CASE REPORT / OLGU SUNUMU

DOI: 10.4274/mjima.galenos.2021.2020.10
Mediterr J Infect Microb Antimicrob 2021;10:10
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2021.2020.10

A Case of Infective Endocarditis Due to *Abiotrophia defectiva*, and Treatment with Ertapenem

Abiotrophia defectiva'ya Bağlı Enfektif Endokardit Olgusu ve Ertapenem ile Tedavisi

Yücel DUMAN[1], Sibel ALTUNIŞIK TOPLU[2], Elif Seren TANRIVERDİ[1], Yaşar BAYINDIR[2]

[1]*İnönü University Faculty of Medicine, Department of Medical Microbiology, Malatya, Turkey*
[2]*İnönü University Faculty of Medicine, Department of Infectious Diseases and Medical Microbiology, Malatya, Turkey*

Abstract

The most frequently reported infections due to *Abiotrophia defectiva* worldwide are bacteraemia and endocarditis. It is estimated that *A. defectiva* causes approximately 5-6% of microbiologically proven endocarditis and plays a role in the etiology of culture negative endocarditis. In this article we reported a patient with infective endocarditis (IE) due to penicillin resistant *A. defectiva*, which caused vegetation in the mitral valve, embolism in the spleen and successfully treated with ertapenem. A 70-year-old female patient was admitted to the emergency service with fever and abdominal pain. The patient had a pronounced widespread abdominal tenderness in the left quadrant. The body temperature was 38.9 °C, C-reactive protein (CRP) level was 12.7 mg/dl and white blood cell count was $13.3x10^3$ mm^3. The patient was hospitalized to investigate fever's reason. It was learned in the anamnesis that she used warfarin. Considering the pre-diagnosis of urinary tract infection, empirical treatment with ceftriaxone 2x1 g/day was started. However, due to the increase in International Normalized Ratio value on the second day of ceftriaxone treatment, ertapenem 1x1 g/day was started by considering drug interaction between warfarin and ceftriaxone. Transesophageal echocardiography of the patient revealed a 1.2x1.2 cm vegetation on the posterior leaflet surface of the mitral valve, and ischemia due to embolism in the spleen was detected on abdominal computer tomography. Penicillin resistant *A. defectiva* grew in the blood culture. The patient was diagnosed as having IE on the seventh day of her admission. Ertapenem treatment was completed in six weeks due to the patient's absence of fever, decreased CRP level, and the absence of *A. defectiva* in the seventh day control blood culture. After treatment, vegetation was not observed in the transthoracic echocardiography of the patient and no signs of ischemia was detected in the spleen. Detection of *A. defectiva* shaped the follow-up process of our patient by bringing the diagnosis of IE to mind. In treatment of *A. defectiva*-related IE, guidelines suggest long-term combination of aminoglycosides with beta-lactams or vancomycin. However, in our patient, treatment was provided by using ertapenem alone for six weeks. In addition, we believed that early diagnosis and treatment in our patient prevented serious complications.

Keywords: *Abiotrophia defectiva*, infective endocarditis, ertapenem

Öz

Tüm dünyada *Abiotrophia defectiva*'ya bağlı en sık bildirilen enfeksiyonlar bakteriyemi ve endokarditttir. *A. defectiva*'nın, mikrobiyolojik olarak kanıtlanmış endokardit olgularının yaklaşık %5-6'sına neden olduğu ve kültür negatif endokardit etiyolojisinde rol oynadığı düşünülmektedir. Bu yazımızda, mitral kapakta vejetasyona ve dalakta emboliye neden olan, ertapenem ile başarılı bir şekilde tedavi edilen, penisilin dirençli *A. defectiva*'ya bağlı enfektif endokardit (EE) olgusu sunulmaktadır. Yetmiş yaşındaki kadın hasta ateş ve karın ağrısı ile acil servise başvurdu. Hastada sol kadranda belirgin, yaygın batın hassasiyeti vardı. Ateş 38,9 °C, C-reaktif protein 12,7 mg/dl, kan beyaz küre sayımı $13,3x10^3$ mm^3 olarak belirlendi. Hasta, ateş etiyolojisinin araştırılması amacı ile yatırıldı. Anamnezde varfarin kullandığı öğrenildi. Üriner sistem enfeksiyonu ön tanısı konularak seftriakson 2x1 g/gün ampirik tedavi başlandı. Ancak seftriakson tedavisinin ikinci günü "International Normalized Ratio" değerlerinin yükselmesi nedeni

Cite this article as: Duman Y, Altunışık Toplu S, Tanrıverdi ES, Bayındır Y. A Case of Infective Endocarditis Due to *Abiotrophia defectiva*, and Treatment with Ertapenem. Mediterr J Infect Microb Antimicrob. 2021;10:10.

Address for Correspondence/Yazışma Adresi: Yücel Duman MD, Turgut Özal Medical Center, Clinic of Medical Microbiology, Malatya, Turkey
Phone: +90 535 559 66 96 **E-mail:** yucel.duman@inonu.edu.tr
ORCID ID: orcid.org/0000-0002-9090-2096
Received/Geliş Tarihi: 10.06.2020 **Accepted/Kabul Tarihi:** 19.02.2021

Published: 24 February 2021

ile varfarin ve seftriakson arasında ilaç etkileşimi düşünülerek seftriakson yerine tedavide ertapenem 1x1 g/güne geçildi. Hastanın transözefagial ekokardiyografisinde (TÖE) mitral kapak posterior liflet yüzeyinde 1,2x1,2 cm vejetasyon ve batın bilgisayarlı tomografisinde dalakta emboliye bağlı iskemi görüldü. Alınan kan kültürlerinde penisilin dirençli *A. defectiva* üredi. Hastaya yatışının yedinci günü EE tanısı konuldu. Hastanın ateşlerinin olmaması, C-reaktif proteininin düşmesi ve yedinci gün alınan kontrol kan kültürünün steril olması nedeniyle başlanmış olan ertapenem tedavisi altı haftaya tamamlandı. Tedavi sonrasında hastanın transtorasik ekokardiyografisinde vejetasyon ve dalakta iskemi bulguları gözlenmedi. Kan kültüründe *A. defectiva* saptanması, EE tanısını akla getirerek hastamızın takip sürecini şekillendirmiştir. *A. defectiva*'ya bağlı EE tedavisinde kılavuzlar aminoglikozidlerle beta-laktamların veya vankomisinin uzun süreli kombinasyonunu önermektedir. Ancak olgumuzda ertapenem tek başına altı hafta kullanılarak tedavi sağlanmıştır. Ayrıca olgumuzda erken tanı konmasının ve tedaviye başlanmasının ciddi komplikasyonları önlediği kanısındayız.
Anahtar Kelimeler: *Abiotrophia defectiva*, enfektif endokardit, ertapenem

Introduction

Abiotrophia defectiva, first described in 1961 by Frenkel and Hirsch[1] in a patient with infective endocarditis (IE), could be found in the normal flora of the oral, genitourinary and intestinal systems of 11% of healthy individuals. It is a non-spore forming, immobile, facultative anaerobic, pleomorphic microorganism that can be seen as Gram-positive cocci, coccobacillus or bacillus in culture[2].

All over the world, bacteremia and endocarditis are the most frequently reported infections due to *A. defectiva*. It is estimated that *A. defectiva*, which is a rare agent causing IE by involving natural and prosthetic heart valves, causes approximately 5-6% of microbiologically proven endocarditis and plays a role in the etiology of culture negative endocarditis[3]. In our country, Vahabi et al.[4] reported the rate of patients with culture-negative IE as 31.1% in their pool analysis of 1,270 patients. *A. defectiva* can rapidly cause valve destruction, leading to heart failure and result in embolism in distal organs. Severe complications can be prevented with early diagnosis and treatment[3]. Therefore, we believe that the identification of *A. defectiva* is important in preventing these complications and that antimicrobial susceptibility studies are important for clinical and epidemiological studies.

In this article, a patient with mitral valve IE due to penicillin-resistant *A. defectiva* that was successfully treated with ertapenem was presented.

Case Report

A 70-year-old female patient who was admitted to the emergency department with complaints of swelling in the legs, abdominal pain, fever, and chills for three days had a body temperature of 38.9 °C. In the physical examination performed in the emergency department, no cardiac murmur was heard, and there was prominent, widespread tenderness in the left quadrant of the abdomen. Laboratory tests revealed that C-reactive protein (CRP) level was 12.7 (0-0.351) mg/dl, and white blood cell (WBC) count was $13.3x10^3$ mm^3 (88.9% neutrophils, 5.7% lymphocytes). Blood culture was taken from the patient. The patient was admitted to the infectious diseases ward in order to investigate the etiology of fever. In the anamnesis of the patient, it was learned that she underwent a tricuspid valve repairment three years ago and was using warfarin. The patient was investigated for fever etiology and 30 leukocytes/mm^3 were determined in the urine microscopy performed after hospitalization. A pre-diagnosis of urinary tract infection was made. Empirical treatment with ceftriaxone 2x1 g/day was started. However, on the second day of ceftriaxone treatment, due to the increase in "International Normalized Ratio" value (7.31), considering the drug interaction between warfarin and ceftriaxone, the patient's treatment was changed with intravenous ertapenem 1x1 g/day.

In the abdominal ultrasonography performed due to the persistence of abdominal pain, subcapsular hypodense areas, predominantly in the upper-middle zones of the spleen, were evaluated in favor of abscess, hematoma or infarction; while hypodense patchy areas in the spleen were interpreted as ischemia in the control abdominal computed tomography. Penicillin-resistant *A. defectiva* was detected in the first blood culture taken at the patient's hospitalization. It was decided to repeat the blood culture before the diagnosis was made. In her follow-up, her physical examination revealed a cardiac murmur that was not detected before. Vegetation was suspected in trans-thoracic echocardiography (TTE) and trans-esophageal echocardiography (TEE) revealed 1.2x1.2 cm vegetation on the posterior leaflet surface of the mitral valve. It was determined that the ejection fraction was normal and there was no evidence of heart failure. Endocarditis was considered with a high probability in the myocardial positron emission tomography performed due to patient's incompatibility to TEE which was recommended to be repeated. Penicillin-resistant *A. defectiva* was detected in the second control blood culture sample taken on the fourth day of the patient's hospitalization. Surgical intervention was not considered for the patient who was thought to have embolism in the spleen. On the seventh

day of the patient's hospitalization, a diagnosis of IE was made due to the presence of vegetation in TEE, which was one of the major criteria of the modified Duke; fever, growth of *A. defectiva* in blood culture, and ischemia in the spleen, which were minor criteria. Since the agent was resistant to penicillin, the patient had no fever after the seventh day, the CRP level started to decrease, and there was no growth in the control blood culture taken again on the seventh day; it was decided to continue the ertapenem treatment and follow-up the patient. Treatment with ertapenem was completed in six weeks. The patient, whose vegetation was not observed in the control TTE after the treatment, was discharged.

Microbiological Evaluation

The blood culture sample was incubated in the BACT/ALERT 3D (BioMérieux, France) fully automated blood culture system. The positive signaling blood culture sample was inoculated on 5% sheep blood agar, chocolate agar and eosin methylene blue agar medium. It was incubated for 24-48 hours. Identification of the pure isolate after incubation was performed with Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) (BioMérieux, France). Antibiotic susceptibility tests were determined with Gradient diffusion method on Mueller-Hinton agar using E-test (BioMérieux, France). Results were evaluated according to the Clinical and Laboratory Standards Institute M45 recommendations[5].

A. defectiva was isolated from the blood culture samples taken from our patient on the first and fourth days. In the antibiotic susceptibility test, it was resistant to penicillin (8 µg/ml) and erythromycin (2 µg/ml), and it was sensitive to ceftriaxone (0.25 µg/ml), vancomycin (0.062 µg/ml), imipeneme (0.125 µg/ml), ciprofloxacin (0.5 µg/ml), levofloxacin (0.5 µg/ml), chloramphenicol (1 µg/ml), and clindamycin (0.062 µg/ml).

Discussion

A. defectiva, a virulent bacterium that affects endovascular structures and is usually isolated from immunocompromised patients, plays a role in many cases of culture negative endocarditis. Unlike other microorganisms, it is an important bacterium that causes heart failure due to heart valve destruction and various complications such as high rate of embolization in other organs[6,7]. *A. defectiva* causes particularly endovascular infections because of its ability to adhere to fibronectin in the extracellular matrix[2,6]. Although *A. defectiva* is generally sensitive to antibiotics, it causes embolic complications such as pancreatic abscess, brain abscess, osteomyelitis, septic arthritis, keratopathy; because it affects the heart valves in 90% of the cases. Studies have shown that it has a 17% recurrence rate despite antibiotic use[6,7]. Immunosuppression, pregnancy, and prosthetic valves are common predisposing factors for this rare infection, but infections have also been reported in healthy individuals in the literature. Small vegetation and embolism are observed in one third of patients with IE caused by *A. defectiva*. It most commonly affects the aortic valve and the second most commonly the mitral valve. Infection can cause the valve to be destroyed, and surgical intervention is required in 30% of patients. Although it is a rare infection, it has a mortality and morbidity rate of 17%[6,8]. Our patient had IE due to *A. defectiva*, which involved the mitral valve and caused embolism in the spleen. Guidelines recommend the combination of penicillin and gentamicin for treatment[9]. However, in our patient, ertapenem was initiated due to the diagnosis of urinary tract infection first made and drug interaction with warfarin. When the diagnosis of IE was made, it was decided to continue the ertapenem treatment because the agent was resistant to penicillin. The general condition of the patient improved, there was no fever, and there was no growth in the control blood culture. After six weeks of ertapenem treatment, it was observed that mitral valve vegetations in TTE and micro-emboli in the spleen disappeared, and the patient was discharged with full recovery.

Although a small number of patients with IE due to *A. defectiva* were published in the literature, most of them resulted in valve replacement despite adequate antibiotic therapy. Despite in-vitro sensitivity of *A. defectiva* to some antibiotics, significant structural destruction of the valves raises concerns about *in vivo* susceptibility to these antibiotics[3,6-8,10]. Stein and Nelson[11] reported that patients with *A. defectiva* endocarditis had higher mortality and recurrence rates and higher treatment failure, despite the use of *in vitro* effective antibiotics. Hashimoto et al.[12] showed that five of nine *A. defectiva* endocarditis required valve replacement despite appropriate antibiotic therapy. Lin and Hsu[13] reported that seven of eight patients with IE (four caused by *A. defectiva* and four caused by *Granulicatella adiacens*) underwent valve replacement due to severe heart failure. It is important to be aware of this etiological agent, as rapid and aggressive treatment of IE due to *A. defectiva* is required to improve clinical outcomes. Historically, it is more difficult to treat *A. defectiva* than Streptococci. Therefore, the American Heart Association recommends that the treatment regimen used be the same used for Enterococcal endocarditis. Typically, this treatment protocol consists of 4-6 weeks of benzylpenicillin/amoxicillin or two-week combination of gentamicin with vancomycin for patients with allergy to penicillin[9,14]. In a retrospective study by Lin and Hsu[13], only 30% of patients were successfully treated with penicillin and gentamicin, and vancomycin and gentamicin combination therapy was unsuccessful in one patient. It is more widely accepted that IE caused by *A. defectiva* has a poor prognosis, usually causing valve destruction and heart failure, and large vegetations. *A. defectiva* has also been shown as one of the microorganisms associated

with the highest systemic embolization rates[15]. For this reason, we think that it is important to suspect this microorganism in patients with culture negative IE and to apply additional tests for identification, and it may be useful to quickly identify the growing microorganism using methods such as MALDI-TOF MS or 16S rRNA. The limitation of our study was that 16S rRNA analysis could not be performed. Once this microorganism is identified, early surgical treatment with appropriate antibiotics should be considered.

Conclusion

As a result, *A. defectiva* is one of the rare but important causes of IE. Detection of *A. defectiva* in blood culture brought to mind the diagnosis of IE and shaped the follow-up process of our patient. On the other hand, IE associated with *A. defectiva* is generally resistant to penicillin, and guidelines recommend long-term combination of aminoglycosides with beta-lactams or vancomycin. However, unlike the recommendations of the guidelines, ertapenem, which was an antimicrobial in the carbapenem group, was used alone for six weeks in our patient. In addition, we believed that early diagnosis and initiation of treatment in our patient prevented serious complications.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A.T., Y.B., Concept: Y.D., Design: Y.D., Data Collection or Processing: S.A.T., Y.B., Analysis or Interpretation: E.S.T., Literature Search: Y.D., E.S.T., Writing: Y.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Frenkel A, Hirsch W. Spontaneous development of L forms of streptococci requiring secretions of other bacteria or sulphydryl compounds for normal growth. Nature. 1961;191:728-30.
2. Giannakopoulos K, Zompolou C, Behnes M, Elmas E, Borggrefe M, Akin I. Infective endocarditis - A word of caution on non-typical bacteria. Eur Rev Med Pharmacol Sci. 2016;20:4782-5.
3. Je H, Song D, Chan CL. Bacterial Endocarditis Caused by *Abiotrophia defectiva* in a Healthy Adult: A Case Report with Literature Review. Ann Clin Microbiol. 2019;22:23-7. Available from: https://synapse.koreamed.org/articles/1119063
4. Vahabi A, Gül F, Garakhanova S, Sipahi H, Sipahi OR. Pooled analysis of 1270 infective endocarditis cases in Turkey. J Infect Dev Ctries. 2019;13:93-100.
5. CLSI. Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria. 3rd ed. CLSI guideline M45. Wayne, PA: Clinical and Laboratory Standards Institute; 2015. Available from: https://clsi.org/standards/products/microbiology/documents/m45/
6. Ramos JN, dos Santos LS, Vidal LM, Pereira PM, Salgado AA, Fortes CQ, Vieira VV, Mattos-Guaraldi AL, Júnior RH, Damasco PV. A case report and literature overview: *Abiotrophia defectiva* aortic valve endocarditis in developing countries. Infection. 2014;42:579-84.
7. Carleo MA, Del Giudice A, Viglietti R, Rosario P, Esposito V. Aortic Valve Endocarditis Caused by *Abiotrophia defectiva*: Case Report and Literature Overview. In Vivo. 2015;29:515-8.
8. Rudrappa M, Kokatnur L. Infective Endocarditis Due to *Abiotrophia defectiva* and Its Feared Complications in an Immunocompetent Person: Rare, But Real. J Glob Infect Dis. 2017;9:79-81.
9. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, Bolger AF, Steckelberg JM, Baltimore RS, Fink AM, O'Gara P, Taubert KA; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation. 2015;132:1435-86.
10. Tuohy MJ, Procop GW, Washington JA. Antimicrobial susceptibility of *Abiotrophia adiacens* and *Abiotrophia defectiva*. Diagn Microbiol Infect Dis. 2000;38:189-91.
11. Stein DS, Nelson KE. Endocarditis due to nutritionally deficient streptococci: therapeutic dilemma. Rev Infect Dis. 1987;9:908-16.
12. Hashimoto T, Jodo S, Furusaki A, Kon Y, Amasaki Y, Atsumi T, Komatsu H, Shimokawa J, Yonezawa K, Koike T. A woman with infectious endocarditis caused by *Abiotrophia defectiva*. Intern Med. 2004;43:1000-4.
13. Lin CH, Hsu RB. Infective endocarditis caused by nutritionally variant streptococci. Am J Med Sci. 2007;334:235-9.
14. Gould FK, Denning DW, Elliott TS, Foweraker J, Perry JD, Prendergast BD, Sandoe JA, Spry MJ, Watkin RW, Working Party of the British Society for Antimicrobial Chemotherapy. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother. 2012;67:269-89.
15. Sahar N, Czachor JS, Shahid M. Clearing the Dust-Off *Abiotrophia defectiva*. J Med Cases. 2019;10:277-9.