Case report

Corynebacterium diphtheriae bloodstream infection: the role of antitoxinUna Sutton-Fitzpatrick ¹, Conor Grant,² Dimitar Nashev,¹ Catherine Fleming²¹Clinical Microbiology, Galway University Hospitals, Galway, Ireland²Infectious Diseases, Galway University Hospitals, Galway, Ireland

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Accepted 17 October 2019

SUMMARY

A 65-year-old male patient presented with fever, fast atrial fibrillation and frank haematuria on return to Ireland from travel in East Africa. He had a systolic murmur leading to a clinical suspicion of endocarditis. He had no specific clinical features of diphtheria. Blood cultures were taken and empiric therapy commenced with benzylpenicillin, vancomycin and gentamicin. *Corynebacterium diphtheriae* was detected on blood culture. The isolate was submitted to a reference laboratory for evaluation of toxigenicity. While initially there was concern regarding the possibility of myocarditis, a clinical decision was made not to administer diphtheria antitoxin in the absence of clinical features of respiratory diphtheria, in the presence of invasive infection and with presumptive previous immunisation. There is no specific guidance on the role of antitoxin in this setting. The issue is not generally addressed in previous reports of *C. diphtheriae* bloodstream infection.

BACKGROUND

Corynebacterium diphtheriae was first described by Friedrich Loeffler as the cause of diphtheria in 1884. Acute pharyngeal diphtheria is caused by infection with toxigenic strains of *C. diphtheriae*. The toxin is encoded by a gene, 'tox', that resides on a bacteriophage.¹ The hallmark of severe respiratory diphtheria is a progressive inflammatory pseudomembrane on the tonsils or pharynx. The most effective treatment is the administration of diphtheria antitoxin which binds to and neutralises circulating toxin that has not yet bound to tissue.² This disease is prevented by the diphtheria toxoid vaccine, and cases have significantly reduced following the global immunisation initiative. However, the vaccine offers no protection against non-toxigenic strains of *C. diphtheriae*, which lack a functional toxin gene. Non-toxigenic *C. diphtheriae* is increasingly recognised as a cause of invasive infections such as septic arthritis, skin and soft tissue infections and endocarditis. Endocarditis caused by *C. diphtheriae*, although rare, has a high associated mortality. In fact, the vaccination campaign may have caused a selective pressure, explaining the increase in proportion of non-toxigenic strains over recent years.³

CASE PRESENTATION

A 65-year-old male patient presented to our hospital 5 days after returning from Kenya with a

2-week history of general malaise, lethargy, fevers and frank haematuria.

He had been travelling in rural Kenya for 10 weeks. He initially felt unwell while in Africa and attended a local clinic. He received 1 day of intravenous metronidazole and ceftriaxone/sulbactam and 6 days of oral cefixime. He had ongoing fevers, night sweats, haematuria, anorexia and malaise. Five weeks prior to admission, he injured the dorsum of his left foot while walking on a beach in Kenya resulting in a tender ulcer with exudate and surrounding erythema (figure 1). He did not take malaria prophylaxis, did not swim in lakes and had no specific animal contact. He reported being fully vaccinated and had previously worked in Africa with an international non-governmental organisation. He had a medical history of hypertension, mild mitral regurgitation, gout and asthma.

On admission to hospital, he had a blood pressure of 71/38 mm Hg, a fever of 39.3°C and was in fast atrial fibrillation. On examination he was diaphoretic, had a petechial rash and a loud systolic murmur at the apex. On the dorsum of his left foot, a 1 cm eschar was visible at the site of the recent skin infection and ulcer. There was no pharyngeal erythema or pseudomembrane on exam. Initial laboratory tests showed white blood cells $11 \times 10^9/L$, neutrophils $9.2 \times 10^9/L$, lymphocytes $0.8 \times 10^9/L$, haemoglobin 10.6 mg/L, platelets $38 \times 10^9/L$, C-reactive protein 206 mg/L, total bilirubin 24 µmol/L, alanine transaminase 51 IU/L, aspartate transaminase 60 IU/L, gamma-glutamyl transferase 148 IU/L and troponin T 226 ng/L. Renal function tests were normal. His malaria screen was negative, he tested negative for HIV, hepatitis B, hepatitis C and leptospirosis, and he had an unremarkable chest X-ray and abdominal and pelvic CT.

INVESTIGATIONS

Blood cultures were taken on admission and these grew *C. diphtheriae* in both bottles after 14 hours. He subsequently had three sets of repeat blood cultures, and *C. diphtheriae* was isolated in both bottles of all three sets. The initial isolate was sent to a reference laboratory to determine whether it was a toxigenic strain. The result from the multiplex real-time PCR assay was *C. diphtheriae* detected, diphtheria toxin gene not detected.

A transoesophageal echocardiogram demonstrated a large mobile vegetation on the mitral valve and severe mitral regurgitation. Antibiotic susceptibility testing was carried out on the blood culture

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To cite: Sutton-Fitzpatrick U, Grant C, Nashev D, et al. *BMJ Case Rep* 2019;**12**:e231914. doi:10.1136/bcr-2019-231914

Figure 1 Left foot ulcer 1 month after admission.

isolate, and this showed that the *C. diphtheriae* had intermediate susceptibility to penicillin and was fully susceptible to ciprofloxacin, ceftriaxone, gentamicin, vancomycin and meropenem.

TREATMENT

He was initially treated with benzylpenicillin, vancomycin and gentamicin. This was changed to ceftriaxone, ciprofloxacin, vancomycin and gentamicin during his admission to the intensive care unit (ICU). Prior to confirming that the *C. diphtheriae* strain isolated from blood cultures was non-toxigenic, treatment with antitoxin was considered. We decided not to administer antitoxin as there was no evidence of upper respiratory tract involvement, no specific features of myocarditis on echocardiography, the patient was likely to have been vaccinated and the majority of cases reported in the literature of invasive *C. diphtheriae* involve non-toxigenic strains. Following the results of antibiotic susceptibility testing, he was changed to 2 g ceftriaxone intravenous monotherapy. At this stage, he had clinically improved and was transferred out of ICU. He went on to have a metallic mitral valve replacement. He recovered well after surgery, and there were no surgical complications. The mitral valve tissue was culture negative but was sent to a referral laboratory, and *C. diphtheriae* was detected with 16S rDNA screening.

OUTCOME AND FOLLOW-UP

He was discharged from hospital following his surgery and completed 6 weeks of intravenous ceftriaxone with our outpatient parenteral antibiotic therapy programme. He was recently reviewed as an outpatient and is clinically well on no antibiotic treatment and shows no signs of recurrence.

DISCUSSION

C. diphtheriae is a non-motile, non-encapsulated gram-positive bacilli. Both toxigenic and non-toxigenic strains exist. Typical diphtheria is caused by infection with toxigenic strains of *C. diphtheriae* leading to respiratory or cutaneous symptoms. Non-toxigenic strains can also cause disease and are increasingly recognised as causes of severe invasive disease such as endocarditis and bacteraemia as well as abscesses and bone or joint infections. In contrast to toxin-induced disease, infections with non-toxigenic strains are not preventable by vaccination and pathogenic mechanisms are not clearly understood.

The source of our patient's infection is uncertain. Entry of non-toxigenic *C. diphtheriae* by invasive processes has not been fully elucidated but has been described as being caused by percutaneous trauma, skin and throat colonisation and dental caries.⁴⁻⁶ A paper published in 2006 looked at seven cases over a 5-year period in Vancouver who had bacteraemia due to *C. diphtheriae*. Six of the seven cases were non-toxigenic strains, and only one case had endocarditis. Most patients in this review presented simultaneously with skin lesions, indicating skin breaks as a probable route of entry.⁷ Before becoming unwell, our patient reported cutaneous trauma, with the subsequent development of local signs of infection. This occurred while in sub-Saharan Africa, where *C. diphtheriae* is thought to be more prevalent. We postulate that the portal of entry of *C. diphtheriae* in our patient was through this laceration and first manifested as a local cutaneous infection.

Risk factors for developing invasive infection with non-toxigenic strains have been identified as homelessness, pre-existing valvular disease, alcoholism, intravenous drug use, diabetes, liver cirrhosis and poor dentition.^{6,7} Fatality is high with invasive infections, approximately 36%–47%.^{7,8}

Infective endocarditis due to non-toxigenic *C. diphtheriae* is uncommon, however, there is increasing frequency of reported cases in the literature. The first case ever reported was in 1893, but the majority of cases have been reported in the past 30 years. Little is known about the epidemiology as non-toxigenic *C. diphtheriae* is not included in the case definitions for surveillance of diphtheria in Europe. A 2007 literature review identified 74 cases of *C. diphtheriae* endocarditis and noted that mainly the left side of heart was affected, and men were affected more than women. Eighty-one per cent of these cases were caused by non-toxigenic *C. diphtheriae*.⁹ In 2008, five cases were reported in Brazil. Four of these cases occurred in female patients aged 7–14. This group studied the adherence patterns of the bacteria and reported that all isolates seemed to have distinct bacterial adhesive properties that could favour blood-barrier disruption and systemic dissemination of the bacteria.⁵ In 2011, a group in New Zealand reported 10 cases of *C. diphtheriae* endocarditis over a 14-year period. Eighty per cent of these cases had pre-existing prosthetic valves.¹⁰

The issue of whether to administer antitoxin in this setting has not been addressed in the literature previously, and there is no specific guidance in this setting. The current guidance advises that patients who have probable or confirmed respiratory diphtheria should receive antitoxin.^{11,12} In this case, we did not administer antitoxin given the lack of clinical signs of respiratory diphtheria, the presumptive vaccination history and the fact that invasive infection with *C. diphtheriae* is largely due to non-toxigenic strains. It is also important administering antitoxin is not without risk; antitoxin is a horse serum product, and there is the potential for an anaphylactic reaction.

There are no recommended guidelines for the treatment of infective endocarditis caused by *C. diphtheriae*. Expert opinion has suggested using both a beta-lactam and an aminoglycoside due to their synergistic properties.¹³ The study published in New Zealand in 2011 demonstrated a positive outcome when treated with either a beta-lactam alone or in combination with an aminoglycoside, and no significant difference in patient outcome was seen between the two treatment groups.¹⁰ Overall treatment in reported cases has varied depending on local practice, and there are reports of resistance to some antimicrobial agents, thus, treatment should be guided by the antibiotic susceptibilities of the isolate. Early treatment with appropriate antibiotics is important given the high fatality rate of these infections.

Patient's perspective

I would like to complement the specialist teams who dealt with my case in a thoroughly competent and professional manner. At all stages of diagnosis and treatment I was kept apprised of progress in an open and friendly manner. My initial shock on learning of the extent of my condition and the need for extensive treatment with antibiotics and surgery was ameliorated by the team's kindness and consideration. I am well on way to full recovery for which I am very grateful.

Learning points

- Endocarditis due to invasive non-toxigenic *Corynebacterium diphtheriae* is reported in the literature with increased frequency, which may reflect a selective pressure of the successful vaccination campaign.
- Early identification of cases is important as invasive infection with *C. diphtheriae* has a high fatality rate.
- Diphtheroids, when isolated from blood cultures, often represent contaminants. This case highlights how important it is to consider all blood culture isolates as potential pathogens and to take into account the clinical context.
- In returning travellers presenting with fever, clinicians need to consider rarer causes of imported infections.
- Based on current evidence, antitoxin should only be given if there is clinical evidence of potential respiratory diphtheria. There is a lack of clear guidance on the use of antitoxin in non-respiratory cases where systemic toxicity is suspected.

Acknowledgements Prof Martin Cormican and Dr Helen Tuite.

Contributors US-F and CG contributed equally to this paper. Both of these authors were involved in treating the patient and drafting the case report as well as doing final edits. DN was involved in treating this patient as well as critically reviewing this case report. CF was involved in treating this patient and critically reviewed this case report and suggested changes for the final edit. All authors approved the final version and are in agreement to be accountable for all aspects of the work in

ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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