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Case Report

Bone and Joint Infection Caused by Clindamycin and Penicillin-G Resistant, Toxigenic *Corynebacterium ulcerans*

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Abstract

Corynebacterium diphtheriae, C. ulcerans, and *C. tuberculosis* are the three species belonging to the *diphtheriae* complex. *C*. While *C. diphtheriae* infections are becoming rare in developed countries, thanks to vaccination, *C. ulcerans* and *C. pseudotuberculosis* infections still are rare but increase and are often caused by contact with domestic animals. It should be noted, however, that vaccination protects against diphtheria toxin-producing strains. Here we report an uncommon case of bone and joint infection caused by toxigenic *Corynebacterium ulcerans* resistant to both clindamycin and penicillin G, in a vaccinated patient. This patient owned a dog whose samples showed carriage of toxigenic *C. ulcerans*.

Introduction

In developed countries, diphtheria due to *C. diphtheriae* is now a rare disease, thanks to vaccination. Nevertheless, one should not forget that diphtheria and diphtheria-like diseases can also be caused by other toxigenic corynebacteria: *Corynebacterium pseudotuberculosis* and *Corynebacterium ulcerans.* The latter is increasingly reported in industrialized countries as shown in some reviews where the cases listed, with a few exceptions, all come from these countries [1,2]. This can be explained by the lack of diagnostic resources in other countries, but also by the fact that transmission between domestic animals and humans is increasing, or better diagnosed, in developed countries. Various domestic animals are carriers of *C.ulcerans*, but dogs in particular, as shown by the 2023 activity report and studies from the French National Corynebacteria Reference Center [3,4]. Other studies have shown the link between these strains isolated from humans and those from their pets, using various comparison techniques such as ribotyping or next-generation sequencing [5,6]. Analysis of antibiotic resistance in strains isolated from dogs, showing resistance to certain antibiotics [7], in particular penicillin and clindamycin, as we describe here with an uncommon case of Bone and Joint Infection (BJI).

Case report

A 74-year-old man was admitted to the Trousseau University Hospital (Tours, France) in January 2021 for the surgical treatment of a left tibiotalar arthrosis, by a Talaris total ankle prosthesis. His medical history includes vitamin K

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antagonists for atrial fibrillation and two hip and knee joint prostheses.

Three months after the ankle replacement, the patient complained about a swollen anterior scar with suppuration for about three days, which led him to be urgently hospitalized in order to be revised surgically.

During surgery, bacteriological sampling was performed (n = 5), and all cultures became positive within 48 hours. Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF, Bruker Daltonics GmbH, Bremen, Germany) identified *Corynebacterium ulcerans*, with an excellent score (>2) *using the MALDI Biotyper IVD library*. Additional tests were performed by the *Corynebacterium* French National Reference Center (Institut Pasteur – Paris) which confirmed the initial identification and detected the presence of the *tox* gene by qPCR.

A throat swab taken two days later to search for a potential colonization site was negative for *C. ulcerans*. No other sites were tested.

Empirical treatment combined piperacillin/tazobactam and linezolid. Once *C. ulcerans* was identified, an early switch to amoxicillin/clavulanic acid was carried out to treat this microorganism and the other anaerobes present in one of the samples. The strain was susceptible to amoxicillin (MIC = 0.19 mg/L, E-Test Biomérieux, Marcy-l'Étoile, France), ciprofloxacin, vancomycin, trimethoprim-sulfamethoxazole, and linezolid, but resistant to penicillin G (MIC = 0.25 mg/L) and clindamycin (MIC = 2 mg/L).

The patient's condition improved but complete recovery was not achieved. Particularly necrotic tissue appeared on the scar. A second surgery was therefore performed to trim the scar ten days after the first one, with new bacteriological sampling. All the new samples (n = 5) were negative for *C. ulcerans*.

The evolution was favorable, and treatment with amoxicillin 2 g three times a day for three months was pursued.

Further questioning of the patient, a former farmer, revealed that he owns a dog. In addition, the patient received his last diphtheria vaccine booster in January 2021.

In order to substantiate the origin of the infection, the veterinarian was contacted to collect canine samples which, although the dog was asymptomatic, were positive for toxigenic *C. ulcerans*. The dog was also treated with amoxicillin.

C. ulcerans is a fastidious, facultative aero-anaerobic Gram-positive bacillus, first isolated in 1926. *C. ulcerans*, such as *Corynebacterium diphtheriae* and *Corynebacterium pseudotuberculosis*, harbor a lysogenic phage that carries the *tox* gene, encoding an exotoxin. These three species can be responsible for diphtheria, a potentially lethal disease caused by toxigenic strains. In France, thanks to very high vaccination coverage (98% of children [3]), diphtheria due to *C. diphtheriae* has disappeared, with all 24 infections observed between 2002 and 2018 being imported cases [8]. However, diphtheria-like infections due to toxigenic *C. ulcerans* have outnumbered those caused by toxigenic *C. diphtheriae* in many industrialized countries [6,9].

C. ulcerans has been isolated from a variety of domestic and wild animals, and although its transmission is mainly zoonotic, human-to-human transmission has been reported [1,10]. Historically, the main sources of *C. ulcerans* infection were consumption of unpasteurized milk or exposure to livestock [11], but pets are increasingly involved in infections [3].

Interestingly, our strain was resistant to both penicillin G and clindamycin. This seems to be rare. According to the annual activity report of the *Corynebacterium* National Reference Center, 13 isolates of toxigenic *C. ulcerans* were confirmed between 2016 and 2018 in France [8]. Although clindamycin resistance seems to be frequent (33 to 60%) [3], only one strain was resistant to both penicillin G and clindamycin. Furthermore, only another strain was also isolated from bone and joint infection (BJI) during this period.

Data suggest that diphtheria vaccination may protect against the development of disease caused by toxigenic *C. ulcerans* [12]. Nevertheless, the patient had received a diphtheria vaccine booster three months before the onset of symptoms. Despite an immune response measured at 3.87 IU/mL (EIA Virotech, Russelsheim, Germany) (threshold = 0.10 UI/mL), he still developed a BJI.

Discussion

This case of BJI infection caused by *C. ulcerans* is rare as shown in some reviews and articles. Indeed in developed countries, most human infections involving *C. ulcerans* are respiratory infections, sometimes similar to diphtheria with pseudomembranous angina, or cutaneous and subcutaneous infections that can lead to abscessation [1,13]. Vaccination is directed against diphtheria toxins and is therefore effective against *C. ulcerans* strains producing these toxins. It is therefore effective against the effects of diphtheria toxin but does not protect against carriage or infection by non-toxigenic strains. Moreover, the fact that a strain carries the tox gene does not mean that the toxin is necessarily produced and secreted by the strain and also that the toxin may have a slightly different molecular structure [14]. Moreover, vaccination can eradicate cases of diphtheria caused by *C. diphtheriae*, since the carrier is strictly human, but this is not the case for *C. ulcerans*, whose reservoir is zoonotic, and animals remain the main source of contamination for humans [3,13,15]. The question of vaccination in animals may arise, but the reservoir is very large, and covering all animals to eradicate carriage seems utopian. Perhaps vaccination of companion animals (dogs and cats) could be considered, but vaccination coverage would have to be high to be effective.

Conclusion

In conclusion, we report an uncommon case of BJI caused by toxigenic *C. ulcerans* resistant to both clindamycin and penicillin G. Although molecular comparison wasn't possible between the patient's strain and that of his dog, it seems very likely that the patient's dog was the source of the infection.

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This represents a limitation of the study since the source of infection is highly probable but cannot be formally confirmed.

Further clinical and microbiological investigations are required to evaluate the protection conferred by diphtheria vaccination, regarding *C. ulcerans* infections.

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Ethical considerations declaration

The patient's consent was obtained to publish this case report.

Author contributions

José Bras-Cachinho: acquisition of data, analysis and interpretation, writing of the manuscript.

Louis Bernard, Laura Chaufour, Coralie Lemaire, and Nadège Lépine: revision of the document, final approval for publication.

Marie-Frédérique Lartigue: writing of the manuscript, revision of the document, final approval for publication.

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