Corynebacterium ulcerans cutaneous diphtheria

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We describe the case of a patient with cutaneous diphtheria caused by toxigenic *Corynebacterium ulcerans* who developed a right hand flexor sheath infection and symptoms of sepsis such as fever, tachycardia, and elevated C-reactive protein, after contact with domestic cats and dogs, and a fox. We summarise the epidemiology, clinical presentation, microbiology, diagnosis, therapy, and public health aspects of this disease, with emphasis on improving recognition. In many European countries, *C ulcerans* has become the organism commonly associated with cutaneous diphtheria, usually seen as an imported tropical disease or resulting from contact with domestic and agricultural animals. Diagnosis relies on bacterial culture and confirmation of toxin production, with management requiring appropriate antimicrobial therapy and prompt administration of antitoxin, if necessary. Early diagnosis is essential for implementation of control measures and clear guidelines are needed to assist clinicians in managing clinical diphtheria. This case was a catalyst to the redrafting of the 2014 national UK interim guidelines for the public health management of diphtheria, released as final guidelines in March, 2015.

Introduction

Cutaneous diphtheria presents as a painful ulcerating lesion at the site of inoculation and is often associated with erythema and local oedema; a grey membrane analogous to that present in respiratory diphtheria is also occasionally evident. Historically, the most commonly identified causative bacterium has been *Corynebacterium diphtheriae*, first noted in diphtheritic membranes by Klebs in 1883,[1] but a second species in this genus, *Corynebacterium ulcerans*, can also cause both cutaneous and respiratory diphtheria.[2–4] Among toxigenic strains of both these species, systemic sequelae can also arise, including myocarditis and peripheral neuropathy; the probability of developing these sequelae and their severity are related to the extent of the local (either cutaneous or respiratory) diphtheria lesion and the immune status of the patient. Diphtheria antitoxin was developed in the late 19th century and a toxoid vaccine was developed in the 1920s. Subsequent immunisation programmes in the UK and USA in the 1940s, and inclusion of diphtheria vaccine in the WHO Expanded Program on Immunization in May, 1974, have had notable effects on reported case numbers.[5] However, geopolitical changes beginning in the 1990s have led to decreases in vaccine coverage in some regions, particularly in eastern Europe, and have been associated with an increase in the incidence of diphtheria worldwide.[6,7] In the UK, high coverage of diphtheria vaccination has been sustained since the 1990s, at 95% in children,[8] yet cases are still reported.

We describe a case of cutaneous diphtheria caused by *C ulcerans* in a UK-born London resident, an incident that was a catalyst to the redrafting of the 2014 national UK interim guidelines for the public health management of diphtheria in England and Wales, released as final guidelines[8] in March, 2015. In this patient, a necrotising flexor sheath infection necessitated plastic surgical debridement and the patient developed symptoms characteristic of sepsis and a rash with eosinophilic infiltration on histological examination, but without cardiac or neuropathic complications. We review the epidemiology, clinical presentation, microbiology, therapy, and public health aspects of this infection, highlighting the importance of continued vigilance for cutaneous diphtheria in patients presenting with skin and skin-structure infections.

Case presentation

A 67-year-old woman presented to the emergency department with a 3 day history of a small non-traumatic raised nodule on the dorsum of her right hand. She reported a pronounced increase in pain, swelling, and redness of her right hand immediately before presentation, and two episodes of systemic fever and rigors. She also complained of itching on the volar surface of the ipsilateral forearm. Her past medical history included hypothyroidism, for which she was on thyroid replacement therapy. She denied any travel history in the preceding 12 months, and before that had not visited countries where diphtheria is known to be prevalent. She did report being an avid gardener and had an extensive animal contact history, with 16 pet cats (including several feral felines that she had rehomed or fostered), six pet dogs, and contact with a semi-tame fox that entered the house for food. She reported feeding and petting the domesticated animals but denied direct contact with the fox, or receiving any bites or scratches from any of the animals. Although one feline had malignant neoplastic disease, none had been reported with respiratory symptoms or cutaneous ulcers.

Physical examination of the patient confirmed deep non-blanching erythema of both the dorsal and palmar aspects of the right hand with tense oedema of the tissues and associated tenderness. A necrotic lesion at the base of the index finger was noted, but the skin was intact. Blanching, raised erythema of the distal right forearm was apparent, which by contrast with the hand, was non-tender and itchy, with an appearance consistent with an allergic urticarial response (figure 1). Tachycardia (105 beats per min) and fever (38·2°C) were noted, with other physiological observations remaining normal. Laboratory blood analysis revealed a raised white blood cell count ($10·9 \times 10^6$ cells per L), with a

normal haemoglobin count (123 g/L), platelet count (249×10^9 cells per L), and blood clotting parameters. She had an increased concentration of C-reactive protein (186 mg/L), but all other laboratory indices including lactate and blood chemical analysis values were within normal limits, and the electrocardiogram was normal. Two sets of blood cultures and a swab of the necrotic lesion did not yield microbial growth. Radiographs of the affected hand showed no bony injury, but evident soft tissue swelling at the base of the right index finger (figure 2).

The patient was admitted and treated empirically with cefuroxime and clindamycin, and referred for plastic surgical consultation. Findings at surgical exploration were consistent with a flexor sheath infection. Two tissue samples from the first exploratory procedure did not reveal any organism on direct Gram staining, but subsequently showed growth of Gram-positive rods described as diphtheroids (corynebacterium-like), which were not further speciated on presumption of being contaminants and were discarded. Specific cultures for mycobacteria and fungi were negative. Histopathological analysis of a biopsy sample from the palmar aspect of her right hand showed necrotic fat and fibrovascular material (figure 2). A second surgical exploration on the next day allowed further local debridement and application of a surgical vacuum dressing. Short-term bacterial, mycobacterial, and fungal cultures at this stage yielded no growth. Histopathological analysis of the debrided tissue again showed extensive necrosis, whereas, by contrast, a proximal right arm skin biopsy in the area of blanching erythema showed viable tissue with an eosinophilic infiltrate (figure 2).

During the subsequent 5 days, some clinical improvement in the hand was evident, although erythema substantially increased, extending up the right arm to the scapula and to a non-confluent patch across the contralateral flank and abdominal wall. She returned to the operating theatre at day 7, when surgical exploration showed improvement in tissue viability (figure 1). Care was continued as an outpatient with oral rifampicin and doxycycline, avoiding β-lactam drugs, because of the undefined cause for the eosinophilic rash. After discharge, tissue samples taken during the day 7 exploratory procedure continued to be cultured using selective techniques, including 5 day incubation in a brain-heart broth then subculturing for 48 h on horse blood agar. This revealed again a pure growth of Gram-positive rods of diphtheroid appearance (figure 2). Identification on this occasion via a matrix-assisted laser desorption ionisation-time of flight (MALDI-TOF) Biotyper (Bruker Daltonik GmbH, Bremen, Germany) showed this isolate to be *C ulcerans* (figure 2), with a relative intensity of matched peaks score of 2·28, suggesting secure genus identification and probable species identification. Disc susceptibility testing[9] showed sensitivity to penicillin, meticillin, erythromycin, tetracycline, fusidic acid, ciprofloxacin, rifampicin, trimethoprim, and resistance to clindamycin. At the Public Health England Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU; London, UK), the isolate underwent confirmatory identification tests (cysteinase positive with an API Coryne [bioMérieux, Marcy l'Etoile, France] profile 0111326) and was revealed by PCR to carry the A portion of the diphtheria toxin gene.[10,11] Phenotypic confirmation of toxin production was shown by the Elek test.[12] Multilocus sequence typing of the isolate showed it to be sequence type 287.

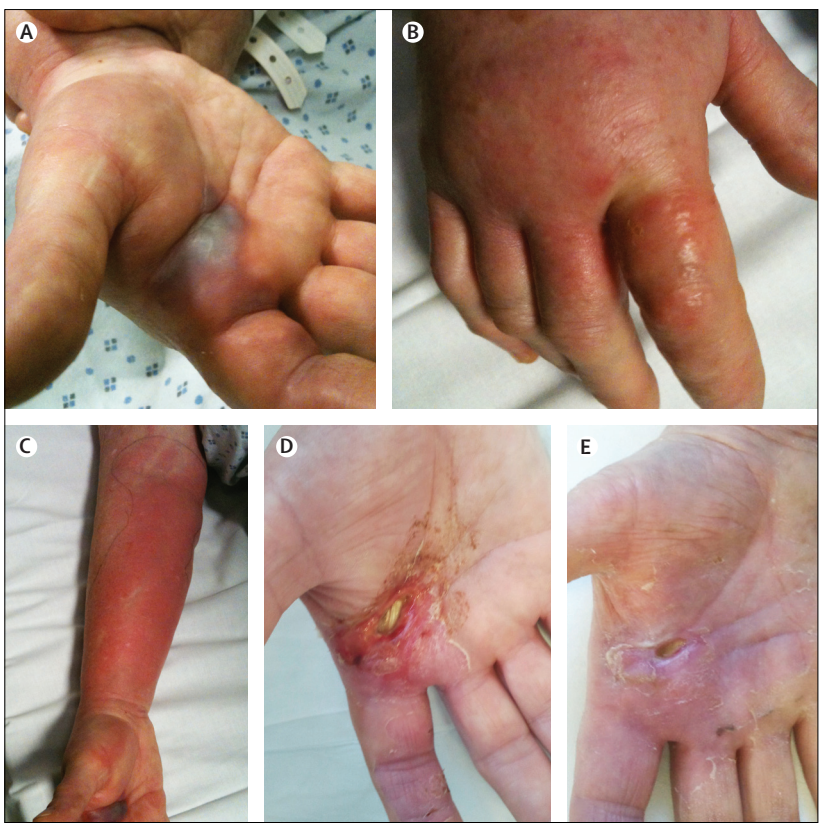

Figure 1: **Clinical presentation and progression of *Corynebacterium ulcerans* cutaneous diphtheria**
(A) Palmar aspect of the hand at time of presentation. (B) Dorsal aspect of hand at time of presentation. (C) Ipsilateral forearm with spreading inflammatory response at time of presentation. (D) Palmar aspect of hand after surgical debridement of synovial sheath necrotic tissue at 7 days after presentation. (E) Palmar aspect of hand at 28 days after presentation and debridement.

After 21 days of antibiotic therapy (cefuroxime and clindamycin, then doxycycline and rifampicin), the patient recovered full functionality in her right hand (figure 1) and her C-reactive protein concentration decreased to 23·3 mg/L. The patient could not recall whether she ever had been immunised against diphtheria, and serum retrieved at day 7 of the patient's admission did not reveal diphtheria antitoxin (limit of detection <0·016 IU/mL).

Incident control was coordinated by the local unit of the Health Protection Agency (since April, 2013, renamed Public Health England Health Protection Team) to oversee the ongoing case management and public health

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