

Emphysematous endocarditis caused by AmpC beta-lactamase-producing *Escherichia coli*

A case report

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Abstract

Rationale: Infective endocarditis (IE) is a life-threatening disease, mostly caused by gram-positive bacteria. Gram-negative bacteria were identified as a causative organism in relatively small number of cases. Although, antibiotic-resistant *Escherichia coli* is common cause of gram-negative endocarditis, AmpC beta-lactamase (BL)-harboring *E coli* is very rare cause of IE. Furthermore, emphysematous endocarditis is also a very rare manifestation of *E coli* infection.

Patient concerns: We report a case of 80-year-old female patient presenting with dizziness, fever, and altered mental status, who was finally diagnosed with emphysematous endocarditis caused by *E coli* harboring an AmpC BL gene.

Diagnosis: Her chest computed tomography revealed air bubbles surrounding the annulus of a mitral valve and a transesophageal echocardiogram revealed a hyperechogenic mass fixed on the posteromedial side of the mitral annulus with 2 eccentric mitral regurgitation jets. Blood cultures grew *E coli* which harbored the DHA-type AmpC BL. The organism belonged to a B2 phylogenetic group, and multilocus sequence typing analyses revealed that the strains were of ST-95.

Interventions: She was treated with meropenem following the resistant profiles, and surgery was recommended by the healthcare professional, but denied by the patient's guardians. She was transferred to another hospital due to a refusal for further treatment.

Lessons: Emphysematous endocarditis is an uncommon complication of *E coli* bacteremia. Certain phylogenetic groups may be associated with development of *E coli* endocarditis.

Abbreviations: BL = beta-lactamase, IE = infective endocarditis, MLST = multilocus sequence typing, ST = sequence type.

Keywords: AmpC beta-lactamases, case report, endocarditis, *Escherichia coli*

1. Introduction

Infective endocarditis (IE) is a life-threatening disease that results in cardiac dysfunction and the development of metastatic infections. Gram-positive bacteria cause 80% of all IE cases; however, gram-negative bacteria are also causative agents.^[1] With the exception of the HACEK organisms (i.e., *Haemophilus*,

Aggregatibacter, *Cardiobacterium*, *Eikenella*, and *Kingella*), *Escherichia coli* is the most frequent cause of IE^[2] and often presents concomitantly with other infection, including urinary tract infection.^[3,4] Despite being associated with healthcare setting, in most reports *E coli*-associated endocarditis was found to be developed by antibiotic susceptible organisms. In several cases involving antibiotic-resistant *E coli*,^[5-7] resistance was mediated by extended spectrum beta-lactamases (ESBLs). Here, we report a case of emphysematous IE caused by *E coli* harboring an AmpC BL gene. Phylogenetic characterization of the isolated bacteria was also performed.

2. Case presentation

An 80-year-old female patient presented to the emergency department complaining of dizziness, fever, and an altered mental state. The patient had a history of hypertension, diabetes mellitus (which was treated with metformin), and acute pyelonephritis due to *E coli* that was treated with an oral third-generation cephalosporin for 2 weeks, 6 months earlier. On admission, the patient had a blood pressure of 111/47 mm Hg, heart rate of 106 beats/min, and body temperature of 38°C. A physical examination failed to identify the cause of her altered mental state; however, a faint systolic murmur was auscultated. Laboratory examinations revealed a white blood cell count of 8906/mm³ with 97.1% neutrophils, 8.6g/dL of hemoglobin (Hb), and a platelet count of 58,000/mm³. The serum creatinine level was 3.36mg/dL, blood urea nitrogen was 78mg/dL, C-reactive protein was 19.38mg/dL, and procalcitonin was >100ng/mL. HbA1C was 6.4%. Magnetic resonance imaging of the brain

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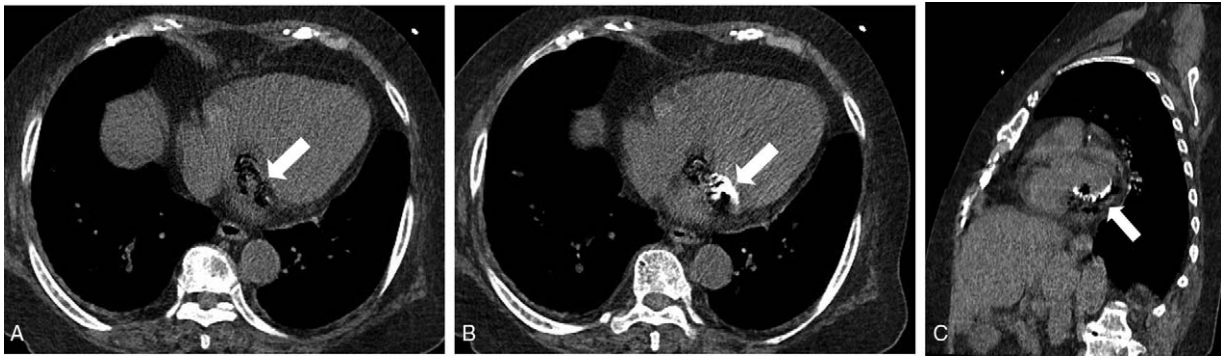


Figure 1. Noncontrast-enhanced axial (A and B) and short-axis cardiac (C) CT images revealing abnormal air bubbles surrounding the calcified mitral valve annulus (arrows). CT=computed tomography.

revealed multifocal acute infarctions involving the bilateral anterior and posterior vascular territories, including the cerebellums, which suggested an embolic infarction.

Noncontrast-enhanced chest computed tomography (CT) revealed abnormal air bubbles surrounding the annulus of a calcified mitral valve (Fig. 1), and a transthoracic echocardiogram revealed calcified and thickened mitral valve leaflets. Similarly, the mitral annulus was also calcified with moderate mitral regurgitation; however, there was no evidence of echogenic-mass like vegetation. Conversely, a transesophageal echocardiogram revealed a hyperechogenic mass fixed on the posteromedial side of the mitral annulus (Fig. 2A) with 2 eccentric mitral regurgitation jets (Fig. 2B), suggesting mitral annular destruction. All other valves were grossly and functionally normal.

Gram-negative bacilli were isolated from 3 separate blood and urine cultures, and ceftriaxone and amikacin were administered on day 1. *Escherichia coli* were identified initially from the urine samples, and subsequently from blood cultures. All isolates were resistant to cefazolin, ceftazidime, cefepime, ciprofloxacin, gentamicin, imipenem, meropenem, piperacillin-tazobactam, and ertapenem. Following resistance profiling, meropenem was administered. The patient was diagnosed with possible IE according to modified Duke criteria (fever; vascular phenomena; microbiological evidence of minor criteria; and predisposition to valvular heart disease were met). Surgery was recommended by the healthcare professional, but denied by the patient's guardians. The patient was transferred

to another hospital following 25 days of treatment due to a refusal for further treatment; she died 2 weeks after the transfer.

Escherichia coli isolates were cultured on Trypticase soy agar (TSA), and DNA was extracted using the QIAamp DNA mini kit (Qiagen GmbH, Hilden, Germany). Polymerase chain reaction (PCR) was performed to identify the *AmpC* BL gene present in each isolate and DNA sequencing and phylogenetic analyses were performed using multilocus sequence typing (MLST) genes (http://mlst.warwick.ac.uk/mlst/dbs/Ecoli/documents/primersColi_html).^{18,91}

Escherichia coli resistance was not due to the presence of ESBLs, and their resistance to ceftazidime suggested the presence of an AmpC BL. To identify the BL gene present, 7 primer sets were used to target CMY, CIT, DHA, FOX, MOX, ACC, and EBC genes. All strains harbored the DHA-type *AmpC* BL. Phylogenetic analyses were performed using the *chuA* and *yjaA* genes. The presence of both genes indicated that the isolates belonged to a B2 phylogenetic group, and MLST analyses revealed that the strains were of ST-95.

3. Discussion and conclusions

This is the first reported case of native valve emphysematous endocarditis caused by AmpC BL-producing *E coli* that rarely cause IE; however, this is changing due to the aging population and greater number of healthcare-related infections.^{11,31} Classically, endocarditis is more frequently associated with gram-positive bacteria, but previous study reported that gram-negative bacteria are more frequently associated with intracardiac abscess, intracardiac device

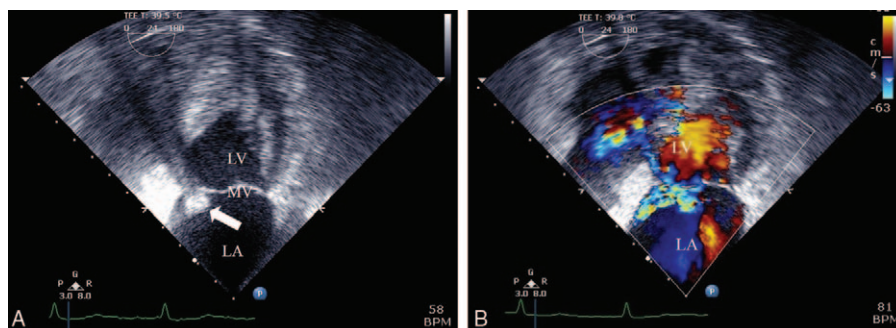


Figure 2. Transesophageal echocardiography images showing a hyperechogenic mass fixed on the thickened MV leaflets with calcification of the mitral annulus (arrow) (A) with 2 eccentric mitral regurgitation jets (B). LA=left atrium, LV=left ventricle, MV=mitral valve.

infection, and healthcare-associated infection.^[2] Various organisms, including anaerobic, gas-forming bacteria, and *E coli*, cause emphysematous infections in various organs.^[10–12] However, emphysematous IE caused by *E coli* has only been reported in veterinary infections.^[13] Although *E coli* is not a typical organism of IE, we failed to obtain a tissue specimen to confirm the diagnosis of IE due to refusal of surgical treatment. We had diagnosed the case as possible IE because our case met the modified Duke criteria for possible IE.^[14] Our case met the 4 minor criteria as following: predisposing condition of a valvular problem, sustained fever during effective antibiotic treatment, microbiological evidence for positive blood culture of *E coli*, and a vascular embolic phenomenon (brain embolic infarction). Immunological phenomena of IE were not evident in our case. Because immunological phenomena are known to be present in relatively late stage of IE, we think that our case did not present these due to she was in acute stage of infection. In this case, emphysema of the paravalvular area was detected using a noncontrast CT scan. Transthoracic and transesophageal sonography failed to detect the emphysema due to poor penetration of the air surrounding the valve. Reports from the ultrasonography described emphysematous infections arising from intra-abdominal infections;^[12,15] however, the gold standard for diagnosis of emphysematous infections is CT. Therefore, we recommend that CT scans be used to diagnose intracardiac complications arising from *E coli* bacteremia.

The *E coli* isolates in this study harbored an AmpC BL encoded by the DHA gene. DHA-type AmpC BLs were first described in *Salmonella enteritidis* in 1997,^[16] with 11 variants being identified since then.^[17] DHA-type AmpC BLs are common in *Klebsiella pneumoniae*, while they are rarer in *E coli* than CMY-type BLs.^[18] Notably, in a Korean study, DHA-type BLs were present in 2.7% of cefoxitin-resistant *E coli* cases.^[19] The risk factors of infection with AmpC BL-producing Enterobacteriaceae include a history of cerebrovascular accident and use of fluoroquinolones, cephamycin, or oxyimino cephalosporin.^[20,21] In this case, the source of the AmpC BL-producing *E coli* was unknown; however, prior urinary tract infections may have resulted in colonization by such strains.

The virulence factors in *E coli* that are associated with IE are not known. Micol et al^[3] reported that phylogenetic groups B2 and D were associated with extraintestinal infections, including IE; however, virulence genes varied within the same phylogenetic group. The *E coli* isolates in this study were of phylogenetic group B2 (ST-95), and are known as extraintestinal pathogenic *E coli*. No virulence factors associated with IE were identified, necessitating additional investigations.

In conclusion, we reported the emphysematous IE caused by DHA-type AmpC-BL producing *E coli* which was classified as ST-95 B2 phylogeny.

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