CASE REPORT

Community-acquired multidrug-resistant Gram-negative bacterial infective endocarditis

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SUMMARY

We describe two cases of bacterial endocarditis secondary to multidrug-resistant Gram-negative organisms. In both cases, the diagnosis was made in accordance with the modified Duke's criteria and confirmed by histopathological analysis. Furthermore, in both instances there were no identifiable sources of bacteraemia and no history of contact with hospital or other medical services prior to the onset of symptoms. The patients were managed in similar fashion with prolonged broad-spectrum antibiotic therapy and surgical intervention and made complete recoveries. These cases highlight Gram-negative organisms as potential agents for endocarditis, as well as expose the dissemination of such multidrug-resistant bacteria into the community. The application of an integrated medical and surgical approach and therapeutic dilemmas encountered in managing these cases are described.

BACKGROUND

Although Gram-negative bacteraemia is commonly encountered especially with *Escherichia coli*, endocarditis with non-HACEK (an acronym for *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, *Kingella*) Gram-negative bacilli remains rare.[1] For instance, a large multicentre prospective cohort study found Gram-negative bacteria to be responsible for only 1.8% of all cases of definite infective endocarditis.[2] *E. coli* and *Pseudomonas aeruginosa* were together responsible for over half of these cases. Similarly, the two largest available reviews on *E. coli* endocarditis were together able to identify 43 definite cases.[3 4] In comparison, there are nearly 200 reported cases of *P. aeruginosa* producing endocarditis; however, over 95% of these cases were related to intravenous drug use, unlike the patients reported here.[5]

Other conventional risk factors for Gram-negative bacterial endocarditis include hepatic cirrhosis,[6] prosthetic heart valves and sources of bacteraemia such as urosepsis.[3–5] Pertinently, none of these risk factors were seen in either of the patients reported here. This case report thus illustrates the shift of primary infection with multidrug-resistant Gram-negative bacteria into the community and its potentially deadly consequences.

CASE PRESENTATION

Case 1: A 55-year-old housewife presented with high-grade fever and chills, and breathlessness for 2 weeks. The breathlessness had worsened from New York Heart Association grade I to grade IV over the same period of time, progressing to orthopnoea at the time of presentation. There was no history of associated cough, wheezing or chest pain. Her husband was a farmer and had no medical problems.

Medical history included type 2 diabetes mellitus and essential hypertension for the past 5 years. She had not undergone any instrumentation or dental procedures in the last 3 months. She denied any history of substance abuse. On retrospective questioning, she denied any contact with healthcare facilities for herself or for her relatives over the past year.

At admission, the patient was febrile with an axillary temperature of 39°C and hypotensive (systemic blood pressure 70 mm Hg systolic). General physical examination also revealed tachycardia (heart rate 160/min) and tachypnoea (respiratory rate: 36/min). Mild pallor was noted. There were no peripheral signs of infective endocarditis. Jugular venous pressure was normal and peripheral oedema was absent. Cardiac auscultation revealed a grade 2 short systolic murmur in the mitral area. Respiratory system examination showed bilateral extensive fine inspiratory crepitations.

Case 2: A 22-year-old housewife presented with high-grade fever for 1 month, and left-sided abdominal pain for 1 week. There was no history of associated breathlessness, palpitations or chest pain. Her husband was a farmer and had no medical problems.

There was no significant medical history, no history of instrumentation in the past 3 months and no history of substance abuse. Family history was unremarkable. On retrospective questioning, she denied any contact with healthcare facilities for herself or for her relatives over the past year.

At admission, she was haemodynamically stable and febrile with an axillary temperature of 40°C. Her heart rate was 140/min. Severe pallor was also noted on general physical examination. There were no other peripheral signs of infective endocarditis. Jugular venous pressure was normal and peripheral oedema was absent. Cardiac auscultation revealed a grade 3 pansystolic murmur in the mitral area. Abdominal palpation showed a tender, moderately enlarged spleen. Respiratory system examination was normal.

INVESTIGATIONS

Case 1: Routine investigations showed mild anaemia (haemoglobin: 10.7 g/dL), leukocytosis (13.5×10^3/μL) and elevated erythrocyte sedimentation rate (97 mm/h). Mild renal failure was also

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noted (serum urea: 76 mg/dL, creatinine: 2.0 mg/dL). Chest X-ray, ECG and abdominal ultrasound were normal.

Transthoracic echocardiography demonstrated severe mitral regurgitation with normal left atrial size. Multiple vegetations were seen on the anterior and posterior mitral leaflets with rupture of the chord attached to the tip of the anterior mitral leaflet.

Four blood cultures drawn 1 h apart from two separate sites grew identical strains of *E. coli*. Species identification was performed on the basis of routine microbiological and biochemical tests. Antimicrobial susceptibility testing by Kirby-Bauer disc diffusion technique showed resistance to ciprofloxacin, amikacin, ceftriaxone, ceftazidime, tetracycline and cotrimoxazole and sensitivity to piperacillin-tazobactam, cefoperazone-sulbactam and meropenem, consistent with an extended spectrum β-lactamase (ESBL) producing organism.

Histopathology of the excised valvular tissue showed fibrinoid necrosis interspersed with neutrophilic infiltrates and granulation tissue.

Follow-up blood cultures 1 week after initiation of antibiotic therapy with meropenem were negative. Urine culture performed at admission was sterile.

Case 2: Routine investigations confirmed severe anaemia (Hb: 6.7 g/dL) and also showed leukocytosis (23.9×10^3/μL) and elevated erythrocyte sedimentation rate (129 mm/h). Renal function tests were normal (serum urea: 27 mg/dL, creatinine: 0.6 mg/dL). Chest X-ray and ECG were normal.

Transthoracic echocardiography demonstrated severe mitral regurgitation with normal left atrial size. A single large vegetation was seen on the anterior mitral leaflet.

Four blood cultures drawn 1 h apart from two separate sites grew identical strains of *P. aeruginosa*. Species identification was performed on the basis of routine microbiological and biochemical tests. Antimicrobial susceptibility testing by Kirby-Bauer disc diffusion technique showed resistance to ciprofloxacin, amikacin, ceftriaxone, ceftazidime, tetracycline and cotrimoxazole, as well as second-line antibiotics including piperacillin-tazobactam, cefoperazone-sulbactam and meropenem and sensitivity only to the reserve drug colistin.

Abdominal ultrasonography confirmed splenomegaly, and also revealed multiple splenic abscesses. CT was not performed to minimise risk of contrast-induced nephrotoxicity as the patient was receiving prolonged therapy with colistin.

Histopathology of the excised mitral valve showed extensive fibrinoid deposits and coagulative necrosis, enmeshed with Gram-negative bacterial colonies.

Follow-up blood cultures 1 week after initiation of therapy with colistin were negative. Urine culture performed at admission was sterile.

DIFFERENTIAL DIAGNOSIS

Case 1: Community-acquired bacterial infective endocarditis secondary to ESBL producing *E. coli*

Case 2: Community-acquired bacterial infective endocarditis secondary to multidrug-resistant *P. aeruginosa*

TREATMENT

Case 1: Empirical parenteral antibiotic therapy was started with ceftriaxone (2 g intravenous q24 h) which was then changed to meropenem (1 g intravenous q8 h) in accordance with the sensitivity pattern of the isolate. Although the patient did not deteriorate further in the interval between admission and availability of blood culture reports, the presence of heart failure secondary to acute mitral regurgitation with cardiogenic shock was considered as grounds for surgical intervention. Mitral valve replacement was emergently performed on the third day of hospital stay using a 27 mm ATS Medical valve with chordal preservation technique. Intraoperative findings were confirmatory of the echocardiographic diagnosis and also showed necrosis of the tip of the anterior papillary muscle with presence of purulent material.

Antibiotic therapy with meropenem was continued for 4 weeks. The patient was also started on oral anticoagulation with acenocoumarol (2 mg orally once daily) and antiheart failure measures including furosemide and digoxin. Glycaemic control was maintained with insulin.

Case 2: Empirical parenteral antibiotic therapy was started with ceftriaxone (2 g intravenous q24 h) and then changed to colistin (3×10^6 IU intravenous stat followed by 10^6 IU intravenous q8 h) in accordance with the sensitivity pattern of the isolate. Despite treatment with colistin for 10 days, the patient continued to suffer high-grade fever and also complained of persistent left-sided severe abdominal pain. Moreover, clinical examination did not show reduction in splenic size or tenderness. Infection with a highly resistant organism was thus considered as grounds for surgical intervention. Mitral valve replacement was performed on the twelfth day of hospital stay using a 31 mm ATS valve. Intraoperative inspection showed multiple small vegetations on the posterior mitral leaflet in addition to the solitary vegetation echocardiographically visualised on the anterior mitral leaflet.

Splenectomy was simultaneously performed for multiple splenic abscesses unresponsive to parenteral antibiotic therapy.

Postoperatively, antibiotic therapy with colistin was continued for 4 weeks. Oral anticoagulation was maintained with acenocoumarol (3 mg orally once daily).

OUTCOME AND FOLLOW-UP

Case 1: The patient became afebrile on the fifth day of hospital stay and was discharged after completion of 4 weeks of therapy with meropenem. She was followed up at regular intervals for the next 18 months. Serial transthoracic echocardiography demonstrated a well-functioning prosthetic valve and normal left ventricular function. Renal function tests normalised during hospital stay. There were no further instances of infective endocarditis.

Case 2: The patient became afebrile on the 15th day of hospital stay and was discharged after completion of 4 weeks of therapy with colistin. She did not develop any toxicity during the course of antibiotic administration. She was followed up at regular intervals for the next 12 months. Serial transthoracic echocardiography demonstrated well-functioning prosthetic valve, and normal left ventricular function. There were no further instances of infective endocarditis.

DISCUSSION

Both patients described in this report fulfilled the modified Duke's criteria for infective endocarditis with both major criteria, that is, recovery of the microorganism from four separate blood cultures drawn over 1 h, and echocardiographic demonstration of valvular vegetations. Moreover, histopathological evidence of infective endocarditis was also obtained in both instances. This was noteworthy considering the rarity of Gram-negative endocarditis.

Notwithstanding its relative uncommonness, Gram-negative endocarditis remains associated with a high mortality rate. Both *E. coli* and *P. aeruginosa* endocarditis frequently produce heart failure. Moreover, *P. aeruginosa* frequently produces ring and

annular abscesses, major systemic emboli and neurological complications.[5] Difficulty in sterilisation of the vegetations with antibiotic therapy alone is also an important consideration. The emergence of ESBL-producing Enterobacteriaceae and multidrug-resistant strains of *Pseudomonas* has further complicated the management of Gram-negative bacterial endocarditis by excluding many antibiotics that are otherwise effective in endocarditis. For these reasons, cardiac surgery remains an integral component of therapy in such cases.[3 7]

Possibly due to its infrequency, there are few available guidelines for pharmacological management of Gram-negative bacterial endocarditis. Standard parenteral combination antibiotic therapy with ceftriaxone and an aminoglycoside is acceptable for susceptible strains albeit in higher dosing.[8] On the other hand, ESBL producing strains require a carbapenem with or without an aminoglycoside.[1] *P. aeruginosa* usually responds to antipseudomonal drugs such as piperacillin or ceftazidime in combination with an aminoglycoside. Maximal dosing of appropriate parenteral antibiotics after in vitro susceptibility testing with frequent monitoring for adverse effects has been recommended as an approach to infection with multidrug-resistant strains.[9] However, there is no available data on the efficacy of reserve drugs such as colistin in sterilising vegetations. We were therefore forced to resort to early cardiac surgery in the second case.

A brief comparison with other reported cases of multidrug-resistant Gram-negative bacterial endocarditis reveals several points of interest in our patients. George *et al*[10] reported a similar case of ESBL producing *E. coli* endocarditis, which was treated successfully with parenteral meropenem and tigecycline for 6 weeks. However, the patient in question did have a source of bacteraemia in the form of a recent urinary infection, had received unspecified antibiotics and had been in hospital and an intensive care unit prior to developing endocarditis. These features are risk factors for multidrug-resistant Gram-negative infection and were not present in either of our cases. Another case reported by Yang[11] described an individual having diabetes with urosepsis who subsequently developed tricuspid valve endocarditis. Once again there was a clear source of infection and an absence of hospital stay or prior antibiotic therapy was entirely compatible with the sensitive strain of *E. coli* isolated. While the cases reported by George *et al* and Yang were both managed by antibiotic therapy alone, another case reported by Rangarajan *et al*[12] involved an elderly man with urosepsis and Gram-negative bacteraemia who then developed mitral valve endocarditis. This individual had pre-existing coronary artery disease with a compromised left ventricular function, which might have contributed to rapidly decompensating heart failure after onset of infective endocarditis, finally necessitating surgical intervention. Our patient with *E. coli* endocarditis possessed neither risk factors for coronary artery disease nor evidence of overt cardiac dysfunction before the index illness, and yet required surgery due to progressive heart failure with cardiogenic shock, highlighting the aggressive nature of infection in this instance.

A recent review of *P. aeruginosa* endocarditis cases in Detroit, Michigan, USA showed good results with antibiotic therapy alone.[13] Most cases were treated with a combination of high dose cefepime-tobramycin or meropenem-tobramycin. This trend contradicted older guidelines favouring aggressive surgery in patients with *Pseudomonas endocarditis*.[14] However, none of the 10 cases described were infected with highly resistant strains comparable to the second patient in our report. The continuous evolution of increasingly resistant strains of *P. aeruginosa* and other gram-negative bacteria thus lends support to the relevance of surgical intervention in infective endocarditis.

Infection with multidrug-resistant strains of Gram-negative bacteria has traditionally been linked to contact with some form of healthcare. Dissemination of these strains to the community represents a significant escalation of virulence, culminating in cases like those reported here. A likely consequence of access to the far larger population in the community is an increase in the absolute incidence of Gram-negative bacterial endocarditis. Absence of high-risk features should not be a bar to screening for endocarditis in patients with persistent Gram-negative bacteraemia, especially in regions where multidrug-resistant strains are known to exist within the community.

Learning points

- Gram-negative bacteria are a rare cause for community-acquired endocarditis but are frequently associated with a complicated clinical course.
- Multidrug-resistant strains can pose significant problems for medical management of infective endocarditis.
- Aggressive therapy with parenteral antibiotics and early surgical intervention can produce good clinical results in such challenging cases.

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Competing interests None.

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