy such as cidofovir (33, 34), intravenous immunoglobulins or novel experimental drugs may be detrimental. Cidofovir is an approved treatment of cytomegalovirus retinitis in AIDS patients. The limiting factors are nephrotoxic side-effects, thus cidofovir should be administered only under strict medical supervision. High-risk patients should be hospitalized for supportive treatment. Contact of high-risk individuals with infected animals should be prevented.

Public health aspects

Based on our current experience, patients with suspected cowpox infection should be questioned carefully about contact with pets and new pet purchases. New cases should be reported to the local public health authorities to prevent larger epidemics among both humans and animals. As domestic cats are thought to be infected by direct contact during hunting of wild rodents, there is little room for preventive measures.

The clustered dates of infection and the human incubation periods of 4–14 days suggest that all rats had already been infected when obtained from the pet shop and may have stemmed from the same breeder. The

4-day incubation period in case 4 matches the earliest time-frame for Milker's nodule, which is also spread by skin inoculation. The rat was noted to have conjunctivitis, sneezing, and a crust on its nose at the time of purchase. None of the other rats were observed to have skin lesions at the time of purchase. Further zoonotic spread of this cluster of infections was minimized by the rapid clinical and PCR diagnosis, followed by prompt action of the human and veterinary dermatologists together with the public health authorities in Munich. Public and individual actions to prevent spread of infection must be in accordance with local law and guidelines, including multidisciplinary management of infected patients and animals.

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