Case Report

A paediatric case of lymphadenitis by toxigenic *Corynebacterium ulcerans*

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Introduction: *Corynebacterium ulcerans*, a potentially toxigenic zoonotic agent, may produce diphtheria toxin and causes varied types of infections in humans. Cases of infection due to toxigenic *C. ulcerans* infection have been increasingly reported.

Case presentation: A 6-year-old Japanese girl who had been vaccinated using diphtheria toxoid presented with fever and swelling in the left neck. Ultrasonography showed cervical lymphadenitis with cellulitis. *C. ulcerans* was isolated from the drainage specimen. The infection was cured with erythromycin administration. Her anti-diphtheria toxoid antibody level was at an adequate level for diphtheria prevention on admission and was significantly increased 3 weeks later. Zoonotic infection was considered likely, because a family cat had shown rhinitis and skin ulcers prior to symptom onset in the child.

Conclusion: In addition to the number of reported cases of infection in adults, *C. ulcerans* infection in previously vaccinated children should also be a subject of concern in Japan.

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Introduction

Corynebacterium ulcerans was first isolated from the throat of a patient with respiratory diphtheria-like illness in 1926 (Gilbert & Stewart, 1926). *C. ulcerans* produces diphtheria toxin and causes various symptoms such as classic respiratory *Corynebacterium diphtheria*-like symptoms, dermatitis and lymphadenitis. Respiratory diphtheria-like illness is a serious disease characterized by pseudomembrane formation and frequent cardiac or neurological sequelae. This condition requires urgent treatment with diphtheria antitoxin and antibiotics. On the other hand, lymphadenitis by *C. ulcerans* is curable by antibiotics and drainage (Urakawa *et al.*, 2013). *C. ulcerans* is a zoonotic agent that infects humans drinking unpasteurized milk or in close contact with infected dogs, cats or various other animal species (Vandentorren *et al.*, 2014). Thirteen cases of adult *C. ulcerans* infection have been reported in Japan (Yoshimura *et al.*, 2014). To the best of our knowledge, this case represents the first report of paediatric *C. ulcerans* in Japan.

Case report

A 6-year-old Japanese girl was admitted to our hospital with a 2-day history of fever and swelling of the left neck. Her past medical history was unremarkable, and she had no history of travel to a foreign country. She

had received routine diphtheria vaccinations four times over 5 years prior to this illness.

Physical examination revealed an axillary temperature of 38.4 °C and a painful erythematous mass in the left neck. No scratches were evident. The mass was approximately 5 × 2 cm in size and hard. The pharynx appeared normal. Blood examination showed: white blood cell count, 12 400 µl⁻¹; neutrophils, 73 %; lymphocytes, 17 %; and C-reactive protein, 2.3 mg dl⁻¹. Ultrasonography showed lymphadenitis with cellulitis (Fig. 1).

Fever subsided the next day after starting administration of sulbactam/ampicillin, but the mass enlarged and became extremely tender. On hospital day 4, needle drainage was performed. Culture of the drained pus revealed Gram-positive bacilli. After drainage, the painful mass gradually reduced in size. On hospital day 6, the patient was discharged with administration of oral sulfamonomethoxazole. Four days later, the left neck mass recurred. Needle drainage was again performed, but no organisms were cultured. *C. ulcerans* was isolated from the initial sample at this time. Antimicrobial susceptibility testing showed that the strain was susceptible to ampicillin, penicillin G, erythromycin and minocycline. We treated the patient with oral azithromycin for 3 days, followed by erythromycin for 10 days. At follow-up after 1 month, the mass had completely disappeared and did not recur.

Fig. 1. Ultrasonography showing an unclear boundary and hypoechoic lymph with a maximal size of 9×7 mm. Blood flow is observed in the lymph nodes. The surrounding subcutaneous tissue appears hyperechoic.

The isolates were identified as toxigenic *C. ulcerans* by biochemical differentiation as follows. Biotyping was performed using the API CORYNE system (SYSMEX bioMérieux). Diphtheria toxin production was confirmed by a modified Elek test (Engler *et al.*, 1997) and Vero cell cytotoxicity tests (Miyamura *et al.*, 1974). The anti-diphtheria toxoid antibody level was 0.757 IU ml^{-1} at onset, increasing to 6.05 IU ml^{-1} after 3 weeks.

The family cat had shown eye discharge, sneezing and skin ulcers before the onset of symptoms in the patient. Unfortunately, *C. ulcerans* was not able to be grown from swabs of the bulbar conjunctiva, pharynx or skin of the domestic cat, probably because antibiotics had been administered prior to specimen collection.

All other members of the patient's immediate family had been immunized with diphtheria toxoid vaccine (DT) four times and showed no symptoms. Cultures of throat swab specimens from family members all showed negative results. DT was provided for the patient's mother, because her anti-diphtheria toxoid antibody level was significantly below the protective level of $>0.1 \text{ IU ml}^{-1}$.

Discussion

Reports of *C. ulcerans* infection have markedly increased in recent years (Wagner *et al.*, 2012). Most cases have involved older adults who were not up to date with immunization against *C. diphtheriae*. Paediatric cases of *C. ulcerans* infection are extremely rare, because children generally receive a routine series of DT injections. To the best of our knowledge, only four paediatric cases of *C. ulcerans* have been described in the literature (Table 1). Unfortunately, detailed descriptions about immunization histories and levels of anti-diphtheria toxoid antibody have been lacking (Hart, 1984; Pers, 1987; Kisely *et al.*, 1994; Public Health England, 2000). Illness occurred in our patient despite the presence of what was considered an adequately protective level of anti-diphtheria toxoid antibody ($>0.1 \text{ U ml}^{-1}$), although symptoms were mild and pseudomembrane formation was not observed. *C. ulcerans* initially infects the throat, and the colonized bacteria subsequently produce diphtheria toxin and form a pseudomembrane that causes serious dyspnoea. Acquired anti-diphtheria toxoid antibody might be helpful in preventing formation of the pseudomembrane but may not prevent invasion through cervical lymphadenitis from the throat via the blood or lymphangion to allow early colonization by *C. ulcerans*. Furthermore, we have suggested the possibility of a partial immunity response due to differences between the DT produced by *C. diphtheriae* and some *C. ulcerans* strains (Sing *et al.*, 2005).

We should consider *C. ulcerans* as prevalent among animals (Katsukawa *et al.*, 2012; Hirai-Yuki *et al.*, 2013). It has been reported previously by Shimono *et al.* (2012) that surveillance of cats in Tokushima Prefecture, where the patient lives, found *C. ulcerans* colonizing 4.2 %, and anti-diphtheria toxin antibody was present in 10.5 % of cats. We recommend that pet owners wash their hands after touching animals, and wear a mask and gloves if the animal shows signs of illness.

Table 1. Paediatric cases of *C. ulcerans* infection

Year	Age/sex	Country	Symptom	Route	Reference
1983	12 years	UK	Pharyngitis	Cows' milk	Hart (1984)
1987	9 years/boy	Denmark	Respiratory diphtheria-like illness	Unknown	Pers (1987)
1994	9 years/girl	UK	Pharyngitis	Unknown	Kisely <i>et al.</i> (1994)
2000	Girl	UK	Sore throat	Unknown	Public Health England (2000)

In conclusion, we suggest that, while DT immunization might be effective in preventing severe respiratory disease caused by *C. ulcerans*, lymphadenitis may occur in children despite DT vaccination and having protective antibody titres because DT vaccination does not prevent colonization by corynebacteria. Close contact with sick animals should be avoided whenever possible.

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