Small vessel vasculitis associated with culture-negative infective endocarditis related to a cardiac device: a case report

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Background

Culture-negative endocarditis is uncommon, occurring in less than a third of all cases of infective endocarditis (IE). Culture-negative IE related to a cardiac device is an even greater diagnostic challenge due to its insidious presentation, with onset of symptoms ranging between 3 and 12 months after device implantation. Sensitivity of the modified Duke’s criteria remains low in culture-negative and cardiac device-related IE (CDRIE) since classical signs and symptoms of IE are often absent. Small vessel vasculitis has been reported as an immune response to IE. Recognizing immunological phenomenon related to IE is of paramount clinical importance, prompting the search for an underlying infection and avoiding the use of immunosuppressive medications which would otherwise result in an adverse outcome.

Case summary

An 81-year-old Caucasian male presented to the ambulatory medical unit with a two-week history of a symmetrical, generalized purpuric rash. He had an indwelling permanent pacemaker following a transcatheter aortic valve implantation for severe aortic stenosis five years ago. Blood tests showed an iron deficiency anaemia, thrombocytopenia and normal renal function, both CRP and ESR were raised at 61  and 30 mm/hr, respectively. Skin biopsy demonstrated small vessel cutaneous vasculitis. Transthoracic echocardiography revealed a mobile mass measuring 0.9 × 1.7 cm, confirmed on transoesophageal echocardiogram as pacing lead endocarditis. Blood cultures were persistently negative. The patient underwent pacemaker lead extraction, following which the vasculitic rash improved.

Discussion

Blood cultures in IE are more likely to be negative if there is a prior antibiotic administration or causative micro-organisms with limited proliferation which fail to grow in conventional media conditions. Transesophageal echocardiography (TOE) offers improved sensitivity and diagnostic yield when compared to transthoracic echocardiography (TTE) in patients with a high clinical suspicion of CDRIE. The evidence in the literature describing culture-negative IE associated with small vessel vasculitis is limited. However, it is recognized that cutaneous small vessel vasculitis may be associated with an underlying bacterial infection. IE produces an inflammatory response, resulting in the deposition of circulating immune complexes and cutaneous signs which are included in the modified Duke’s criteria to aid diagnosis. Management of CDRIE requires a multi-disciplinary team approach with an ‘Endocarditis Team.’ Pacemaker lead infection requires transvenous lead extraction if it is a newly implanted lead. Locking stylets, extraction sheaths or snare retrieval are usually required in cases of older implanted leads. Surgical lead extraction remains the gold standard for larger vegetations (>20 mm) or associated valve endocarditis.
Learning points

- Culture-negative infective endocarditis (IE) related to a cardiac device is a diagnostic challenge since most of the classical signs and symptoms of IE are absent.
- The presence of cutaneous small vessel vasculitis should prompt investigation to exclude an underlying source of infection in high-risk patients, particularly those with an indwelling cardiac device.
- Pacemaker lead infection requires percutaneous lead extraction, however surgical lead extraction is indicated with large vegetations >20 mm or with coexistent valve endocarditis.

Introduction

Culture-negative infective endocarditis (IE) is a challenging diagnosis associated with increased morbidity and mortality. Immunological phenomena in the presence of a cardiac device should raise the suspicion of IE.

Circulating immune complexes and micro-emboli on the vascular endothelium are thought to be responsible for the clinical manifestations of vasculitis in IE. Immunological phenomena such as Osler’s nodes, Roth spots and glomerulonephritis are included in the modified Duke’s criteria to support a working diagnosis of IE (Table 1). There are few case reports in the literature describing cutaneous vasculitis in association with bacterial infections and native valve IE. We report the first case of small vessel vasculitis associated with culture-negative endocarditis related to a cardiac device.

Timeline

| Date                  | Event                                                                                                                                                                                                 |
|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3 years prior to index admission | Single lead permanent pacemaker device post transcatheter aortic valve replacement.                                                                                                                     |
| Index admission       | Presents with a generalized rash, scrotal swelling and skin necrosis. Methicillin-susceptible Staphylococcus aureus, Pseudomonas and Enterococcus from skin swabs. Surgical debridement of necrotic skin tissue. |
| 2 weeks following discharge from index admission | Readmitted from ambulatory care with a worsening skin rash. Skin lesion biopsy suggestive of cutaneous, small-vessel vasculitis. transthoracic echocardiogram and transesophageal echocardiogram |

Case presentation

An 81-year-old Caucasian male was admitted from the ambulatory medical unit with a two-week history of a progressive, generalized purpuric rash. There was no history of fever, either low-grade or persistent and no systemic malaise. The patient did not report exposure to farm animals, recent foreign travel, or dental work.

The rash was symmetrical distributed over both hands, forearms, and legs (Figure 1). Past medical history included type II diabetes mellitus, iron deficiency anaemia, permanent pacemaker (PPM) implant following transcatheter aortic valve implantation for severe aortic stenosis in 2017 and permanent atrial fibrillation (AF). The patient had been investigated for iron deficiency anaemia since 2015 with gastroscopy and colonoscopy and was anticoagulated with Apixaban 5 mg twice daily for permanent AF. There was no relevant family history or history of cardiovascular events.

Six weeks earlier he had been admitted with a similar symmetrical and generalized rash, in addition to scrotal swelling and skin necrosis.
were no symptoms of malignancy. There was no pain or systemic symptoms of infection including fever and there was no existing skin rash. He did not experience any breathlessness, chest pain or intermittent claudication, or any signs of heart failure, palpable peripheral stigmata of IE, or any signs of heart failure, palpable masses, or lymphadenopathy.

Clinical examination was otherwise unremarkable. There were no pathological evidence of IE at surgery or autopsy, after antibiotic therapy for at least 4 days, or no pathological evidence of IE at surgery or autopsy, after antibiotic therapy for at least 4 days. The patient received antibiotic therapy. Serology for Coxiella burnetii (Q fever) or (with an immunofluorescence assay) phage 1 IgG antibody titre of >1:800.

Two weeks later he was readmitted with worsening of the pre-existing skin rash. He did not experience any breathlessness, chest pain or systemic symptoms of infection including fever and there were no symptoms of malignancy.

Skin swabs grew methicillin-susceptible *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterococcus*. The patient had slow clinical improvement with intravenous 4 g piperacillin/0.5 g tazobactam (Tazocin) given every 8 h after a course of meropenem and clindamycin had failed to improve the rash. Blood cultures obtained prior to the administration of antibiotics and following antibiotic treatment were negative. The patient underwent surgical debridement for a diagnosis of Fournier’s gangrene and continued to improve prior to discharge.

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Two weeks later he was readmitted with worsening of the pre-existing skin rash. He did not experience any breathlessness, chest pain or systemic symptoms of infection including fever and there were no symptoms of malignancy.

The patient was haemodynamically stable with an irregularly, irregularly, irregularly, irregularly, irregularly, irregularly, regular pulse and afebrile. Cardiac auscultation revealed a new 3/6 systolic murmur heard loudest over the lower left sternal border. Clinical examination was otherwise unremarkable. There were no peripheral stigmata of IE, or any signs of heart failure, palpable masses, or lymphadenopathy.

Electrocardiography showed rate controlled atrial fibrillation and bifascicular block. Chest x-ray was clear with an appropriately sited single-lead PPM. The Blood results revealed an iron deficiency anaemia with a haemoglobin of 99 g/L, white cell count was normal at 6.2×10⁹/L although C-reactive protein and erythrocyte sedimentation rate were raised at 61 mg/L and 30 mm/h respectively. He was thrombocytopenic with a platelet count of 125×10⁹/L. Renal function was normal with a creatinine of 72 µmol/L.

Anti-nuclear, anti-smooth muscle, anti-ribonuclear protein complex and chromatin antibodies were all positive indicating the possibility of positive immunologic phenomena. Blood cultures obtained prior to antibiotic administration were negative, along with a further four negative aerobic and anaerobic cultures taken during the admission while the patient received antibiotic therapy. Serology for Coxiella burnetii and brucella was not performed as part of the requested tests.

The patient underwent a skin lesion biopsy following dermatology review. This showed a single, small vessel lesion with fibrinoid necrosis and associated inflammatory cells in keeping with vasculitis. There were no dysplastic or malignant changes.

Transthoracic echocardiogram (TTE) revealed a filamentous, mobile mass measuring 0.9×1.7 cm adhering to the right atrial wall (Figure 2; see Supplementary material online, Video S1). The transcatheter heart valve was well seated with preserved left ventricular systolic function, mild to moderate tricuspid regurgitation, right ventricular dilatation and severe bi-atrial dilatation with an intermediate

### Table 1  Modified duke’s criteria for diagnosing infective endocarditis

| Definite IE | Possible IE | Rejected IE |
|-------------|-------------|-------------|
| • 2 major criteria, or | • Findings consistent with IE that fall short of definite, but not rejected | • Firm alternate diagnosis explaining evidence of IE, or |
| • 1 major and 3 minor criteria, or | • Resolution of IE syndrome with antibiotic therapy for ≤4 days, or | • Resolution of IE syndrome with antibiotic therapy for ≤4 days, or |
| • 5 minor criteria | • No pathological evidence of IE at surgery or autopsy, after antibiotic therapy for ≤4 days | • No pathological evidence of IE at surgery or autopsy, after antibiotic therapy for ≤4 days |

| Major criteria | Minor criteria |
|---------------|---------------|
| 1. Positive blood culture for IE: | 1. Predisposition: predisposing heart condition or injecting drug use. |
| a. Typical microorganisms for IE from two separate blood cultures—Viridans streptococci, *Streptococcus galliearius*, HACEK group organisms, *Staphylococcus aureus* or community acquired *Enterococcus* in the absence of a primary focus. | 2. Fever ≥39.0°C |
| b. Persistently positive blood culture, defined as recover of a microorganism consistent with IE from; blood cultures drawn >12 hours apart or all of 3 or a majority of ≥4 separate blood cultures, with first and last drawn at least 1 hour apart. | 3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhage, Janeway lesions. |
| 2. a. Evidence of endocardial involvement—positive echocardiogram for vegetation, abscess, pseudoaneurysm, intracardiac fistula, new valvular perforation or aneurysm and new partial dehiscence of prosthetic valve. | 4. Immunological phenomenon: glomerulonephritis, Osler’s nodes, Roth’s spots, rheumatoid factor. |
| 3. a) Evidence of endocardial involvement—positive echocardiogram for vegetation, abscess, pseudoaneurysm, intracardiac fistula, new valvular perforation or aneurysm and new partial dehiscence of prosthetic valve. | 5. Microbiological evidence: positive blood culture but not meeting major criterion. |

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Figure 1 Non-blanching, purpuric rash of the left forearm on presentation.
probability of pulmonary hypertension. Transoesophageal echocardiogram (TOE) confirmed a mobile structure in the right atrium measuring 2 cm in length and attached to the pacing lead as it entered the superior vena cava (see Supplementary material online, Video S2).

The case and images were reviewed in a departmental multidisciplinary team (MDT) meeting with the consensus of a lead vegetative given the clinical presentation and oscillating, mobile mass seen on echocardiography.

The patient was initially commenced on vancomycin 750 mg twice daily injections, oral rifampicin 600 mg twice daily and gentamicin 80 mg twice daily injections for a ‘possible’ diagnosis of IE based upon the modified Duke’s criteria (positive echocardiographic imaging, predisposing heart condition and immunological phenomena), the patient continued all 3 drugs for 4 days and was later switched to vancomycin only following high serum gentamicin levels. The patient remained on vancomycin for 5 more days after the pacemaker lead extraction.

One week after, the patient was transferred to the local tertiary centre for lead extraction. The pacemaker lead was extracted 10 days from admission using a right femoral vein approach, with the lead removed using simple traction technique and trapped under the clavicle. The tip of the lead remained in the left subclavian vein since it was unlikely to cause any future complications.

He was discharged back to the district hospital 3 days after the procedure. The vasculitic rash was noticeably less extensive and almost completely resolved on discharge (Figure 3). No additional echocardiographic imaging was performed prior to discharge and there were no plans to investigate the finding of pulmonary hypertension.

The patient had multiple falls in the interim with rib and pelvic fractures and received a new diagnosis of dementia. Prior to routine outpatient clinic review, the patient was re-admitted 9 months later from his index admission with increasing shortness of breath and signs of right heart failure. The patient died as a result of congestive cardiac failure, pulmonary hypertension and valvular heart disease.

**Discussion**

Culture-negative endocarditis is uncommon, occurring in 2.5–31% of all cases of IE. The reasons for this are two-fold: firstly, antibiotic administration prior to blood cultures reduces the likelihood of a positive result, secondly causative micro-organisms with limited or no
In cases of suspected culture-negative endocarditis, with onset of symptoms ranging between 3–12 months after pacemaker implantation. Fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) has excellent pooled sensitivity of 87% and specificity of 94% for diagnosing CIED infection, although its sensitivity is lower in lead infections when compared to pocket/generator related CIED infection due to limited spatial resolution and motion artefact. 

Duke’s criteria, developed in 1994 by Durack et al., were subsequently modified to account for the improved diagnostic yield with TOE. In spite of this, sensitivity of the criteria is reduced when endocarditis is related to a cardiac device since classical signs and symptoms of culture-negative IE are often absent. The use of 18F-FDG PET/CT has been integrated into the ESC 2015 modified diagnostic criteria, improving sensitivity of the modified Duke’s criteria in cases of prosthetic valve IE (Table 2). In cases of suspected CDRIE such as this, TOE is recommended in addition to TTE due to its increased sensitivity and specificity for CDRIE. Additional imaging modalities such as cardiac CT, 18F-FDG PET/CT and leucocytes labelled SPECT/CT are diagnostically helpful, particularly in detecting complications such as silent emboli. There is a sparsity of cases in the literature which describe culture-negative IE associated with small vessel vasculitis. Cutaneous vasculitis should prompt investigation to exclude an underlying source of infection in high-risk patients such as those with indwelling cardiac devices. In a study of 766 patients presenting with cutaneous vasculitis, 27 were found to have an underlying bacterial infection. Six out of those 27 patients had a confirmed diagnosis of IE.

The morbidity and mortality of device related IE is high. In a systematic review of 184 patients, medical therapy alone with antibiotics was associated with a mortality between 46 and 100%. Surgical lead extraction is the gold standard treatment although mortality remains lower in lead infections.

Table 2: ESC modified criteria (highlighted in red) for diagnosing infective endocarditis

| Major Criteria | Minor Criteria |
|---------------|---------------|
| Definite IE | 1. Positive blood culture for IE: |
| • 2 major criteria, or | a. Typical microorganisms for IE from two separate blood cultures—Viridans streptococci, Streptococcus gallacticus, HACEK group organisms, Staphylococcus aureus or community acquired Enterococci in the absence of a primary focus. |
| • 1 major and 3 minor criteria, or | b. Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood cultures drawn >12 hours apart or all of 3 or a majority of ≥4 separate blood cultures, with first and last drawn at least 1 hour apart. |
| • 5 minor criteria | c. Single positive blood culture for Coxiella burnetii (Q fever) or (with an immunofluorescence assay) phage 1 IgG antibody titre of >1:800. |
| Possible IE | 2. a) Evidence of endocardial involvement— positive echocardiogram for vegetation, abscess, pseudoaneurysm, intracardiac fistula, new valvular perforation or aneurysm and new partial dehiscence of prosthetic valve. |
| • Findings consistent with IE that fall short of definite, but not rejected | b) Positive imaging as detected by abnormal activity in 18F-FDG-PET/CT or radiolabelled leucocytes SPECT/CT around newly implanted < 3 months prosthetic valve. |
| • Resolution of IE syndrome with antibiotic therapy for ≤4 days, or | c) Definite paravalvular lesions by cardiac CT. |
| • No pathological evidence of IE at surgery or autopsy, after antibiotic therapy for ≤4 days | |

1. Predisposition: predisposing heart condition or injecting drug use.
2. Fever ≥38.0°C
3. Vascular phenomena (including those detected by imaging alone): major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhage, Janeway lesions.
4. Immunological phenomenon: glomerulonephritis, Osler’s nodes, Roth’s spots, rheumatoid factor.
5. Microbiological evidence: positive blood culture but not meeting major criterion. 

proliferation fail to grow in conventional media conditions. In the present case, the patient received several broad-spectrum antibiotics during his first admission, which may have contributed to persistently negative blood cultures. Nevertheless, blood cultures obtained prior to antibiotic administration in the index admission were also negative, thereby suggesting culture-negative IE may occur despite no previous antibiotic administration.

Culture-negative endocarditis related to a cardiac device is a diagnostic challenge with reported prevalence ranging between 0.5 and 7%. There is a variable presentation of cardiac device-related IE (CDRIE), with onset of symptoms ranging between 3–12 months after pacemaker implantation.

Consequently, a delay in diagnosis is often reported. Edelstein et al. estimated an average delay in diagnosis of five and a half months from disease onset.

The TTE has poor sensitivity in diagnosing CDRIE and therefore its diagnostic value is limited in this context. In a comparative study of 23 patients with definite pacemaker lead infections, the sensitivity of TTE was only 30%. This compared to a sensitivity and specificity of 91 and 100% respectively in those who underwent TOE. In certain cases, traditional imaging tools such as TTE/TOE are inconclusive when differentiating thrombus from vegetation in suspected cardiac implantable electronic device (CIED) infections. In cases of diagnostic uncertainty, fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) has excellent pooled sensitivity of 87% and specificity of 94% for diagnosing CIED infection, although its sensitivity is lower in lead infections, although mortality remains lower in lead infections.
Management of CIED infection requires a MDT approach with an 'Endocarditis Team', comprising microbiologists, pharmacists, cardiologists, and cardiac surgeons. In our case, TOE images were discussed in a MDT meeting with a decision to perform lead extraction without further delay to avoid an unfavourable clinical outcome. Although no histopathological analysis was performed after lead extraction, the noticeable disappearance of the vasculitic rash is highly suggestive of an inflammatory cause of culture-negative IE rather than thrombus. Snare-retrieval of the mass provides for definitive histopathological assessment in inconclusive cases despite appropriate imaging. Nevertheless, this technique may be unsuccessful, particularly if the lesion is densely fibrotic or heavily calcified. Pacemaker lead infection requires transvenous lead extraction if it is a newly implanted lead. Locking stylets, extraction sheaths or snares are usually required in cases of older implanted leads. However, surgical lead extraction remains the gold standard in patients with larger vegetations (>20 mm) or associated valve endocarditis.⁴,¹³

**Conclusion**

In conclusion, the presence of small vessel vasculitis should raise the suspicion of IE despite negative blood cultures, particularly in patients with an implanted cardiac device. Repeating blood cultures and performing TOE helps in making a clear diagnosis in most of these cases, including ours. Other diagnostic imaging tests, for example cardiac CT and/or ¹⁸F-FDG PET/CT or leucocytes labelled SPECT/CT are useful when the diagnosis remains in doubt. The high clinical suspicion of IE such as in this case prompted for identification and treatment with TOE and lead extraction which is essential to reduce the high morbidity and mortality associated with this condition.

**Lead author biography**

Dr Maged El-Gaaly graduated from medical school of Ainshams University, Cairo, Egypt in 2008. He has worked in multiple tertiary centres in Cairo with a main interest of general cardiovascular medicine before moving to the UK in 2015. He is currently an acute medicine trainee in West Yorkshire deanery with a specialist interest in transthoracic echocardiography and cardiovascular imaging.

**Supplementary material**

Supplementary material is available at European Heart Journal — Case Reports online.

**Slide sets:** A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

**Consent:** A written consent for submission and publication of the images and associated text has been obtained from the patient in line with COPE guidance.

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