Possible human-to-human transmission of toxigenic *Corynebacterium ulcerans*

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Abstract

Toxigenic *Corynebacterium ulcerans* is an emerging cause of diphtheria. In contrast to the classical diphtheria pathogen *C. diphtheriae,* human-to-human transmission of this primarily zoonotic pathogen has not been clearly documented. Here we report on a two-person cluster suggesting an initial zoonotic and a subsequent human-to-human transmission event.

Keywords: *Corynebacterium ulcerans*, diphtheria, person-to-person transmission, zoonotic transmission, zoonosis
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Introduction

Diphtheria and diphtheria-like illness are caused by *Corynebacterium* species harbouring the diphtheria toxin–encoding *tox* gene. *C. diphtheriae* was responsible for the high morbidity and mortality of this classical infectious disease until the introduction of the respective vaccine—and still is in several parts of the world, especially in less developed countries or after disruption of public health systems by natural or human-made disasters. Local outbreaks or large-scale epidemics are supported by the fact that the human pathogen *C. diphtheriae* is primarily transmitted directly from human to human.

In recent years, diphtheria-like infections with toxigenic *C. ulcerans* have outnumbered those caused by toxigenic *C. diphtheriae* in many industrialized countries [1–3]. Most of the reported human infections with this zoonotic pathogen are related to animal contact and are supposed to be transmitted from animal to human. In contrast to *C. diphtheriae,* so far human-to-human transmission of *C. ulcerans* has not been documented [2,4,5]. Here we report a possible case of human-to-human transmitted toxigenic *C. ulcerans.*

Case report

In October 2014 an ambulatory healthcare center sent a *Corynebacterium ulcerans* strain isolated from a pharyngeal swab of a 13-year-old girl with tonsillitis to the Consiliary Laboratory of Diphtheria (CLoD) for toxigenicity testing by *tox* PCR and, if positive, Elek testing according to the diagnostic algorithm established at the CLoD [6,7]. At the onset of symptoms, the girl had a sore throat which increasingly worsened in the following 2 days. Low fever (temperature <38°C), headache and severe sickness were accompanied by a sweetly foul-smelling whitish mucous in the throat. During the afternoon, swallowing became increasingly harder. On day 3 a pharyngeal swab was taken that grew *C. ulcerans* in pure culture on day 4. On day 5 penicillin was started, leading to immediate improvement of the symptoms after two doses. Penicillin therapy was continued for 14 days. Two control pharyngeal swabs taken on days 10 and 11 did not grow *Corynebacteria.*

Species identification of *C. ulcerans* was confirmed at the CLoD by MALDI-TOFMS (matrix-assisted laser desorption-ionization time-of-flight mass spectrometry) analysis (score:

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2.4) and API Coryne (API code 0111326). Toxigenicity of the isolate was confirmed both by a positive real-time PCR [8] and a positive modified Elek test [9]. The local health authority was immediately informed, all five household family members were tested for *Corynebacteria*. Additionally, all of them received a booster vaccination. Similar to the German management recommendations for contacts to a *C. diphtheriae* patient (http://www.rki.de/DE/Content/Infekt/EpidBull/Merkblaetter/Ratgeber_Diphtherie.html), prophylactic antibiotic therapy was offered but finally was not administered. While both parents and two sisters were free of *C. ulcerans,* the 81-year-old asymptomatic grandmother was found to carry toxigenic *C. ulcerans* in her throat. For multilocus sequence typing (MLST), a modified scheme of *C. diphtheriae* was used [10]. The isolates from the girl and her grandmother had identical alleles, and both belonged to sequence type (ST) 332 (http://pubmlst.org/cdiphtheriae/). After a completed eradication therapy with penicillin, the grandmother tested negative for *C. ulcerans*.

The family lived on a farm in northeastern Bavaria, Germany, with cattle and pigs as well as with a dog, a pet cat and three farm cats. All animals were asymptomatic. The girl was reported to have only contact with the pet cat and to a lesser extent with the dog, but not with the three free-roaming farm cats or the stable animals. Her grandmother basically had no close animal contact but worked sometimes in the stable, however without having close cattle contact or milking the cows. She was the only person in the household to occasionally drink fresh cow's milk after boiling. Although recommended by the local health authority and the CLoD, testing the animals was unfortunately not possible. Neither the girl nor her grandmother had an underlying disease or was immunosuppressed.

Discussion

In the last few years, reports on human infections by toxigenic *C. ulcerans* outnumber those caused by toxigenic *C. diphtheriae* in Europe [1–3]. In the past 5 years (2010 to November 2014), 80% of the 46 *C. ulcerans* from humans sent to the German CLoD were toxigenic, whereas only 8% out of 182 *C. diphtheriae* were so. The majority of them were isolated from extrapharyngeal sites, but a few reported cases were associated with respiratory diphtheria or diphtheria-like disease. Transmission between farm animals like pigs and cattle or pet animals, such as dogs or cats, and humans can occur [11–14]. In the case reported here, we found two members of the same household harbouring toxigenic *C. ulcerans* in the throat, causing diphtheria-like disease in one of them. Unfortunately, it was not possible to sample the farm and pet animals.

In contrast to the human pathogen *C. diphtheriae,* which is predominantly transmitted *via* droplets from person to person, resulting in outbreaks or epidemics, human-to-human transmission of the zoonotic pathogen *C. ulcerans* has so far not been documented [2,4,5]. Moreover, secondary diphtheria cases linked to an index case of *C. ulcerans* infection or symptomatic *C. ulcerans* outbreaks have not been published until now.

Only three instances of human toxigenic *C. ulcerans* infections involving more than one person have been reported previously. The first two-patient cluster comprised a young woman with a sore throat and an asymptomatic person identified during an outbreak investigation in a religious community in a remote area of North Devon, England, in 1981 [15]. The most likely mode of transmission was drinking raw milk obtained from an infected cow herd, since the organism could be isolated from bulk milk samples of the respective farm. No evidence for human-to-human transmission is provided [15]. Two additional toxigenic *C. ulcerans* clusters of two were reported from England in 1996 and 1998, respectively [2]: a 20-year-old man with a sore throat and his asymptomatic 18-year-old sibling, both living in a rural area, but without cattle contact (also mentioned as personal communication without additional data in [4] and [16]), as well as a 35-year-old man with classical respiratory diphtheria and his asymptomatic 11-year-old son who owned five household dogs, and who tested negative for *C. ulcerans* (also mentioned in [16]). For the two most recent cases, the authors speculate that the absence of any apparent source of infection might indicate the possibility of person-to-person transmission [2]. However, for both clusters, no additional data on domestic pet contact (in the first instance), on the intensity of pet animal contact or on the presence or absence of symptoms in the animals or on the types of clinical material tested (in the second instance) were reported.

In the case reported here, three potential reasons for the two human infections by a molecularly identical toxigenic *C. ulcerans* strain can be discussed.

Firstly, two independent zoonotic transmission events might be possible, one most likely by contact with an asymptomatically infected pet animal (cat or dog) in the case of the girl and the other probably by ingestion of possibly improperly boiled raw cow's milk. However, no reports on cattle as *C. ulcerans* carriers or as a source for human infections are known so far from Germany; the most recent reports from other European countries date back more than 15 years and are mainly from England and France. Therefore, and for probabilistic reasons, this scenario is the least likely.

Secondly, both persons might have been infected by the same asymptomatic carrier animal. The anamnestic and epidemiologic evidence does not support this hypothesis, since closer animal contact was basically denied for the grandmother.

Thirdly, person-to-person transmission might have occurred after an initial zoonotic transmission to one of the persons. On the basis of the contact investigation and previous reports on the epidemiology of *C. ulcerans,* the most probable scenario is that the girl was infected by one of the two domestic animals, most likely the single cat with access to the house. This two-step scenario of an initial zoonotic and a subsequent person-to-person transmission seems to be the most likely hypothesis.

Interestingly, in all four two-person clusters, including the present one, there was only a single symptomatic patient; secondary diphtheria cases did not develop from the index case, suggesting a very low risk of person-to-person transmission of symptomatic *C. ulcerans* diphtheria compared to *C. diphtheriae.* Among others, this observation might be linked to the observation that the cytotoxic activity of diphtheria toxin from *C. ulcerans* is probably significantly lower than that from *C. diphtheriae* [17].

Moreover, the girl's tonsillitis had developed despite a completed first vaccination round with diphtheria toxoid at the first year of life and a booster dose in 2013, provided according to German vaccination recommendations. This is in concordance with a previous analysis of patient data from a report by Tiwari *et al.* [18], where 11 out of 15 patients with diphtheria-like illnesses due to toxigenic *C. ulcerans* were fully or partly vaccinated [19]. Similarly, half of 48 patients with symptomatic infections caused by toxigenic *C. ulcerans* detected in the United Kingdom between 1986 and 2008 were fully (21/48) or partially (3/48) immunized [2]. However, because a proven vaccine against diphtheria caused by toxigenic *C. ulcerans* is not available, the diphtheria toxoid vaccine directed against *C. diphtheriae*–caused diphtheria has to be used in the hope of preventing at least partly serious diphtheria-like symptoms by toxigenic *C. ulcerans* as well.

Investigations of the population structure of circulating *C. ulcerans* in humans and animals based on modern sequence-based methods have just started. The MLST scheme previously developed for *C. diphtheriae* [20] has now been adopted for *C. ulcerans,* and the first STs have been defined and included into the Pubmlst database (http://pubmlst.org/cdiphtheriae/) [10,13,21]. ST 332 has been found so far twice in Germany; one isolate was derived from an asymptomatic cat and one from the wound of a woman [10]. Interestingly, two distinct *C. ulcerans* ST clusters comprising four and three isolates (ST 288 and ST 287), respectively, have recently been described in strains isolated between 2007 and 2012 in England, but no epidemiologic links could be established in either cluster [21].

Conclusion

Our case report raises the possibility of person-to-person transmission of toxigenic *C. ulcerans.* Although this obviously occurs much less frequently than with toxigenic *C. diphtheriae,* it is prudent to advise public health authorities to manage diphtheria-like infections caused by toxigenic *C. ulcerans* similarly to those caused by *C. diphtheriae* with respect to contact tracing, subsequent eradication antibiosis and booster vaccination, as suggested previously [4]. Moreover, because zoonotic transmission might usually be the initial event, source tracing should include investigation of both livestock and pet animals as well as a food intake interrogation, especially with regard to raw milk.

Transparency declaration

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