Corynebacterium ulcerans cutaneous diphtheria.

Dr Luke SP Moore[a,b*] FRCPath

Dr Asuka Leslie[c] MFPH

Dr Margie Meltzer[c] FFPH

Dr Ann Sandison[b] FRCPath

Prof Androulla Efstratiou[d] PhD

Prof Shiranee Sriskandan[a,b] FRCP

[a] *National Centre for Infection Prevention & Management, Imperial College London, Du Cane Road, London. W12 0NN. United Kingdom.*

[b] *Imperial College Healthcare NHS Trust, Hammersmith Hospital, Du Cane Road London. W12 0HS. United Kingdom. (LSPM & SS Department of Infectious Diseases; AS Department of Histopathology)*

[c] *North West London Health Protection Team, 61 Colindale Avenue, London. NW9 5EQ. United Kingdom.*

[d] *WHO Global Collaborating Centre for Diphtheria & Streptococcal Infections, Public Health England, 61 Colindale Avenue, London. NW9 5EQ. United Kingdom.*

*Corresponding author

Dr Luke SP Moore, National Institute of Health Research Imperial Biomedical Research Centre Fellow, National Centre for Infection Prevention & Management, Du Cane Road, London. W12 0NN. UK.

Email: l.moore@imperial.ac.uk. Tel:+44(0)2033132732. Fax: +44(0)2083833394

Abstract

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 fi nal 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 (fi gure 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 (fi gure 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 testing9

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.

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 implications. This included screening for carriage of *C ulcerans*, confirmation of vaccine status, and tetanus, diphtheria, and inactivated polio vaccine immunisation where appropriate for the index case, three household contacts, and health-care staff involved in invasive procedures. No secondary carriers or cases of diphtheria were identified. Evidence that cats and dogs might act as potential reservoirs for this organism[13] prompted consideration as to whether the contact animals should be swabbed and screened for *C ulcerans*. Veterinary advice was sought, and screening was felt not to be feasible due to the many possible animal contacts and the impracticalities of treating any animals thus identified.

Review and discussion

Epidemiology

After political changes in eastern Europe and central Asia at the end of the 20th century, a resurgence in many vaccine preventable diseases, including diphtheria, was reported across these countries. For diphtheria, this resurgence resulted in more than 115 000 cases and 3000 deaths in post-Soviet Union alone between 1990 and 1997.[6] At the beginning of the 21st century, diphtheria is still reported with alacrity, and is monitored by the European Diphtheria Surveillance Network now under the remit of the European Centre for Disease Prevention and Control.[7] Continuing transmission is documented in Latvia, Ukraine, and Russia, posing a risk of epidemic diphtheria returning to the European Union.[7] In North America, the highest incidence has been historically documented in states with large populations of Indigenous Americans,[5] but a prolonged geographical clustering in Vancouver and Seattle dating back to 1985 or earlier has also been reported.[14] WHO data for 2012 reported 4489 cases worldwide and an estimated 2500 deaths, with diphtheria–tetanus–pertussis vaccination coverage estimated to be 83%.[15]

Historically *C diphtheriae* has been the most common causative agent of toxigenic diphtheria worldwide, although *C ulcerans* is now reported more often in the UK. Moreover, although respiratory diphtheria remains the most common clinical presentation, cutaneous diphtheria continues to be reported in many areas of the world. *C ulcerans* as a cause of cutaneous diphtheria has been reported in European countries,[16] including France,[17] Germany,[18–20] Switzerland,[21] and the UK.[2,22] Cases have also been reported in other areas of the world including Canada,[23] Japan,[24] Brazil,[25] and Sweden (imported from west Africa).[26]

Human beings are the reservoir for *C diphtheriae*, in particular children,[5] and transmission of *C diphtheriae* occurs from person to person, predominantly from the respiratory tract, but occasionally from cutaneous lesions or fomites. A chronic carrier state can exist, but antimicrobial therapy provides effective clearance. By contrast, the *C ulcerans* reservoir is thought to be animals. Cases of

C ulcerans have been reported after consumption of raw dairy products and contact with cattle,2 pigs,20 and domestic pets.4,17,19,21,24,27 *C ulcerans* diphtheria person-to- person transmission has been proposed,2,28 but has yet to be confirmed.

Microbiology

Microbiology

Corynebacteria are Gram-positive rods. Many species from this genus are skin commensals, having a role in human body odour formation,29 and act only as opportunistic pathogens.30

Of the many *Corynebacterium* species, three can potentially cause diphtheria: *C diphtheriae*, *C ulcerans*, and *Corynebacterium pseudotuberculosis*. Although cases caused by non-toxigenic strains have been reported,14,31,32 identification of these three species in a relevant clinical sample is not sufficient alone to establish pathogenicity because non-toxin-producing strains of these species rarely cause disease. Non-toxin-related corynebacterial virulence factors have been proposed, including the presence of a complex cell wall structure containing peptidoglycan and an outer mycolic acid layer—functionally equivalent to the outer membrane of Gram-negative bacteria.33 Corynebacteria also have several adherence mechanisms; for *C diphtheriae*, adherence is predominantly through pili.34 Sequencing of *C ulcerans* has identified similar subunits of adhesive pili of the SpaDEF type and other virulence factors including phospholipase D, neuraminidase H, and endoglycosidase E.35

The exotoxin, secreted from *C diphtheriae* and *C ulcerans*, is associated with classic diphtheria. Toxigenic potential is correlated with corynebacteria lysogenisation by a tox+ phage.36 Sequencing of the toxin gene in *C ulcerans* isolates has revealed differences from *C diphtheriae*. When assessed with cytotoxicity assays, *C ulcerans* toxin- containing supernatants were less potent than those from *C diphtheriae*.37 The toxin itself consists of two subunits. Subunit B binds to the receptor, proposed as heparin- binding epidermal growth factor,38 and is then endocytosed. The acidic endosome environment induces a toxin conformational change, allowing translocation of the

active A subunit into the cytoplasm, where cytotoxic activity results through ADP-ribosylation of elongation factor 2, which inhibits cellular protein synthesis.[39]

Clinical presentation

C diphtheriae and *C ulcerans* can both cause the same range of diseases. Respiratory diphtheria presents typically with a sore throat that can progress to a swollen so-called bull neck, with oropharyngeal examination revealing a strongly adherent pseudomembrane that can progress to cause airway obstruction. By contrast, cutaneous diphtheria is characterised by painful rolled-edge ulcers at the site of inoculation, often associated with erythema and local oedema as in this patient. A grey membrane analogous to that reported in respiratory diphtheria can also be seen occasionally. The low frequency with which cutaneous diphtheria occurs in many areas of the world, combined with the potentially wide differential diagnosis for cutaneous ulcers, contributes to misdiagnoses and delayed diagnoses of cutaneous diphtheria, thereby reinforcing the need to sample and culture all ulcers with a potentially infectious cause when encountered.

Systemic toxin-mediated sequelae (myocarditis or peripheral neuropathy) can occur in up to 15% of cases, predominantly in respiratory diphtheria, but also in patients with extensive local cutaneous disease. Myocarditis can lead to complete heart block[40] and cardiomyopathies,[41] and has a high fatality rate. Toxin- mediated neuropathies can also occur, affecting 15% of patients with diphtheria in one large case series.[42] Bulbar dysfunction was reported in 98% of patients, limb weakness in 70%, and respiratory failure in 20%, with symptoms persisting for a median of 49 days.[42] Allergic presentation of disease has not been reported; in our case, the patient's eosinophilic rash was present before antimicrobial treatment was started and fluctuated throughout the early course of her illness. Although the patient could not specifically recall having ever been vaccinated for diphtheria, a widespread diphtheria vaccination programme was introduced in the UK in the 1940s and we speculate that the patient might have shown a type 1 hypersensitivity reaction to epitopes of the toxin included in early vaccines.

Diagnosis

As noted, a wide differential diagnosis exists for cutaneous ulcers, particularly when history of travel43 or animal contact exists. Samples should be assessed by culture of potential bacterial, fungal, and mycobacterial causes. Histopathological examination of tissue biopsy samples is also essential, particularly when patient history might suggest leishmaniasis.44 Discussion with medical microbiologists and pathologists assists appropriate laboratory diagnostics in such cases.

The preponderance of commensal corynebacteria on the skin complicates identification of pathogenic species when wound samples are analysed, and can further contribute to delayed diagnosis. Delineation of *C diphtheriae* from other corynebacteria has historically been through the use of selective agar and other screening tests,45 which allow subdivision to different *C diphtheriae* biotypes (ie, var gravis, mitis, intermedius, or belfanti). If diphtheria selective agars are not used, which is common for non- nasopharyngeal samples, confirmation of species within the *Corynebacterium* genus is based on biochemical differences, which historically has been a challenge.46 Despite iterative taxonomical changes since 1992 that have made coryneform-like bacterial identification more precise,47 these factors have contributed to the misidentification and non-identification of *C diphtheriae*, and particularly of *C ulcerans*, in cutaneous syndromes consistent with diphtheria.

To assist with bacterial identification, new techniques are becoming widely available in clinical laboratories; prime among these is mass spectroscopy, predominantly in the form of MALDI-TOF. Introduction of this platform has substantially improved the speed of bacterial identification and is cost effective in many settings.48 MALDI-TOF has been shown to provide accurate identification of both *C diphtheriae*49 and non-diphtheriae corynebacteria,50,51

Yet in wider clinical laboratory practice MALDI-TOF might not provide especially reliable identification of other Gram- positive bacilli52 and corroboration by a molecular identification method might be indicated. In the case presented, use of MALDI-TOF underpinned the diagnosis, allowing identification of diphtheroids, which were previously not routinely speciated.

Identification of *C diphtheriae, C ulcerans*, or *C pseudotuberculosis* from clinical samples must then be followed by determination of toxigenic potential, historically with the Elek test.53 Difficulties with this method are well documented,54 and modifications have been described that decrease the test time from 48 h to 16 h.12 However, this still delays formal diagnosis, and PCR-based genotypic tests (as an adjunct to phenotypic detection) have been developed.11 Previous difficulties in detection of toxigenicity by PCR arising from tox gene sequence variation between *C diphtheriae* and *C ulcerans*55 have been overcome by development of real-time PCR methods that detect the tox gene of both species.56 A negative PCR result is particularly useful for the rapid exclusion of toxigenicity, preventing the need for further control measures.8 Genotypic laboratory methods also have a role in typing for *C diphtheriae* and *C ulcerans*, thereby contributing to public health disease control. Genotyping has been done by several different methods, but criticisms have been widespread.57 Several different genotyping methods have been trialled, but difficulties with discriminatory ability and test reproducibility have been reported.57 Clustered, regularly interspaced short palindromic repeats and mini-satellites are promising genomic markers for high-resolution typing schemes, but are not widely used;58 instead multilocus sequence typing might now prove the definitive technique to identify *C diphtheriae*59 and *C ulcerans*.60

In addition to microbiological investigations, diagnostic tests to search for the sequelae of toxigenic diphtheria should be done in confirmed cases. These tests include electrocardiography and echocardiography for myocarditic complications, and nerve conduction studies if symptoms suggest peripheral neuropathies. Electrocardiographic monitoring can show early indications of incipient heart block, whereas nerve conduction studies can show distal motor latencies, which can persist for a prolonged period.42

Therapy

Treatment for diphtheria focuses on antimicrobial therapy and adjunctive antitoxin use. In respiratory diphtheria, airway management might be necessary and should be considered early in

the course of disease. In cutaneous diphtheria, although patients occasionally need surgical intervention, assessment should be sought early to decide whether affected tissues might need debridement, as was done in this case.

Much of the evidence for antimicrobial therapy in diphtheria derives from studies in the early 1970s, stemming predominantly from case series of *C diphtheriae* rather than *C ulcerans*, and from cases of respiratory rather than cutaneous diphtheria. Erythromycin remains the mainstay of therapy[61] showing substantial in-vitro activity (mini mum inhibitory concentration for var gravis or intermedius 0·025–0·05 mg/L; for var mitis 0·5 mg/L).[62] Although occasional instances of plasmid-mediated resistance have been documented for more than 25 years,[63] continuing *C diphtheriae* resistance surveillance has shown erythromycin susceptibility to be generally maintained,[64] and with few cases of multidrug resistance reported.[65] However, antimicrobial susceptibility testing on all diphtheria toxin-producing *Corynebacterium* species is strongly recommended. Of note, erythromycin adverse effects include an association with prolonged QT syndrome[66] and a theoretical concern of potentiation of myocarditis sequelae from diphtheria toxin. Therefore, the appropriateness of erythromycin should be carefully considered. Newer macrolides have shown minimum inhibitory concentrations similar to that for erythromycin,[64] and although no large-scale studies on in-vivo efficacy have been reported, case studies have documented success.[67] The main alternative therapy, penicillin, initially generated concerns regarding higher in-vitro minimum inhibitory concentrations for *C diphtheriae*,[61,64]

but these concerns were not supported by the findings of a randomised controlled trial in a paediatric Vietnamese population. This trial showed no difference in time to membrane resolution or bacteriological clearance between penicillin and erythromycin, but noted a faster median time to fever resolution with penicillin (27 h vs 46 h with erythromycin).[68]

However, with respect to bacterial clearance, macrolides and lincosomides are preferred to penicillins in the carrier state. A trial done in the 1970s showed carrier state clearance of 84% with benzathine benzylpenicillin, 92% with erythromycin, and 93% with clindamycin.[69]

Crucially, in the case presented here, the patient was initially given a cephalosporin and clindamycin for suspected necrotising soft tissue infection, yet the disease progressed, and the *C ulcerans* isolate was established to be resistant to clindamycin in vitro. The patient was discharged and continued to take rifampicin and doxycycline, to which the isolate was susceptible.

Integral to management of diphtheria, particularly if the risk of toxin-mediated sequelae is high, is diphtheria antitoxin.[28] The antitoxin neutralises only non-tissue- bound toxin and should therefore be given early in the course of the disease, on the basis of clinical suspicion rather than laboratory diagnosis. Although the protective effect of this antitoxin was first described for *C diphtheriae*, evidence suggests that this antitoxin also has a role in *C ulcerans* diphtheria, despite tox genes and prophages varying between these two species at the molecular level.[70]

However, availability is a major issue for diphtheria antitoxin, with production reliant on equine bleeding and antibody harvesting. In 2009, a worldwide survey showed that many European countries held no or only expired stock of antitoxin.[71] Alternatives to equine-derived antitoxin might become available in the future, and a candidate human monoclonal antibody that binds to the diphtheria toxin receptor binding domain has recently been described.[72]

Public Health

Consistent with UK national guidelines[28] current at the time of the case described, the local health protection unit was notified and an incident team was convened to oversee the necessary public health measures. Implicit for all cases of respiratory or cutaneous diphtheria is the need for contact tracing to identify individuals at risk (panel). For human contacts, nasal and pharyngeal swabs and samples from any open wounds should be sent for culture testing before starting chemoprophylaxis with either parenteral benzathine benzylpenicillin or oral erythromycin. Carriers of a toxigenic corynebacteria should be treated and have control measures instigated; if these carriers are inpatients, measures should include barrier nursing until two sets of cultures (nasal and pharyngeal, and wound where appropriate) taken 24 h after stopping antimicrobial chemotherapy, and again at least 24 h later, remain negative.[5,8]

In addition to chemoprophylaxis, vaccination also plays an essential part in managing the public health implications of a diphtheria case. Vaccine administration (one booster for individuals previously immunised, three monthly low-dose diphtheria-containing vaccines if unimmunised)[8] is not only necessary as a preventive intervention for contact with diphtheria, but also as an adjunct to treatment for the index case during convalescence, since natural infection does not always confer immunity.[2] In *C ulcerans* diphtheria, as also noted for antitoxin use, tox gene and prophage variation between *C diphtheriae* and *C ulcerans* makes the effectiveness of vaccination in these cases a relative unknown.[70] Despite international immunisation programmes, serosurveillance studies suggest that about 50% of adults in the UK, Germany, Italy, and Sweden do not have protective titres of diphtheria antibody, and this absence of protection increases to more than 70% in older-age cohorts.[73]

As previously reported,[1,2] the transition since the 1990s to most diphtheria cases resulting from *C ulcerans* rather than from *C diphtheriae*, as exemplified in this Grand Round, has necessitated changes to the nature of the risk assessment undertaken and demanded clarity as to the public health and clinical actions subsequently needed. For cases of *C ulcerans* diphtheria, identification of animal contacts is particularly relevant in view of zoonotic transmission and the potential for animal reservoirs. This identification process can be complex, as seen in this case, and specialist advice is often needed to help to decide whether, when, and how animals should be sampled. In the UK, this advice is obtained from the Animal Health and Veterinary Laboratories Agency, which considers various factors including how likely are identified animals to have been the only potential source of the infection (in this case, the wild fox was an unknown source), whether swabs from the animals can be practically obtained (especially since the person taking the sample risks injury), and the animal welfare implications (arising from sampling and forced administration of antimicrobials when *C ulcerans* might be a commensal in many animals). Additionally, the costs of treatment of animal contacts might be high and owners cannot be legally required to treat their animals. Strict hygiene observance and vaccination of the index case and human contacts, as done in this case, are

therefore often the mainstay of incident management. Some areas of the world show immunisation schedule disturbances due to various causes; the 2015 outbreak in South Africa[74] and case in Spain[75] highlight the need for continued vigilance and action to prevent a resurgence of diphtheria.

Conclusion

C ulcerans, although less common worldwide than *C diphtheriae*, is nevertheless an important cause of both respiratory and cutaneous diphtheria (as in this case). Although our patient presented with distant cutaneous eosinophilic reaction, most likely to toxin dissemination, no classic cardiac or peripheral neuropathic complications were noted. The infrequent incidence of diphtheria in many developed areas of the world, compared with the frequency of isolation of other *Corynebacterium* species, contributes to potentially delayed and missed diagnoses, particularly of cutaneous disease. Therefore, to ensure diphtheria cases are identified appropriately, prudent guidelines would deem full speciation of diphtheroids mandatory for *Corynebacterium* species cultured from patients with unusual skin infections, a positive travel history, or recent animal contact. The extent of cutaneous diphtheria might be underestimated because many laboratories do not routinely speciate *Corynebacterium* species from wound samples, and cases can resolve from antimicrobial therapy given for other bacterial infections. Advances in rapid diagnostics from both proteomic phenotyping of bacteria through MALDI-TOF and in genotypic determination of toxin-producing potential might contribute to improved diagnostic ability. However, clear communication with the microbiological laboratory regarding the clinical differential diagnosis is essential. Although antimicrobial therapy remains effective with little evidence of resistance among causative organisms, inadequate availability of antitoxin is a serious concern. Advances in synthetic monoclonal antibody production might provide future viable alternatives to current equine- based production methods. Toxoid vaccination remains effective but worldwide coverage is still not at WHO targets. Some areas of the world show immunisation schedule disturbances from various causes, thereby increasing worries that the incidence of diphtheria might again rise.

Search Strategy and selection criteria

We identified citations for this Grand Round by searching PubMed with the terms "diphtheria", "*Corynebacterium ulcerans*", and "*Corynebacterium diphtheriae*" for articles published in English between Jan 1, 1990 and Sept 1, 2014. Relevant articles resulting from these searches, and important references cited in those articles, were reviewed.

Contributors

LSPM searched the scientific literature. LSPM and SS wrote the first draft of the manuscript with section contributions from AL and MM (public health and epidemiology), AS (histopathology and diagnostics), and AE (diagnostics and management). All authors reviewed, revised, and approved the final draft of the manuscript

Declarations of interests.

Acknowledgements

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Figure 1. Clinical presentation and progression of *Corynebacterium ulcerans* cutaneous diphtheria.

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.

Figure 2. Laboratory and radiographic investigations of *Corynebacterium ulcerans* cutaneous diphtheria.
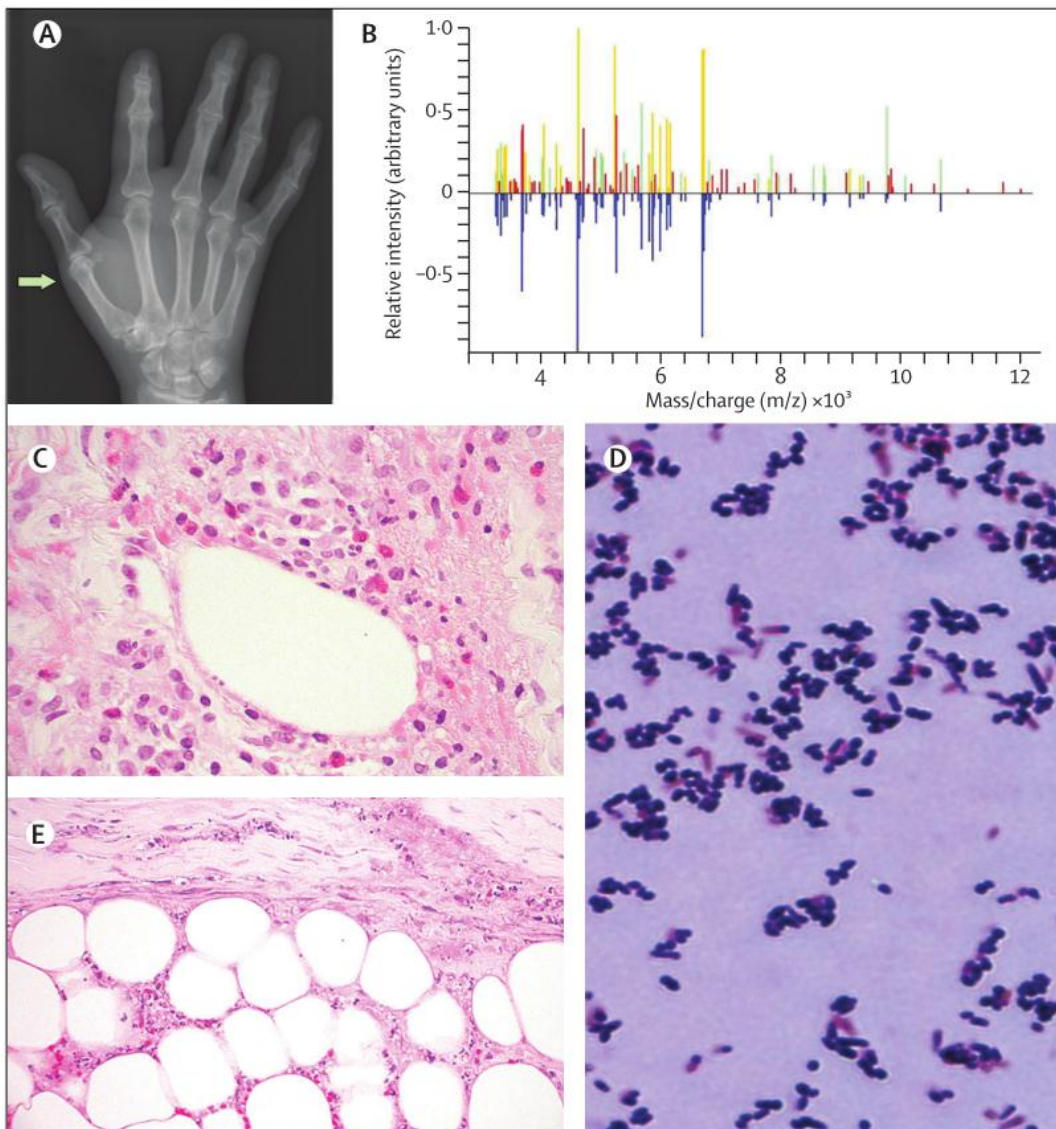

Figure 2: Laboratory and radiographic investigations of *Corynebacterium ulcerans* cutaneous diphtheria (A) Plain hand radiograph; arrow indicates marked soft tissue swelling but no bony destruction. (B) Matrix assisted laser desorption and ionisation time of flight mass spectra from the cultured organism (positive y axis represents *C ulcerans* from patient; negative y axis represents reference *C ulcerans* spectra). (C) Haematoxylin and eosin staining (×100) of the right arm biopsy showing perivascular inflammation rich in eosinophils. (D) Gram staining (×100) of *C ulcerans* grown from tissue biopsy. (E) Haematoxylin and eosin staining (×200) of the right hand tissue biopsy showing necrotic fi bro-fatty tissue with acute inflammatory cell infiltrate.

Table 1. Contact tracing in confirmed cases of diphtheria.

Examples of contacts who should be considered for prophylaxis	Examples of contacts who are unlikely to require prophylaxis
Household contacts - who sleep in the house of the index case - who share kitchen facilities in the case of multiple-occupancy residences such as student accommodation	Friends/relatives who regularly visit the house but do not sleep there
Kissing/sexual contacts	School classroom contacts
Healthcare workers - exposed to airway secretions - exposed to open wounds in cutaneous cases	Healthcare staff that have had contact with the index case without droplet or wound exposure.
Individuals exposed to confirmed animal cases	Work colleagues

Table 1: Modified from 2015 Public Health England.8 The risk of infection is directly related to the duration and closeness of contact with the index case and public health interventions should be guided by accurate contact tracing. The incubation period for diphtheria is 10 days. Therefore, close contacts should be identified for the 10 day period before onset of symptoms. Chronic carriage conditions can exist; if a suspected time of acquisition is identified, close contacts (particularly vulnerable individuals) since that time should be identified. Close contacts should be managed by microbiological investigation (swab culture), chemoprophylaxis, exclusion (of high-risk occupations including food handlers, care workers, and those who work with unimmunised children), and immunisation