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A very rare case of infective endocarditis caused by *Corynebacterium diphtheriae*

Bardzo rzadki przypadek infekcyjnego zapalenia wsierdzia spowodowany *Corynebacterium diphtheriae*

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Abstract

A 16-year-old boy was admitted to a district hospital with fever, headaches, abdominal pain, vomiting, and heart murmur. Thickening of the mitral valve leaflet with regurgitation was diagnosed by a cardiologist, who, suspecting infective endocarditis, referred the patient to a specialist centre. The diagnosis was confirmed by blood cultures showing infection with a non-toxigenic species of *Corynebacterium diphtheriae*. Antibiotic treatment was continued. The boy was urgently referred to cardiac surgery to remove the affected mitral valve and implant a St. Jude 31 mm mechanical prosthesis. The postoperative course was uncomplicated, and after 8 days he was transferred to the Department of Cardiology, where treatment with antibiotics and anticoagulants was continued, maintaining the international normalised ratio of 2.5–3. He was discharged home in good condition with the recommendation to continue antibiotic therapy for another three weeks, monitor inflammatory markers, as well as continue cardiac medications and anticoagulants. Conclusion – *Corynebacterium diphtheriae* can cause endocarditis.

Keywords: infective endocarditis, artificial valve, *Corynebacterium diphtheriae*

Streszczenie

Szesnastoletni chłopiec został hospitalizowany w szpitalu rejonowym z powodu gorączki, bólów głowy i brzucha, wymiotów oraz szmeru nad sercem. Konsultujący kardiolog stwierdził pogrubienie płatka zastawki dwudzielnej z jej niedomykalnością i z podejrzeniem infekcyjnego zapalenia wsierdzia skierował pacjenta do ośrodka specjalistycznego, gdzie potwierdzono diagnozę, rozpoznając zakażenie nietoksynotwórczym szczepem *Corynebacterium diphtheriae*. Kontynuowano leczenie celowanymi antybiotykami. Chłopca w trybie pilnym skierowano na operację kardiochirurgiczną, podczas której wycięto zmienioną zastawkę dwudzielną i w jej miejsce wszczepiono protezę mechaniczną St. Jude 31 mm. Przebieg pooperacyjny był niepowikłany i po 8 dniach chory został przeniesiony na oddział kardiologii, gdzie kontynuowano terapię antybiotykami, zgodnie z antybiogramem, i lekami przeciwkrzepliwymi, utrzymując międzynarodowy współczynnik znormalizowany na poziomie 2,5–3. Pacjenta wypisano do domu w stanie dobrym z zaleceniem kontynuacji antybiotykoterapii przez 3 tygodnie, kontroli wskaźników zapalnych oraz przyjmowania leków kardiologicznych i przeciwkrzepliwych. Konkluzja – maczugowiec błonicy może wywoływać zapalenie wsierdzia.

Słowa kluczowe: infekcyjne zapalenie wsierdzia, sztuczna zastawka, *Corynebacterium diphtheriae*

INTRODUCTION

According to the latest data (2019), infective endocarditis (IE) has an annual incidence of 3–13.8 cases per 100,000 population. Staphylococcal infection is the most common cause (60–80%), while fungi or diphtheria are a rare aetiology[1–3].

Corynebacteria are Gram-positive microbes that may cause multiple systemic diseases, of which diphtheria, caused by a species of *Corynebacterium diphtheriae* producing a toxin that binds to cellular receptors in the pharynx, larynx (where it causes laryngeal diphtheria, or croup), skin, and even kidneys and liver, was the most dangerous before the era of vaccinations. Today, this life-threatening disease is virtually non-existent due to mandatory vaccinations. Other opportunistic *Corynebacterium* species, such as *Corynebacterium pseudodiptheriticum*, may cause bronchitis, tracheitis, endocarditis, bone inflammation, urinary tract inflammation in HIV-positive individuals, as well as exacerbate cystic fibrosis[4]. Corynebacteria can be isolated from a variety of environments, including human skin, food, soil, water, and animals, all of which may be potential routes of transmission to humans[4,5]. IE usually occurs in patients with compromised immune function, uncontrolled diabetes, a history of long-term antibiotic therapy, as well as after treatment with corticosteroids, immunosuppressants, or cytostatics. Risk factors include previous cardiac and neurosurgical interventions, artificial valves, pacemaker systems, all types of intracardiac and intravascular implants and catheters, as well as non-healing postoperative wounds or treatment of dental abscesses without antibiotic prophylaxis, especially in those predisposed to IE[1–3]. The inflammatory process most often involves the mitral valve, leading to its damage and regurgitation. The aortic valve or both valves, or even previously implanted artificial valves may get involved, though less frequently. The diagnosis of IE is based on the Duke Criteria, modified in 2015 by the European Society of Cardiology (ESC), which put main emphasis on pathological criteria (including pathogen detection in the histopathology of vegetations) and clinical criteria. Among the latter, major criteria (including positive blood cultures for IE-specific microbes, positive imaging) and minor criteria (including a history of congenital heart defects, previous surgeries predisposing to IE, fever, immunological diseases) can be distinguished. Isolated splenomegaly found in about 15–50% of cases and a new heart murmur are also important clinical symptoms. These criteria allow for reaching a certain or possible clinical diagnosis or ruling out IE[3,6].

Laboratory workup shows elevated inflammatory markers and positive blood culture. Echocardiography (transthoracic and/or transoesophageal), often supplemented with magnetic resonance imaging and/or computed tomography, is the diagnostic method of choice[3,7].

According to the latest ESC guidelines (2023), patients diagnosed with IE should receive multidisciplinary care provided by the so-called endocarditis team[3].

Conservative treatment involves antibiotics with proven efficacy in IE, administered according to the antibiogram, and medications to improve heart function. Cardiac surgery, including repair of the native valve or its replacement with an artificial one, should always be considered. Treatment outcomes are mainly influenced by the time between first symptoms and the correct diagnosis (as an indicator of the dynamics of pathological changes), as well as the type of pathogen, the location and extent of valvular and endocardial changes, the rate of progression of the inflammatory process, and the type and efficacy of the treatment used[8].

CASE REPORT

A 16-year-old boy from Ukraine, a pigeon breeder, who, as reported by his mother, was vaccinated according to the standard vaccination schedule, including vaccine against diphtheria 4 years before, was admitted to the district hospital emergency department due to influenza-like symptoms, headaches and vomiting after every meal (persisting for 6 days), fever (40°C) and abdominal pain for 2 days. The initial cause of the symptoms was not identified and he was tested negative for COVID-19. However, a loud systolic murmur dominated on auscultation.

Laboratory workup showed elevated aspartate aminotransferase (256 U/L) and alanine aminotransferase (160 U/L) activity, as well as significantly increased C-reactive protein (240 mg/L) and troponin Ths (155 pg/mL; laboratory norm 0–14 pg/mL).

The consulting cardiologist found a thickened posterior leaflet of the mitral valve with its massive regurgitation on echocardiography and, suspecting IE, referred the patient to the Department of Paediatric Cardiology. On admission, the boy was weak, pale, with persistent fever, blood pressure of 101/57 mm Hg, dominant tachycardia of 110/min and the presence of a loud (Levine score of 3–4/6) systolic murmur above the apex of the heart, radiating towards the left axilla. Additionally, an enlarged spleen, 1 cm below the left costal arch, and liver, 2 cm below the right costal arch were observed. There was no peripheral oedema.

Resting electrocardiography (ECG) showed discrete repolarisation disturbances, while Holter ECG revealed single premature supraventricular beats with conduction aberrations (Fig. 1).

Transthoracic echocardiography (TTE) revealed a large vegetation measuring 10 × 12 mm on the posterior leaflet of the mitral valve, with perforation of this leaflet, and massive valve regurgitation. The left ventricle was significantly enlarged, with a left ventricular internal end-diastolic diameter (LVIDD) of 75 mm (Z-score: 4.40). The left atrium was also prominent, with ejection fraction of left ventricle (EFLV) reduced to 45% (Z-score: –2.92) (Figs. 2–4).

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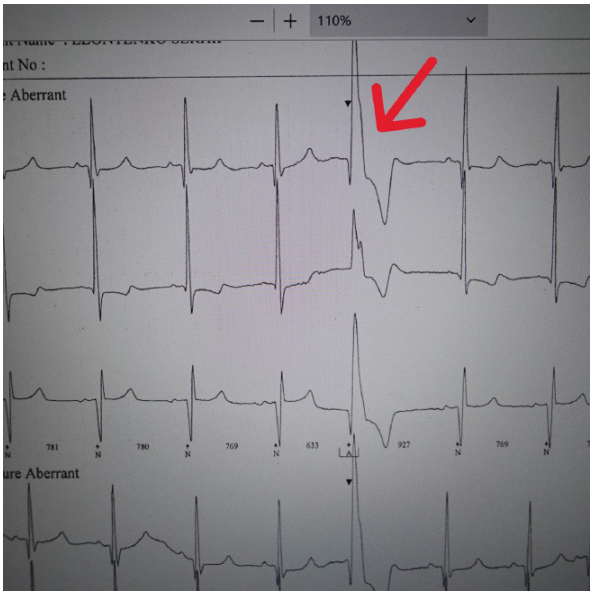

Fig. 1. Holter ECG. Single premature supraventricular beat with conduction aberration

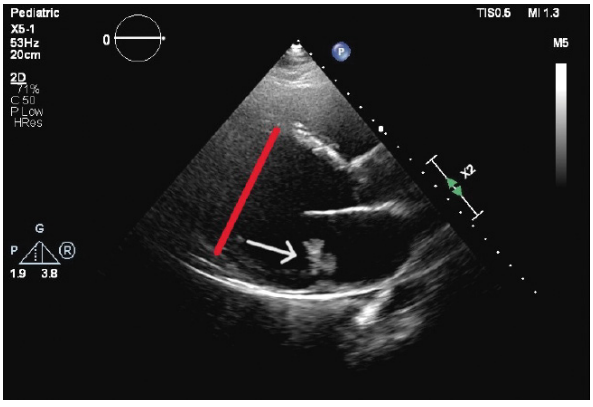

Fig. 2. TTE, long axis view of the left ventricle. A vegetation measuring 10 × 12 mm is visible on the posterior leaflet of the mitral valve (arrow). Note the increased diastolic dimension of the left ventricle (red line 75 mm, Z-score: 4.4; according to Lopez et al., 2017[9])

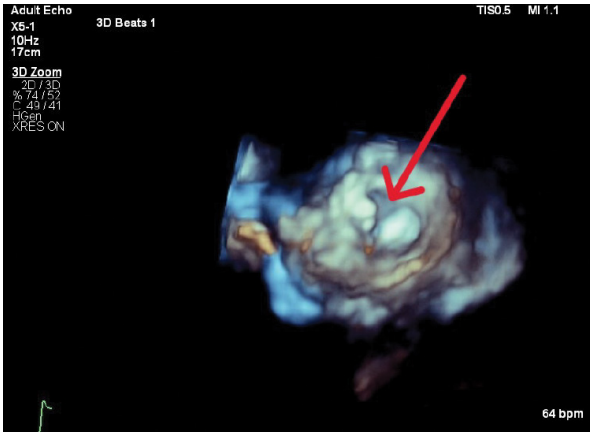

Fig. 3. 3D transthoracic echocardiography, short axis view of the left ventricle. A vegetation on the posterior leaflet of the mitral valve and leaflet perforation (arrow) can be seen

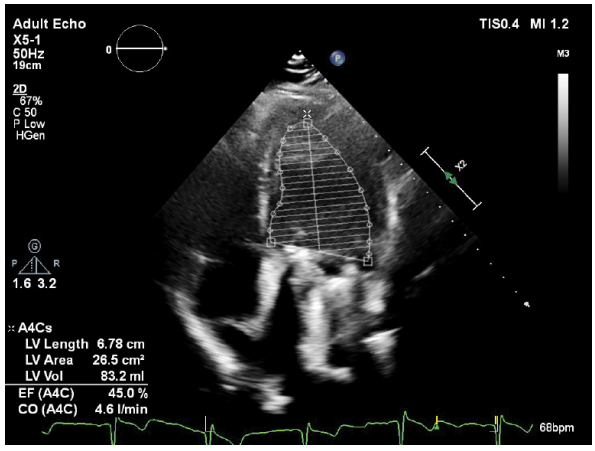

Fig. 4. Echocardiography of left ventricular function using Simpson's volumetric method. Reduced ejection fraction (EF = 45%, Z-score: –2.92; according to Yao et al., 2019[10])

Blood was collected for laboratory analysis and blood cultures; nasal and pharyngeal swabs were taken, and empirical antibiotic therapy with amikacin and cefotaxime was started[3]. Three more positive blood cultures were obtained in the days that followed, from which *Corynebacterium diphtheriae* was isolated – gravis biotype sensitive to cefotaxime, clindamycin, meropenem, and penicillin. An endocarditis team was set up and treatment based on the antibiogram and current ESC guidelines was continued[3].

The inpatient diagnostic findings were verified at the National Institute of Public Health – National Institute of Hygiene, where the diagnosis was confirmed and *Corynebacterium diphtheriae* (a non-toxigenic species) was cultured from the blood (PB-03-LEB/ZP method).

The boy was qualified for cardiac surgery and on day 5 of antimicrobial therapy he was urgently transferred to the Department of Cardiac Surgery. On the same day, under normothermia, the involved fragments of the mitral valve, including the posterior leaflet, were excised through the interatrial septum and a 31 mm St. Jude mechanical prosthesis was implanted in the mitral position. The collected material was sent for microbiological and histopathological analyses.

The patient was extubated on postoperative day 1. He breathed on his own and with the use of nasal canula oxygen therapy. Pharmacotherapy included positive inotropes, i.e. dopamine and milrinone. Diuresis was supported with furosemide. Antibiotic therapy with vancomycin and meropenem was continued; fluconazole and anticoagulants were introduced. On day 3 the patient was transferred from the intensive care unit to the Department of Cardiac Surgery, and then after another 5 days to the Department of Paediatric Cardiology, where his clinical condition was assessed as good and stable, with laboratory findings indicating no inflammatory markers. Follow-up ECG showed persistent discrete repolarisation disorders, while Holter ECG found single premature ventricular and supraventricular beats without any conduction aberrations (4 vs. 13).

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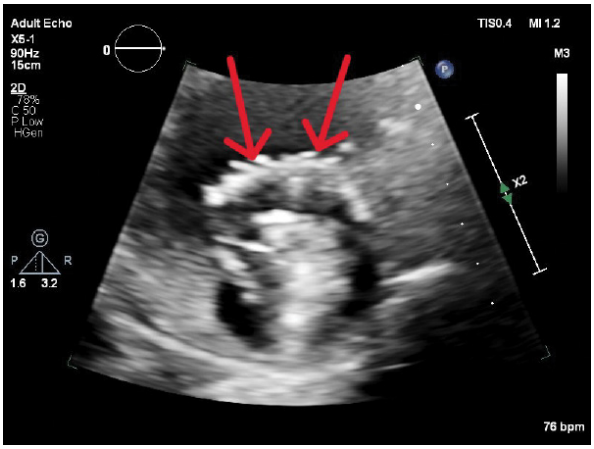

Fig. 5. Short-axis ECHO of the left ventricle. Normal function of the mechanical valve, without residual paravalvular leakage. Typical echocardiographic image of the implanted artificial valve in the mitral field, which produces ultrasonic reverberations and shadows (so-called multiple reflections) that make direct ECHO imaging of the valve function difficult (arrows)

Follow-up TTE revealed persistently reduced left ventricular function (EFLV: 45–55%). The mechanical valve function was normal, with no residual leakage in its vicinity (Fig. 5).

Antibiotic therapy was continued throughout hospital stay. Heart failure (HF) was managed with ACE inhibitors, spironolactone and bisoprolol. Anticoagulation with warfarin was used, maintaining the international normalised ratio (INR) in the optimal range (2.5–3). Once his general condition stabilised and inflammatory parameters normalised, the boy was discharged home in good condition. It was recommended, based on the ESC guidelines, to continue antimicrobial therapy in an outpatient setting in order to extend it beyond 6 weeks post valve implantation. Additionally, treatment of HF and long-term use of warfarin were recommended, and an early, i.e. 2-week, follow-up with biochemical tests was scheduled at a cardiology clinic. In the event of disturbing symptoms, the patient was asked to immediately report to the centre. Furthermore, the patient and his caregiver received extensive education on the risk of recurrence and preventive measures, with particular emphasis on oral hygiene and individual risk profile[3].

DISCUSSION

According to the available literature, non-toxigenic *Corynebacterium diphtheriae* species are an uncommon cause of IE. Muttaiyah et al. described a series of 10 patients with *Corynebacterium diphtheriae* IE who received an artificial valve, pointing to the beneficial effect of beta-lactams in combination with aminoglycosides[11]. On the other hand, in their analysis of 30 cases of *Corynebacterium* IE, Bläckberg et al. showed increasing bacterial resistance to benzylpenicillin (penicillin G), with preserved sensitivity to vancomycin[12]. Recently, Cabanilla et al. described a poor course of IE caused by *Corynebacterium striatum* infection involving three native valves in a 36-year-old woman with aplastic anaemia and a 46-year-old man with aortic valve IE, who ultimately died of exacerbated COVID-19 pneumonia[13]. A similarly tragic course of the disease was observed in a 91-year-old man with IE caused by *Corynebacterium striatum*, who died of sepsis and cerebral embolic complications. This species of bacteria may also be responsible for chronic bone inflammation[14]. It is not only artificial valves, but also any materials placed in the venous or arterial system and catheters in dialysed patients that predispose to *Corynebacterium* IE[15].

One of the most extensive reports on IE caused by *Corynebacterium* was published by Belmares et al., who assessed 129 patients with this diagnosis. The researchers showed that in most patients the inflammatory process involves the left heart and is more common in adult men, as well as that about 33% of IE cases present with mitral valve involvement, with about 25% of these patients requiring implantation of an artificial valve. It was also found that IE caused by toxin-producing strains of *Corynebacterium diphtheriae* or *Corynebacterium pseudodiphtheriticum* has lower survival rates[16].

Cardiac complications of IE may include acute HF due to valve damage, leaflet perforation or rupture of chordae tendineae, as well as periannular extension of infection, fistulas to the heart chambers, atrioventricular block or paravalvular leak. The most common extracardiac complications may include embolism of the central nervous system (CNS), lungs, coronary arteries, liver, kidney, spleen or limbs. Peripheral septic embolism, septic glomerulonephritis, septic arthritis, vertebral osteomyelitis or disseminated intravascular coagulation are also relatively common[2]. It cannot be ruled out that the patient's history of headaches and vomiting could have been related to CNS microembolism. However, strong evidence to support this is missing as no brain imaging was performed due to the absence of focal CNS symptoms.

The clinical course of IE described in this paper was initially typical of an infectious disease, with positive cultures indicating a non-toxic species of *Corynebacterium diphtheriae*. The diagnostic workup in the district hospital was performed correctly, especially the heart murmur auscultation, which prompted cardiac consultation. Confirmation of mitral valve insufficiency with suspected IE was an important diagnostic step allowing for effective patient management in a specialist centre by replacing the damaged mitral valve with an artificial one.

It is not known how the boy contracted the infection, and the link to pigeon breeding is poorly documented, especially since it had taken place several years before. On the other hand, subacute 'creeping' endocarditis, which manifested only after a long time, cannot be rule out.

Interestingly, according to the mother, all of her children had been previously vaccinated against diphtheria in

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Ukraine: the patient in question 4 years ago, his 17-year-old sister 7 years ago, and his 14-year-old brother 5 years ago. As soon as the family doctor learned from the boy's mother about his *Corynebacterium diphtheriae* infection, he immediately vaccinated his siblings with a booster dose against diphtheria. Additionally, a booster vaccination of the patient in question is also planned for the near future.

It should be noted however that vaccination elicits the production of antibodies only against the toxin produced by diphtheria bacteria, and has no significant effect on colonisation with the microorganisms themselves. The presented case confirms that heart damage in the course of diphtheria is caused not only by the toxin, but also by bacteraemia following infection with even non-toxic species of *Corynebacterium*[17].

CONCLUSIONS

Infective endocarditis is an insidious and life-threatening disease, in which diphtheria aetiology should be considered, even though such cases are extremely rare.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Consent for publication

The boy's mother gave her consent for the publication.

Author contribution

Original concept of study: AlM, LSzyd. Collection, recording and/or compilation of data: LZ, GZ, OW, AgM, MP. Analysis and interpretation of data: LSzen, LSzyd. Writing of manuscript: AlM, LSzen, AgM. Critical review of manuscript: JK, KK, MP. Final approval of manuscript: AlM, JK, GZ, LSzyd.

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