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′-GGGCTGATGATTGTTGTGTATTGTTCTT-3′; antisense: 5′-GGCTTAACGCTTTGCTTGTTTCG-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 anti-
toxin was not considered, in view of the comparatively mild
symptoms. After 4 months, both ulcerations were almost com-
pletely 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 relat-
edness 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 nonpas-
teurized, 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 prod-
ucts. Therefore, the source of infection for this case remains
unclear, and a person-to-person transmission cannot be ex-
cluded, even though this has not been documented yet.

Similarly to C. diphtheriae, some C. ulcerans strains are in-
fected 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 phos-
holipase D, as is also known from C. pseudotuberculosis [7].
Toxigenic C. ulcerans strains were shown to affect the throat,
cauing 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 com-
mercially 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], sim-
ilar tox gene–positive, but nontoxicogenic, strains have not been
documented for C. ulcerans. Nevertheless, phenotypic confir-
mation of toxin production (e.g., by Elek test) should be re-
quested 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 clas-
sical diphtheria as caused by C. diphtheriae; however, extra-
pharyngeal infections caused by C. ulcerans seem to be ex-
tremely 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
[i.e., chronic membranous ulcers, repeated detection of C.
ulcerans in association with S. aureus, and production of diph-
theria 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 vac-
cinated, 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 un-
remembered 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 diph-
theria 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 pub-
lished 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 diph-
theria 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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