Infection of the Skin Caused by *Corynebacterium ulcerans* and Mimicking Classical Cutaneous Diphtheria

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Extrapharyngeal infections caused by *Corynebacterium ulcerans* have rarely been reported previously, and diphtheria toxin production has usually not been addressed. This case demonstrates that strains of *C. ulcerans* that produce diphtheria toxin can cause infections of the skin that completely mimic typical cutaneous diphtheria, thereby potentially providing a source of bacteria capable of causing life-threatening diseases in the patient's environment. Therefore, it is recommended to screen wound swabs for coryneform bacteria, identify all isolates, carefully assess possible toxin production, and send questionable strains to a specialist or a reference laboratory.

Case report. A 71-year-old male patient from Berlin, Germany, presented to the orthopedic clinic of the Benjamin Franklin Medical Center in September 1999 with 2 nonhealing lesions that had persisted over the previous 10 months. Two ulcers measuring 7 cm and 1 cm in diameter were found medially of the right tibia and distally of the right lateral malleolus, respectively. They were covered with gray membranes and emanated a sweetish smell. In addition to a healed fracture of the right tibia and a chronic osteomyelitis of the right tibia (known since 1954), the patient did not present any symptoms. The erythrocyte sedimentation rate was mildly elevated (17 and 31 mm after 1 and 2 h, respectively); all other laboratory parameters were normal.

Swabs were taken from the ulcers, and gram-positive rods and cocci, as well as a few neutrophils, were observed microscopically. After incubation for 18 h at 37°C and 5% CO2, *Staphylococcus aureus* and a gram-positive, catalase-positive bacillus growing in small gray-whitish colonies (1–2 mm in diameter) were detected on blood agar. The bacilli were identified as *Corynebacterium ulcerans* by use of the API CORYNE system (bioMérieux), which elsewhere has been shown to reliably identify *C. ulcerans* [1]. The CAMP-test gave the reverse reaction (i.e., inhibition of hemolysis by *S. aureus*, which is also characteristic of *C. ulcerans* [2]). Antimicrobial susceptibility was tested as broth microdilution (for *S. aureus*) and disk diffusion test on Iso-Sensitest agar with 5% horse blood (for *C. ulcerans*), and both isolates exhibited susceptibility to clindamycin, erythromycin, and cephalosporins. Growth of both bacterial species was confirmed in a second swab taken from the ulcers.

PCR was performed on DNA extracted from the *C. ulcerans* isolate by use of diphtheria toxin–specific sense and antisense primers corresponding to nucleotides 77–100 and 535–555, respectively, of the phage carrying the diphtheria toxin gene (tox) gene (GenBank X00703; sense: 5′-GGGCTATGATG-TTGTGATCTCT-3′; antisense: 5′-GGCTTTACGCTGTTCGGCTTGTC-3′). These primers were designed to cover almost the entire coding sequence for the A chain, including the catalytically active Glu at position 516–518. Identical results were obtained for both the isolate and a toxin-positive control strain of *C. diphtheriae*, whereas a toxin-negative strain did not exhibit a diphtheria toxin–specific amplification product. Toxigenicity was subsequently confirmed by a modified Elek test [3]. Weak immunoprecipitation bands by the isolate after 48 h indicated significant, but comparatively lower, toxin production as compared to *C. diphtheriae*. Species diagnosis and toxin production were subsequently confirmed by a specialist in coryneform bacteria.

On further inquiry, the patient remembered having a sore throat and fever with swelling of the palate at the time of onset of the ulcerations. Control smears taken from nose and throat of the patient did not reveal any growth of *C. ulcerans*–like colonies. Antitoxin levels of 0.5–1.0 IU/mL were detected in serum samples with a commercially available ELISA (Virion/Serion).

Although there are no previous reports of person-to-person spread of *C. ulcerans*, the patient was isolated and received local antiseptic and systemic iv antibiotic (cefuroxim, 2 × 1.5 g/d;
clindamycin, 4 × 600 mg/d) treatment. Treatment with antitoxin was not considered, in view of the comparatively mild symptoms. After 4 months, both ulcerations were almost completely healed, and a repeat swab culture revealed no growth of either C. ulcerans or S. aureus.

Discussion. C. ulcerans was first described by Gilbert and Stewart (reviewed elsewhere [4]), who detected its close relatedness to C. diphtheriae. The main reservoir of C. ulcerans is considered to be cattle and other domestic livestock, where it can cause mastitis in cows. Consequently, most infections have been described in rural populations [4, 5]. The agent has been repeatedly isolated from raw milk, and drinking of nonpasteurized, contaminated milk has been linked to the acquisition of the infection [5, 6]. Symptomless carriers, however, have also been found [5]. Of interest, our patient denied any animal contacts except to those with his pets, a dog and a parakeet, as well as any traveling activity or ingestion of raw dairy products. Therefore, the source of infection for this case remains unclear, and a person-to-person transmission cannot be excluded, even though this has not been documented yet.

Similarly to C. diphtheriae, some C. ulcerans strains are infected with a lysogenic bacteriophage introducing the tox gene and the capacity of the bacteria to produce diphtheria toxin, although in considerably lower amounts than C. diphtheriae [4]. Strains of C. ulcerans often additionally produce phospholipase D, as is also known from C. pseudotuberculosis [7]. Toxigenic C. ulcerans strains were shown to affect the throat, causing diphtheria-like, sometimes fatal, diseases that cannot easily be distinguished from genuine diphtheria [8–10].

The microbiological diagnosis strictly depends on both the correct species identification and the evaluation for toxigenicity. Today, C. ulcerans can be identified by the use of commercially available test kits that differentiate between C. ulcerans and the closely related species C. diphtheriae and C. pseudotuberculosis. The toxin gene can be detected by PCR [11]. Although it has been shown for C. diphtheriae that not all PCR-positive strains are biologically active and actually express the toxin [12], similar tox gene–positive, but nontoxigenic, strains have not been documented for C. ulcerans. Nevertheless, phenotypic confirmation of toxin production (e.g., by Elek test) should be requested for all PCR-positive strains.

Nearly all human isolates reported had been cultured from the throat, and today pharyngeal infections due to C. ulcerans may be more frequent in industrialized countries than is classical diphtheria as caused by C. diphtheriae; however, extrapharyngeal infections caused by C. ulcerans seem to be extremely rare [4], and often toxin production has not been checked. The present case appears to include all clinical and microbiological characteristics of typical cutaneous diphtheria [13] (i.e., chronic membranous ulcers, repeated detection of C. ulcerans in association with S. aureus, and production of diphtheria toxin). On the one hand, it is well documented that serum titers of diphtheria antitoxin decline with age, causing the necessity to regularly revaccinate adults [14–16]. On the other hand, cutaneous diphtheria caused by C. diphtheriae can induce titers of antitoxin and thereby cause systemic immunity [17]. Our patient could not remember having ever been vaccinated, and in Germany booster injections of tetanus toxoid usually do not include diphtheria toxoid. Thus, it is possible that the detected protective titers of diphtheria antitoxin in the patient’s serum, instead of resulting from a previous but unremembered vaccination, arose from the cutaneous disease in question and/or the episode of pharyngitis. Classic diphtheria is extremely rare in Germany, only 1 case of pharyngeal diphtheria having been reported in 1999. Because symptoms of cutaneous manifestations are relatively mild and diphtheroids are not easy to differentiate, however, some cases of infection with C. diphtheriae or C. ulcerans might go undetected and, therefore, unreported. The medical importance of C. ulcerans is further highlighted by a report of respiratory diphtheria published recently in the Morbidity and Mortality Weekly Report [18]. In the accompanying editorial note, the fact that “most U.S. clinical laboratories lack the expertise and materials to reliably identify toxigenic C. diphtheriae” is a cause for grave concern, and there is no reason to assume that the respective laboratory practices are more readily at hand in other countries. The present case illustrates that (1) besides pharyngeal disease, infections with C. ulcerans can perfectly mimic cutaneous diphtheria and (2), consequently, all corynebacteria from wounds (if growing as predominant organisms or in pure culture) should be identified to the species level and possibly analyzed for toxin production following the recently published guidelines [19, 20]. If any of these reactions should yield unclear results, it is highly recommended to send the strain to a specialist or reference laboratory for confirmation of species and/or toxigenicity.

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References


