A Case of Facial Cellulitis and Necrotizing Lymphadenitis due to Cowpox Virus Infection

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We describe a patient with facial cellulitis/erysipelas due to cowpox virus inoculation in the respiratory epithelium of the nose. A cytopathic agent was isolated in cell culture, and the diagnosis of cowpox was confirmed by electron microscopy and polymerase chain reaction. The most likely source of infection was exposure to the family cats. In addition to the severe edematous cellulitis of the face, the clinical course was dominated by several areas of subcutaneous, necrotizing lymphadenitis, from one of which a huge abscess formed that had to be incised. Hyperbaric oxygen treatment was provided to prevent development of dermal necrosis. The healing process in the numerous areas of lymphadenitis was markedly protracted, and 1 persisting node (which yielded positive results on polymerase chain reaction) had to be excised 2 years after onset of disease. This is the first reported case of inoculation of cowpox virus in the respiratory mucosa of the nose. It resulted in a clinical course totally different than that for inoculation in the skin. We also present a short review of findings on orthopoxvirus infection that focuses on the chain of transmission.

Facial infection of the skin and soft tissues can be due to a number of bacterial agents, but it can also be due to viruses such as herpes simplex virus type 1, varicella zoster virus, and a range of poxviruses. Formerly, variola virus had humans as its exclusive host, but with its eradication through mass vaccination, the total number of poxvirus infections has been dramatically reduced. However, cases of zoonotic poxvirus infection have occasionally involved humans. Such cases may present diagnostic difficulties and may have devastating outcomes [1]. We report a case of cowpox infection with a prolonged disease course, and we discuss the viral, diagnostic, epidemiological, and therapeutic aspects.

CASE REPORT

In early November 2000, a 7-year-old girl living in the southeast of Sweden sought medical attention from a general practitioner. She presented with an inflammatory, erythematous swelling of the skin beneath the right ear and painless lymphadenopathy in the regional parotid and upper jugular lymph nodes. She had no history of skin injury in the affected region of the head and neck. Two weeks before the onset of symptoms, the patient had visited Spain. She had received childhood vaccinations against mumps, rubella, measles, poliomyelitis, Haemophilus influenzae, and diphtheria-tetanus-pertussis, but she had not received vaccination against tuberculosis or smallpox. There was no history of immunodeficiency or atopia.

The patient had a low-grade fever (temperature, ~38°C) and general malaise, and because a bacterial infection was suspected, she was treated orally with penicillin. Despite the administration of treatment, the symptoms progressed, and the patient was referred to the Department of Otolaryngology at Blekinge County Hospital (Karlskrona, Sweden) on 26 November 2000. Three weeks after the onset of the first symptoms, her condition worsened. Extensive edema developed in the upper part of the right side of the neck and on the right side of the face, extending into the contralateral side and involving the eyelids; it also developed on the mental region and the upper part of the right side of the neck (figure 1A and 1C).
Physical examination was performed at the time of hospital admission and revealed a whitish, necrotizing mass in the right anterior nasal cavity that was surrounded by granulations at the anterior border of the lower nasal concha. Numerous solid lymph nodes (diameter, 3–25 mm) were palpable in the right cheek, near the right nostril, near the right eye (including the upper eyelid), and more laterally, anterior to the border of the right parotid gland.

The WBC count (11.3 × 10^3 cells/L) was nearly normal (normal WBC count, <9.6 × 10^3 cells/L). Other laboratory values were slightly elevated: the C-reactive protein level was 14 mg/mL (normal level, <5 mg/mL), the serum alkaline phosphatase level was 7.9 μkat/L (normal range, 1.0–4.5 μkat/L), and the lactate dehydrogenase level was 9.3 μkat/L (normal range, 3.0–7.0 μkat/L). Plasma electrophoresis revealed a slightly raised level of IgG3 (1.4 g/L; reference values, 0.13–1.05 g/L), but the findings were otherwise normal.

**Bacteriologic study findings.** A nasal swab culture yielded *Streptococcus mitis* (low numbers), *Haemophilus parainfluenzae* (low numbers), and *Neisseria* species, including 1 oxidase positive rod-like bacterium. Samples were obtained for *Mycobacterium tuberculosis* culture, and the results were negative.

The overall interpretation was that the local skin infection was a phlegmon caused by *H. influenzae* (although culture results were negative). Treatment with intravenous cefuroxime was started on a tentative basis.

**Histologic study findings.** Biopsy from the nose mass revealed necrotic material with granulocytes.

**Radiographic study findings.** CT revealed deep edema of the right cheek, the right parotid gland, and the right side of the neck. Edema of the respiratory epithelium of the anterior ethmoidal cells and the nasal concha on the right side could also be visualized (figure 1B).

**Subsequent clinical course.** One week after the acute exacerbation a slight improvement of the cellulitis under the eye occurred. Around the areas of facial lymphadenitis the skin still showed a bluish discoloration. However, since the patient’s general condition improved, she was discharged from the hospital and followed up on weekly visits to our outpatient clinic.

The cellulitis completely resolved within 3 weeks after onset,
but the lymphadenitis in the buccal and periorbital areas developed into subcutaneous abscess cavities, which ranged in size from 3 to 40 mm. The largest of these abscess cavities measured 40 × 25 mm and extended from the paranasal region into the right cheek (figure 1D). The subcutaneous fat layer at the site of the abscess cavity underwent a complete necrosis. Repeated needle punctures produced a whitish, smeary discharge, a specimen of which was sent for general and specific bacterial culture and, subsequently, for virus isolation on 19 December 2000.

Approximately 6 weeks after the onset of symptoms, the dermis in the region of the paranasal abscess became extremely thin and was at risk of necrosis and perforation. Three punctuations, which were made under general anesthesia during an interval of 3–5 days, had no effect on the condition, and incision became inevitable. Because of the risk of dermal necrosis, hyperbaric oxygen (HBO) treatment was chosen as therapy, to improve the chances that the infection would resolve and to stabilize the atrophied skin before incision. The patient underwent 5 courses of HBO treatments, in 6 hourly intervals, between the 21st and the 23rd of December in the pressure chamber at the Karlskrona Naval Base.

After the first course of HBO treatment, the huge paranasal abscess was evacuated by incision, and a drain was inserted. The discharge diminished gradually, and the drain was removed after 5 days. The patient’s condition quickly improved, and 6 weeks after she underwent HBO therapy and the incision, the skin had recovered completely, including a reappearance of the subcutaneous fat layer. However, some lymph nodes continued to vary in size, and the bluish discoloration of the adjacent skin areas remained. Nodes of 2–3 mm in diameter in general showed spontaneous regression, but nodes with a diameter of 5–15 mm required needle aspirations several times, for up to 5 months after the onset of the disease. Histologic examination of the discharge showed degenerated hyperplastic unidentifiable cells. Examination of fine-needle biopsy specimens from the upper jugular lymph nodes, which never necrotized, revealed reactive lymphadenitis.

The aspirate obtained on 19 December was subjected to virus isolation at the Department of Virology at Malmö University Hospital (Malmö, Sweden). Ten days after inoculation on green-monkey kidney cells, a cytopathic effect (CPE) appeared, which, on subpassage, yielded syncytial formation of the cells. The CPE was caused by an agent that was filterable through a 0.45-μm filter. The results of PCR and immunofluorescence testing for mumps virus were negative.

The CPE pattern directed our suspicions to poxvirus infection, and the culture material was sent to the Swedish Institute for Infectious Disease Control in Stockholm on 9 February 2001 for investigation for poxvirus. Orthopoxvirus-like particles were detected in the culture medium by electron microscopy (figure 1G). The diagnosis was further confirmed by PCR analysis, which noted a 339-bp fragment of the viral thymidine kinase gene, where direct sequencing revealed 100% homology with an earlier published Swedish isolate, H2 [2]; direct sequencing also revealed, as expected, 99% homology with vaccinia virus sequences. A serum sample, which had been collected 5 weeks after the onset of symptoms, was positive for antibodies to orthopoxvirus (vaccinia virus) by plaque reduction neutralization test.

The healing process of the numerous areas of lymphadenitis was markedly prolonged. Two years after onset of symptoms, a single firm node situated in the medial angulus of the right eye was removed (figure 1E). Electron microscopy evaluation of this node yielded negative results, but PCR of the node was positive for orthopoxvirus DNA. Sequence analysis showed total homology with the PCR product obtained from the patient in February 2001.

**Epidemiological findings.** After cowpox infection was diagnosed (almost 3 months after the onset of symptoms), the patient recalled having had close contact with 2 domestic cats. One of the cats used to lick her face and nose. Close contact with the cats was especially frequent after she came home from the holiday in Spain. On this occasion, the cat’s tongue penetrated the right nasal cavity; ∼2 weeks later, the first symptoms appeared. No scratches were found on the girl’s nose. The cats were in good health when examined by a veterinarian in February 2001. None of them had lesions of the paws, mouth, or nose or enlarged lymph nodes of the neck. Serum samples obtained from both cats were tested for orthopox virus antibodies at the Swedish Veterinary Institute (Uppsala), and the results were negative.

**DISCUSSION**

Poxviruses are the largest enveloped DNA viruses, with an average dimension of 230 × 300 nm. The virus particle contains a linear, double-stranded genome of 140–300 kb in length that encodes several hundred polypeptides. Vertebrate poxviruses contain 8 genera, of which 4 (Orthopoxvirus, Parapoxvirus, Yatapoxovirus, and Molluscipoxvirus) contain viruses pathogenic to humans [3], all of which, with the exception of smallpox (variola), vaccinia virus, and molluscipoxvirus, are transmitted to humans by animals (zoonosis).

Smallpox was caused by the variola virus, a member of the Orthopoxvirus genus. It was globally eradicated in the late 1970s by mass vaccination, which was successful, because the variola virus did not have an animal reservoir. Vaccinia, known as the "Jenner virus," was the virus used for successful smallpox vaccination, but the exact origin of vaccinia virus is uncertain and there is no known natural host.

Vaccination with vaccinia virus provided cross-protection against several orthopoxviruses, including monkeypoxvirus, the third orthopoxvirus. Normally, vaccinia causes mild and local
symptoms, but it may cause severe and even fatal complications in immunocompromised individuals [1].

Monkeypoxvirus acquired attention in 1969–1970, when it was isolated from infected humans in Congo/Zaire. Increasing numbers of human monkeypox infections have been observed in later years in this region of Africa, where infection occurs in the wildlife [4].

Cowpoxvirus, the fourth orthopoxvirus—and the causative agent of our case—is so named because it can infect the teats of cows [2]. However, despite its name, cowpoxvirus does not have cattle as its reservoir host; rather, rodents (such as bank voles and wood mice) serve as its reservoir hosts [5, 6]. Carnivore hosts (such as cats) that hunt rodents can transmit cowpoxvirus to humans. Serological investigations have recognized domestic cats as the most common hosts for cowpoxvirus [7]. Antibodies against orthopoxvirus have been documented in several rodents and carnivores; the species are shown in table 1 and are described elsewhere [5–12].

In our case, the domestic cats did not show any signs of ongoing infection on examination, although the examination was not performed until 3 months after exposure. Also, serological investigation (immunofluorescent staining) did not reveal antibodies to orthopoxvirus.

Human cowpoxvirus infection is a rare disease. A review of 54 cases, most of which were in the United Kingdom, indicated that human cases coincided with autumn peaks of cowpoxvirus infections in voles, wood mice, and domestic cats [13]. In most of the cases involving humans, the source of the infection is domestic cats. The infection is almost always transferred to humans through a skin lesion, but in some cases, it is transferred via the mucosa of the eye. Infection usually starts as an inflamed macula that turns into a papule; finally, a vesicular stage occurs within 7–12 days. The dermal vesicles become pale blue-purple and are more or less hemorrhagic, because of capillary lesions from the growth of virus in the endothelial and pericapillary cells [14].

The lesion is usually painless, as was true for our patient, who never complained of any pain in her nose. The lesion may be located on the skin or mucosa, and it is typically surrounded by marked local edema and regional lymphadenopathy, which may be prolonged, as it was in our case. Furthermore, most of the reported patients have slight systemic symptoms, such as pyrexia, and they sometimes experience sore throat, influenza-like illness, and general malaise that lasts 3–10 days. The time to complete recovery ranges from 3 to 12 weeks and can be even longer. A selection of reported clinical features is presented in table 2 [15–23].

Our patient had a hitherto undescribed route of inoculation via the respiratory mucosa of the nose. The infection resulted in a mucosal inflammation that resolved after 3 weeks. We found necrotic material at the site of the inferior concha that was surrounded by pebble stone-like granulations. The subsequent phase was dominated by subcutaneous necrotizing lymphadenopathy of the regional nodes; this persisted for several months and required therapeutic needle aspirations.

The major abscess in the paranasal region covered by an extremely thin dermis was at risk of necrosis, and the unorthodox decision was made to support surgical treatment with HBO treatment. Several clinical and experimental studies have demonstrated the usefulness of HBO treatment (e.g., the beneficial effect on stimulation of granulocytes and on circulation) [24, 25]. There was a strong clinical impression that HBO treatment had a beneficial effect on the healing process (figure 1D and IF). Incision of the large abscess and placement of a temporary drain were also important; however, several evacuating punctures had been performed earlier while the patient’s condition had continued to deteriorate.

Diagnosis was delayed for our patient, because the initial

Table 1. Reports on spread of orthopoxvirus in western European rodents and carnivores.

<table>
<thead>
<tr>
<th>Country</th>
<th>Mode of detection</th>
<th>Reservoir</th>
<th>Reference(s)</th>
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<tbody>
<tr>
<td>Great Britain</td>
<td>Serologic testing and PCR</td>
<td>Bank voles (prevalence in autumn, 80%), wood mice (prevalence, 27%), and short-tailed field voles (Clethrionomys glareolus, Apodemus sylvaticus, and Microtus agrestis; prevalence, 99% [11 of 12])</td>
<td>[5–7]</td>
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<tr>
<td>Germany</td>
<td>Serologic testing</td>
<td>Cats (prevalence, 2% [44 of 2173])</td>
<td>[8]</td>
</tr>
<tr>
<td>Norway</td>
<td>Serologic testing</td>
<td>Wild carnivores (red foxes [Vulpes vulpes]; prevalence, 11% [7 of 62]) and domestic cats (prevalence, 10.1% [n = 217])</td>
<td>[9]</td>
</tr>
<tr>
<td>Finland</td>
<td>Serologic testing and PCR</td>
<td>Rodents (mainly bank voles [Clethrionomys glareolus]; prevalence, 0%–92%, depending on population dynamics; high prevalence during the peak phase of population for red foxes (prevalence, 50% [7 of 14]) and lynx (prevalence, 1.4% [1 of 73])</td>
<td>[10]</td>
</tr>
<tr>
<td>Sweden</td>
<td>Serologic testing</td>
<td>Lynx (prevalence, 29%; [5 of 17]) and brown bears (prevalence, 2%; [1 of 45])</td>
<td>[10]</td>
</tr>
<tr>
<td>Germany</td>
<td>Serologic testing</td>
<td>Red foxes (prevalence, 6.5% [46 of 703])</td>
<td>[11]</td>
</tr>
<tr>
<td>Austria</td>
<td>Serologic testing</td>
<td>Domestic cats (prevalence, 4% [8 of 200])</td>
<td>[12]</td>
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massive cellulitis of the face resembled a *H. influenzae* phlegmon; however, the results of cultures were negative. There were few indications pointing to a virus infection, and unfortunately, the biopsy specimen from the nose was not sent for virological analysis. Virus isolation from the discharge obtained 3 weeks after hospital admission yielded a syncytium-like pattern that was confirmed to be orthopoxvirus by electron microscopy and was eventually verified as cowpoxvirus by PCR and sequencing. Although it would have been desirable to test tissue specimens for specific viral antigens, no such tests were performed, because the poxvirus particles and DNA that were present were unlikely to be contaminants in an unvaccinated child. Furthermore, examination by PCR and restriction digest performed at the Centers for Disease Control and Prevention (Atlanta, GA) confirmed that the virus isolate was cowpox species.

Antibiotics (penicillin, cefuroxime, and spectramycin) were prescribed to our patient on the basis of sparse findings of bacterial infection and to prevent secondary infection at the sites for puncture and incision. This therapy had no convincing effect on the course of the disease.

At the time of diagnosis, antiviral treatment was considered. Cidofovir is efficient against vaccinia virus infections in mice, although it has been associated with some renal toxicity in humans [26]. Of the other treatment options, immune globulin was considered, as was vaccination with vaccinia virus. However, by this point in the course of infection, most of the symptoms had decreased, except persisting lymphadenopathy.

Most reported cases of cowpox in humans who are infected via cats involve girls aged ≈12 years [17]. A tendency among girls in this age group to cuddle cats, as in our patient, may explain this phenomenon. Unfortunately, the patient never told us that her cat licked her nose until we asked.

In most of the cases, the patient presents with a necrotizing skin lesion or may have a blister with involvement of the regional lymph nodes. However, if the virus has been inoculated via a mucosal membrane (such as the eye [21] or, as occurred in our patient, the nasal mucosa), the result may be massive facial edema resembling erysipelas linked with lymphadenopathy. In such atypical cases, animal contacts and cowpoxvirus infection should be ruled out.

Whether the abolition of smallpox vaccination in Europe during 1971–1977 has led to an increase in the number of cowpoxvirus infections is still a matter of discussion. During the period of 1982–1993, Baxby et al. [13] reported 25 cases after cessation of vaccination in 1971 in Great Britain, as well as 20 cases during 1969–1981. Sweden reported 2 cases in 1990; there has also been our case in 2000 and a still unreported case in 2005. Despite a growing awareness of human cowpox infection in Europe, diagnosis is certainly often missed because cowpox infection may resemble impetigo, anthrax, or erysip-
elast; moreover, the disease often heals spontaneously within 4–6 weeks. It is possible that only the more spectacular cases are reported, making it difficult to estimate any increase in the rate of human cases of cowpox after cessation of vaccination.

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