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Mots clés : *Corynebacterium diphtheriae,* migrants, voyageurs

Keywords: *Corynebacterium diphtheriae*; migrants; travelers

Highlights

We report two imported cases of Corynebacterium diphtheriae infection in Paris in 2016

These two cases illustrate the epidemiology of diphtheria (Afgan refugee, French traveler), the clinical presentation (cutaneous, respiratory carriage), the potential consequences (toxin positive, toxin negative)

The rising number of unvaccinated or incompletely vaccinated individuals, increased lnumber of imported cases, and growing vaccine skepticism could put Europe at risk of diphtheria.

Résumé

Introduction. La diphtérie est une maladie réémergente en Europe. En 2015, 36 cas ont été rapportés contre 53 cas de 2000 à 2009.

Patients. Nous rapportons deux cas d'infection à *Corynebacterium diphtheriae* survenus en 2016 dans un hôpital français : une infection cutanée avec recherche de toxine négative chez un voyageur et un portage respiratoire avec recherche de toxine positive chez un réfugié afghan atteint d'une tuberculose pulmonaire. L'histoire vaccinale était inconnue pour le patient afghan.

Abstract

Background. Diphtheria is re-emerging in Europe. A total of 36 cases were reported in Europe in 2015 versus 53 cases between 2000 and 2009.

Patients. We report two cases of *C. diphtheriae* infection in a French hospital in 2016: a cutaneous infection with negative toxin testing in a French traveler, and a respiratory diphtheria carriage with positive toxin testing in an Afghan refugee diagnosed with tuberculosis. The vaccination history could not be retrieved in the Afghan patient.

Introduction

Corynebacterium diphtheriae (CD) is re-emerging in Europe. A total of 53 cases were reported between 2000 and 2009 [1] whereas 48 cases were declared between 2010 and 2013 in Europe [2, 3]. Twenty-four cases of CD infections had also been reported in 2014 [2] and 36 in 2015 [4] in Europe. In 2016, a fatal case of diphtheria in an unvaccinated child of immigrant parents was reported in Belgium [5]. We report two imported cases of CD infection declared in Paris in 2016: a cutaneous infection in a returning French traveler and an asymptomatic diphtheria carriage in an Afghan refugee.

Case reports

A 38-year-old French male presented to our outpatient clinic in Paris with a three-month history of skin ulcers of the anterior right upper leg after a five-year professional stay in the capital of Madagascar. The physical examination revealed one crusted, large, superficial ulcer surrounded by a few smaller ones. No discharge, foul smell, or clinical aspect of cellulitis was observed (Figure 1). He had no medical history, no recent leg trauma, and no recent history of tonsil inflammation or respiratory symptoms. The first hypothesis was a pyogenic skin infection and outpatient care was started with oral pristinamycin after collection of superficial skin swabs. Bacterial cultures yielded Gram-positive cocci identified as *Staphylococcus aureus,* and Gram-positive rods identified as CD by MALDI-TOF mass spectrometry (MALDI Biotyper IVD Library 5627, Bruker). It was confirmed as CD by a home-made multiplex Polymerase Chain Reaction (PCR) test. The biovar was *S. mitis*. The *tox* gene detection performed by the national reference center by PCR was negative (*tox* -) [6]. CD pharyngeal carriage investigation

performed one week later was negative. Although skin lesions had improved after a one-week treatment, pristinamycin was switched to amoxicillin for an additional week to cover the recommended two-week treatment for CD infection. The outcome was favorable. The patient reported routine vaccination during childhood but missed the recommended booster set for the age of 25 in France [7]. A booster vaccination against diphtheria, tetanus, and pertussis (DTaP) was administered.

On that same month a 21-year-old Afghan male asylum seeker was admitted to the department of pneumology for suspicion of pulmonary tuberculosis. He had left his country eight months earlier and had been living in a refugee center in Paris for the last two months after a four-month stay in a center in Stockholm. His travel path included stays in Turkey, Greece, Austria, and Germany. He had a three-month history of cough and thoracic pain, but no evidence of tonsil inflammation or respiratory distress. The CT scan performed at admittance showed cavitation of the upper right lobe. Airborne precautions were taken upon arrival. The sputum analysis was positive for *Mycobacterium tuberculosis* and CD. The bacterial isolate was confirmed as CD by PCR and MALDI-TOF and was determined to be of *S. mitis* biovar. It was shown to carry the *tox* gene (*tox* +) by PCR and to produce the diphtheria toxin by Elek test. The patient was diagnosed with tuberculosis and asymptomatic carriage of *tox*+ CD for which he received oral amoxicillin for two weeks. As his vaccination history was unknown, he was vaccinated with the DTaP vaccine but no serotherapy was administered. Six refugees from the same center but no social/health care worker were identified as individuals who had close contact with the patient and local authorities were notified. Among them, two persons had left before testing could be performed eight days later. Testing of the four other contacts was performed in our department, as there was no mobile

team to visit the refugee center. All pharyngeal swabs were negative. Every contact person was given vaccination with DTaP (no vaccination history was available) and amoxicillin for 10 days.

Discussion

Diphtheria is once again a growing concern, and these two case reports illustrate some characteristics of this disease and the difficulties faced by physicians when managing such patients.

The two patients were a refugee and a traveler. Refugees are known to be at risk for diphtheria because of frequent incomplete vaccination and promiscuity in the refugee centers. More than 23 cases of cutaneous CD infection (including nine *tox*+ bacterial strains) have been reported among refugees within the last two years in Europe, mainly in Germany and Switzerland, but also in Denmark and Sweden [8-10]. In these studies and in our patient no information on the vaccination status was available. No data on the seropositivity for diphtheria in migrants is available in France but a study recently showed that 76.1% of refugees in Germany had no long-term protection against diphtheria [11].

However, cases reported in returning travelers are uncommon. For instance, 16 cases of imported cutaneous CD infections were reported in Europe between 2000 and 2009 [1]. However, only infections caused by *tox*+ CD are required to be notified, explaining the lack of data on *tox*- CD. The use of the MALDI-TOF approach has improved the identification of CD, and may partly account for the recent increase in CD infection notifications [12]. Nevertheless, travelers to endemic regions are probably at risk of diphtheria especially elderly patients, because of a lack of booster immunization in elderly people. A European sero-epidemiological study reported that increasing age was related to an increase in seronegativity. The seroprotection against diphtheria

dropped from about 75% in individuals aged <15 years to about 30% for those aged >60 years in the Czech Republic where the diphtheria vaccine coverage rate was >95% [13].

Cutaneous CD infection is difficult to diagnose. A chronic ulcer with a grey membrane is the characteristic presentation, but it frequently presents as a non-specific lesion, often appearing on a pre-existing lesion. Pyogenic bacteria may also be found as co-infection or colonization, making the diagnosis even more difficult, as observed in our patient. The patient acts as a reservoir of the bacterium and can cause outbreaks of the cutaneous and respiratory disease [14, 15]. In our case report, the partial improvement with pristinamycin treatment may indicate a co-infection with *Staphylococcus aureus* and not just colonization by the latter. This possible co-infection shows the importance of a routine use of the MALDI-TOF technique to detect a potentially associated CD infection.

The asymptomatic carriage is usually characterized by the incidental finding of a positive pharyngeal swab even though our patient had a positive sputum analysis. This condition is poorly described. A study conducted in 2007 screened 14,000 individuals in six European countries and observed four cases of symptomatic *tox*+ pharyngeal diphtheria, two cases of asymptomatic pharyngeal carriage of *tox*+ CD, and 26 cases of asymptomatic carriage of *tox*- CD [16].

The clinical management of a diphtheria case and contacts is challenging as few exhaustive official guidelines are available in European countries. Recommendations from National Public Health Authorities may also differ between countries about specific points [17, 18]. For instance, French guidelines recommend treating a *tox*+ diphtheria carriage with antibiotics and serotherapy but English guidelines only recommend the antibiotic treatment. The World Health Organization (WHO) guidelines were edited in 1994 [19].

The refugee patient was staying in a refugee center in Stockholm, Sweden, where cases of diphtheria were reported among refugees in 2015 [10]. However, our patient arrived in Sweden in 2016. Therefore either he was a chronic carrier, or he was recently contaminated with an unknown source in France. This stresses the importance of a close collaboration between countries to share information on the medical conditions of refugees, especially in cases like these where the cough due to pulmonary tuberculosis makes the spread of CD even more likely.

Our second case patient did not receive serotherapy although recommended by French guidelines [17]. Emergency treatment with diphtheria serotherapy seems difficult to deliver, making an international collaboration even more important. Colleagues from Finland had to use expired − although verified to be safe − antitoxin for a patient presenting with toxigenic diphtheria [10]. Colleagues from Spain had no available antitoxin and had to get it delivered from a neighboring country. The management of an imported case patient was thus delayed [3]. In 2009 at least 14 countries of the European Union had no national stock of diphtheria antitoxin [20].

Life in refugee centers facilitates transmission and leads to outbreaks because of poor hygiene and promiscuity in individuals originally from countries or regions with no vaccination coverage. Identified case patients need to be appropriately managed and prevention measures correctly implemented. Routine vaccination for every refugee should be standard along with a medical registration system for life-threatening diseases diagnosed in migrant people. The incomplete vaccine-induced immunity in elderly people is also a public health concern, and measures should be taken to ensure regular administrations of booster doses of vaccines. The rising number of unvaccinated or incompletely vaccinated individuals, increased lifespan, and growing vaccine skepticism could put Europe at risk of diphtheria, a vaccine-preventable disease.

Conclusion

CD is re-emerging. Insufficient vaccination coverage, international travel, and increasing migration call for overcoming the lack of knowledge among European physicians about diphtheria. Guidelines need to be updated, completed, and largely disseminated, including the management of asymptomatic CD carriers.

Contribution of authors

All authors either contributed to the management of patients or to the literature search and writing of the article. All authors reviewed and approved the final version of the article.

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Figure 1. Cutaneous diphtheria in a traveler coming back from Madagascar