ESC European Society of Cardiology

European Heart Journal - Case Reports (2021) **5**(9), 1–10
doi:10.1093/ehjcr/ytab345

CASE SERIES
Other

A case series of skin manifestations of infective endocarditis in contemporary era: just another book finding or a useful clinical sign?

Christos Gogos [1]*, Vasileios Moschovidis [1], Chris Adamopoulos[2], Anastasia Trigoni[3], Ioannis Styliadis [1], and Vasileios Sachpekidis [1]

[1]Department of Cardiology, Papageorgiou General Hospital, Nea Efkarpia, 56403 Thessaloniki, Greece; [2]Department of Cardiology, Ippokrateion Hospital, Thessaloniki, Greece; and [3]2nd Department of Skin and Venereal Diseases, Aristotle University of Thessaloniki, Papageorgiou Hospital, Thessaloniki, Greece

Received 9 January 2021; first decision 22 March 2021; accepted 18 August 2021; online publish-ahead-of-print 20 August 2021

Background Infective endocarditis (IE) is a disease of high morbidity and mortality. Infective endocarditis rarely involves skin manifestations in the contemporary era. The identification of typical skin lesions could be helpful in establishing early diagnosis of IE.

Case summary We present four cases of IE hospitalized in our institution within a 12-month period. All patients were young and had skin manifestations on initial presentation (petechiae, splinter haemorrhages, Janeway lesions, and Osler's nodes), which led to a high clinical suspicion of IE confirmed by echocardiography and positive blood cultures. All cases had a complicated course. One patient died and the other three had prolonged hospital stay due to variable complications.

Discussion Clinicians should always assess for skin manifestations in patients with fever especially when suspicion of IE is high. Occurrence of skin lesions in the course of IE may be associated with higher rate of complications and worse prognosis.

Keywords Case series • Infective endocarditis • Skin • Janeway lesions • Osler's nodes • Splinter haemorrhages

Learning points

- Skin findings in the proper clinical setting may lead to early diagnosis of infective endocarditis (IE).
- Skin manifestations of IE may be associated with infection severity and systemic embolization.

Introduction

Infective endocarditis (IE) is a disease of high morbidity and mortality.[1] Infective endocarditis rarely involves skin manifestations but when present, they may lead to timely diagnosis. Occurrence of skin lesions in the course of IE has been associated with higher rate of complications and worse prognosis.[1,2] The present case series

* Corresponding author. Tel: +30 6987970390, Email: gogos-grivas@hotmail.com
Handling Editor: Francesco Giannini
Peer-reviewers: Livia Gheorghe; Andriana Anagnostopoulou; Yehia Saleh; Carla Sousa
Compliance Editor: Linh Ngo
Supplementary Material Editor: Anthony Paulo Sunjaya

highlights the importance of clinical examination for early diagnosis and treatment of IE.

Timeline

Cases	Age	Clinical course	Lesions	Complications
Case 1	53	Day 1: Fever, abdominal pain, and oliguria Day 3: Cerebral infarction, skin lesions spotted, mitral valve (MV) vegetation on echocardiogram (echo) Day 45: Mitral valve replacement (MVR) Day 53: Discharge	Hands lesions • Janeway' s lesions • Petechiae • Splinter haemorrhages	• Acute kidney injury • Cerebral infarction • Congestive heart failure (HF)
Case 2	33	Day 1: Fever, fatigue, and left arm weakness, skin lesions, MV vegetation on echo Day 14: MVR Day 48: Diagnosis of spleen infarcts and mycotic aneurysm of superior mesenteric artery (SMA) Day 61: Discharge	Hands and feet lesions • Janeway's lesions • Osler's nodes • Petechiae	• Acute kidney injury • Cerebral emboli • Spleen emboli • HF • Ventricular tachycardia, supraventricular tachycardia • SMA mycotic aneurysm
Case 3	36	Day 1: Haemodynamic instability and altered mental status, skins lesions, multiple spleen, renal, and cerebral emboli on computed tomography (CT), bicuspid aortic valve (AV) vegetations on echo Days 4: Right lower limb distal embolization Day 11: Death	Hands, feet, and retinal lesions: • Janeway's lesions • Osler's nodes • Splinter haemorrhages • Petechiae • Roth's spots	• Cardiogenic shock • Multiple organ dysfunction syndrome • Cerebral emboli • Spleen emboli • Renal emboli • Lower limb gangrene
Case 4	35	Day 1: Fatigue and fever, skin lesions, AV vegetations on echo Day 3: Ischaemic colitis, multiple cerebral and renal infarcts on CT Day 5: Intracerebral haemorrhage Day 62: Aortic valve replacement Day 70: Discharge	Hands and leg lesions: • Petechiae • Splinter haemorrhages	• Ischaemic colitis • Cerebral infarcts • Renal infarcts • Intracerebral haemorrhage

Case presentation

Patient 1

A 53-year-old male with no medical history presented to the emergency room (ER) complaining of recent onset fatigue along with episodes of fever, abdominal pain, and oliguria. Gross clinical examination on admission revealed hypotension, tachycardia, fever, and diffuse abdominal tenderness (more prominent in the right hypochondrium). Laboratory workup revealed elevated inflammation markers, thrombocytopenia, and acute kidney injury. The patient was admitted with an initial diagnosis of intra-abdominal infection and empiric antimicrobial therapy was commenced despite the absence of specific findings on abdominal computed tomography (CT). On Day 3 he suddenly developed right-sided hemiparesis due to cerebral infarct as shown on brain magnetic resonance imaging (MRI). In search of the aetiology of the brain infarct thorough clinical examination revealed a holosystolic apical murmur along with upper extremities petechiae, splinter haemorrhages of the nail beds, and non-tender erythematous macules on the palms recognized as Janeway lesions

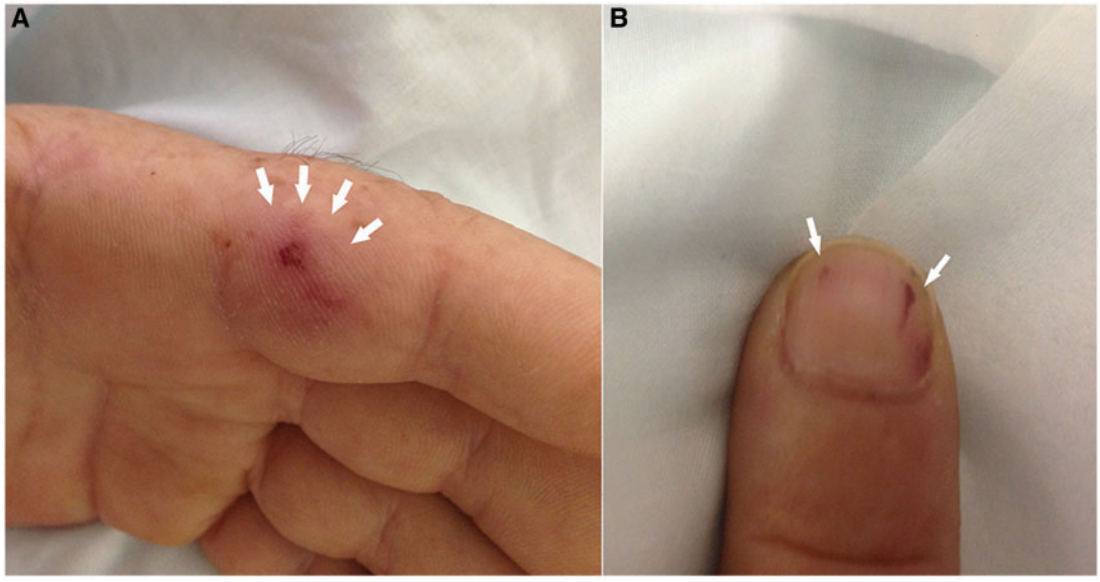


Figure 1 (*A*) Janeway lesion (white arrows) and (*B*) splinter haemorrhages (white arrows).

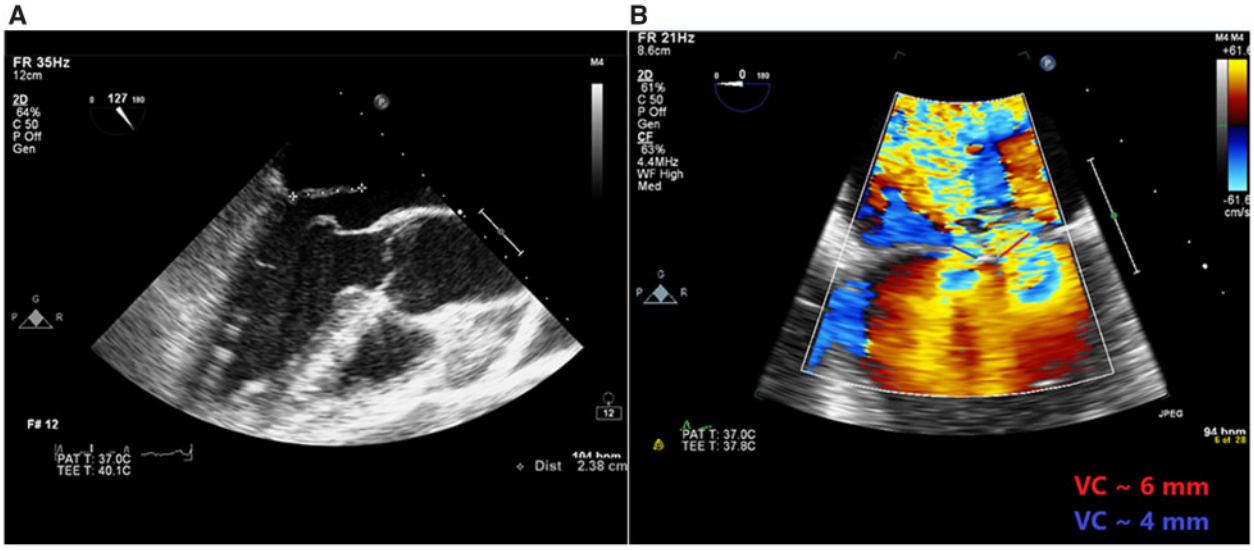
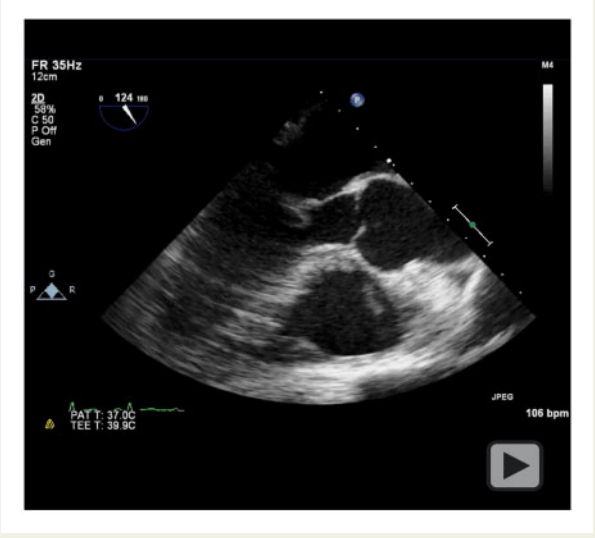
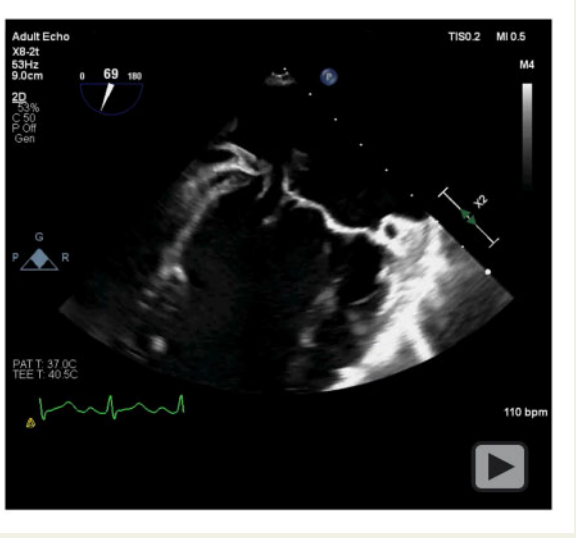


Figure 2 (*A*) Long-axis midoesophageal transoesophageal echocardiography view demonstrating large vegetations (maximum diameter of ~2.4 cm) on the mitral valve and (*B*) four-chamber midoesophageal transoesophageal echocardiography view zoomed in the mitral valve with colour showing two large mitral regurgitation jets (vena contracta of 6 and 4 mm) due to deformation of the valve from infective endocarditis.

(*Figure 1*). Based on these findings IE was strongly suspected. Same day transthoracic (TTE) and transoesophageal echocardiography (TOE) demonstrated large vegetations (maximum diameter of the largest vegetation ~2.4 cm—*Figure 2A*) on the mitral leaflet that resulted in severe valve regurgitation (severe valve deformation with multiple regurgitation jets, systolic flow reversal in the pulmonary veins, vena contracta ~6 mm of the largest mitral regurgitation jet) further supporting this hypothesis (*Figure 2B* and *Video 1*). Infective endocarditis was confirmed when blood cultures grew *Staphylococcus aureus*. Proper antibiotic treatment was started. The patient remained



Video 1 Long-axis midoesophageal transoesophageal echocardiography view demonstrating severely damaged mitral valve with large vegetations on it.



Video 2 Bicommissural midoesophageal transoesophageal echocardiography view demonstrating a large vegetation and perforation of the mitral valve.

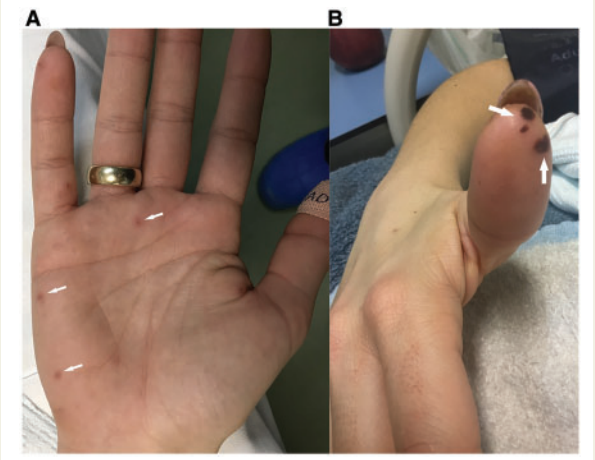
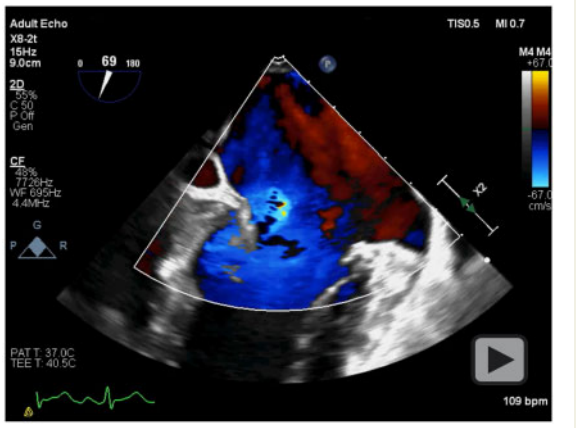


Figure 3 (*A*) Multiple Janeway lesions (white arrows) and (*B*) Osler's nodes (white arrows).



Video 3 Bicommissural midoesophageal transoesophageal echocardiography view with colour Doppler showing regurgitation through perforation of the mitral valve.

haemodynamically stable, with mild congestive heart failure symptoms controlled with low-dose diuretics. He was offered urgent surgical treatment to avoid further embolization which he denied. The rest of his clinical course was uncomplicated and after 6 weeks of antimicrobial therapy he underwent replacement of his mitral valve with a mechanical prosthesis due to persistent severe mitral regurgitation. Patient was seen in the clinic 6 months after discharge. He was doing well and a TTE showed a well-functioning prosthetic mitral valve.

Patient 2

A 33-year-old female patient with no previous medical history was referred to our hospital due to persistent fever, fatigue, and left arm weakness. Patient reported having a dental procedure 6 weeks before the onset of symptoms. Physical examination revealed non-tender macular lesions on palms and soles and painful nodular violaceous skin lesions on fingers and toes, recognized as Janeway lesions and Osler' s nodes, respectively (*Figure 3*). These findings

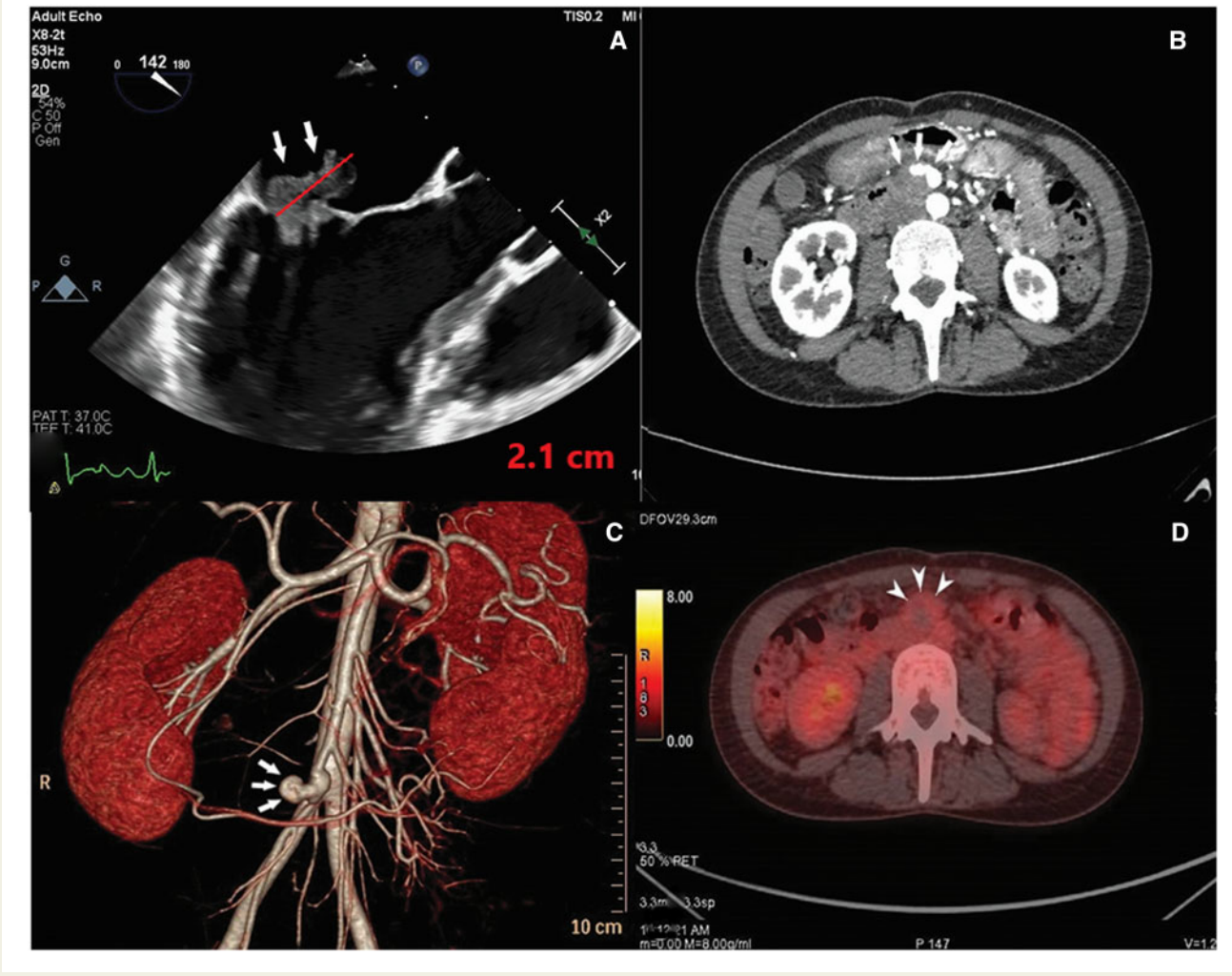


Figure 4 (*A*) Long-axis midoesophageal transoesophageal echocardiography view demonstrating large vegetations (white arrows) on the mitral valve; (*B*) mycotic aneurysm of the superior mesenteric artery on axial computed tomography images of the abdomen (white arrows); (*C*) reconstructed 3D image showing the mycotic aneurysm (white arrows); and (*D*) no signs of active inflammation of the aneurysm were seen on PET scan imaging.

combined with a harsh apical holosystolic murmur and left arm palsy strongly pointed to a diagnosis of IE. Urgent TTE followed by TOE revealed large vegetations (maximum diameter of ∼2.1 cm—*Figure 4A*) on the mitral valve, with posterior leaflet perforation resulting in severe (systolic flow reversal in the pulmonary veins) mitral regurgitation (*Videos 2 and 3* and Supplementary material online, *Video S1*). The mitral valve had no signs of Barlow's disease or previous rheumatic injury. The left ventricle (LV) had normal size and was hyperdynamic with normal ejection fraction (EF). Blood cultures grew *S. aureus*, establishing the diagnosis of IE. Whole-body CT and brain MRI revealed multiple cerebral and spleen emboli. Persistence of fever despite antibiotic treatment and haemodynamic instability due to heart failure and ventricular arrhythmias led to urgent cardiothoracic intervention on the 13th day of hospitalization. The vegetations were excised and the mitral valve was replaced with a mechanical prosthesis. The patient's early post-operative course was complicated with post-pericardiotomy syndrome treated successfully with colchicine and corticosteroids. Four weeks after mitral valve replacement and while being on antibiotic treatment the patient complained of abdominal pain. Repeat abdominal imaging revealed a mycotic aneurysm of the superior mesenteric artery without signs of active inflammation on subsequent Positron emission tomography (PET) scan imaging (*Figure 4B–D*). Patient refused surgical treatment of the aneurysm and a conservative approach was adopted. She remained clinically stable and was discharged home a few days later. At 6-month follow-up, the patient was asymptomatic with good

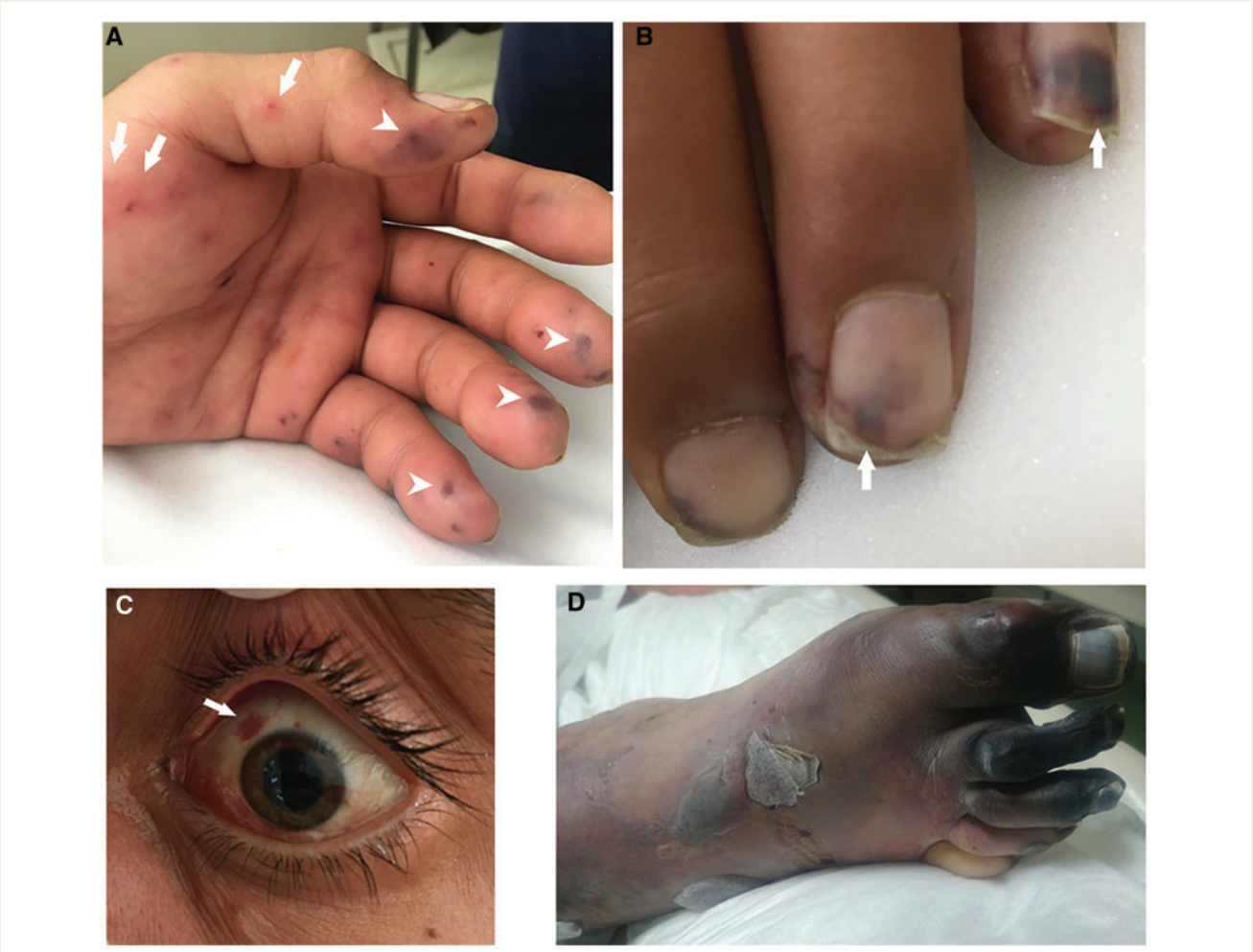


Figure 5 (*A*) Multiple Janeway lesions (white arrows) and Osler's nodes (white arrowheads); (*B*) splinter haemorrhages (white arrows); (*C*) conjunctival haemorrhage; and (*D*) gangrene of the right foot.

function of the mechanical mitral valve and the aneurysm remained stable in size.

Patient 3

A 36-year-old male, with a history of intravenous drug abuse, was referred to the ER with altered mental status. He had fever and progressive shortness of breath for several days before admission. The patient was critically ill with hypotension, tachycardia, tachypnoea, and hypoxaemia; his Glasgow coma scale was 8/15. On clinical examination, petechiae, splinter haemorrhages, Janeway lesions, and Osler's nodes on upper and lower extremities were evident (*Figure 5A and B*). Conjunctival haemorrhages were also noted (*Figure 5C*). Cardiac auscultation revealed a diastolic murmur best heard at the left sternal border. Arterial blood gases revealed severe lactic acidosis. An urgent whole-body CT demonstrated multiple spleen, renal, and brain infarcts suggestive of septic emboli. Subarachnoid haemorrhage was also seen. Due to high suspicion of IE, a TOE was performed that revealed mobile vegetations (maximum diameter of ∼1.1 cm—*Figure 6A* and Supplementary material online, *Video S2*) on the aortic valve which was bicuspid. Severe acute regurgitation of the aortic valve was also noted [Vena contracta (VC) ∼5 mm, holodiastolic flow reversal in the descending aorta—*Figure 6B*]. The LV had normal size and normal EF. Patient was intubated and transferred to the intensive care unit for further advanced support. Blood cultures grew *S. aureus*. Fundoscopy revealed multiple Roth's spots in both retinas. Three days later, embolization of his right distal lower limb occurred which rapidly evolved to gangrene (*Figure 5D*). Despite all efforts the patient continued to deteriorate and died of multiorgan failure on the 11th day of hospitalization.

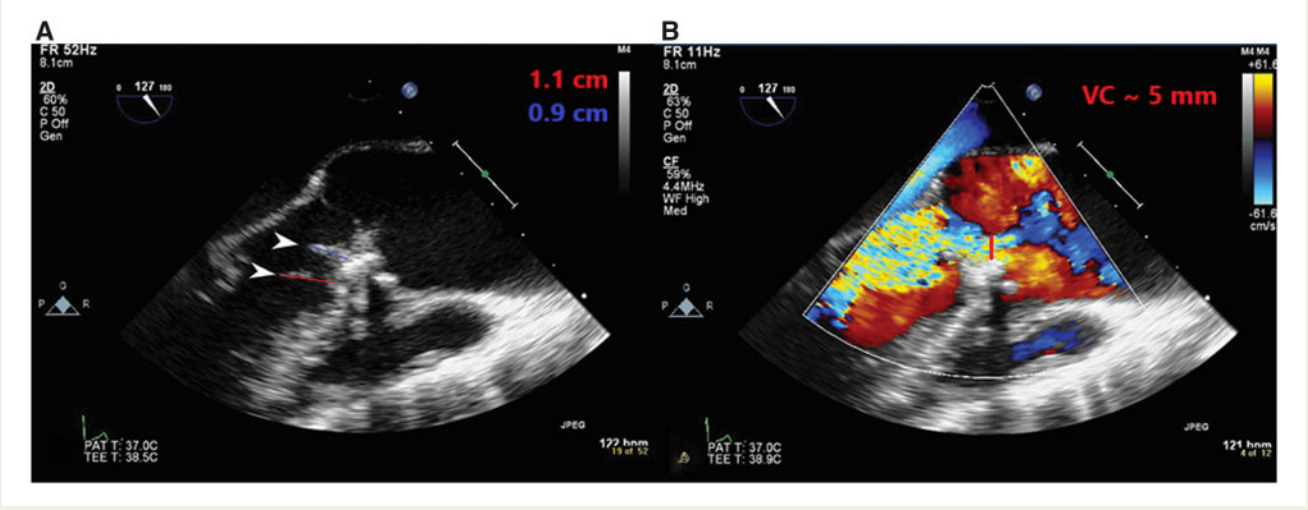


Figure 6 (*A*) Long-axis midoesophageal transoesophageal echocardiography view zoomed in the aortic valve showing vegetations (white arrowheads) on the aortic valve and (*B*) resultant severe aortic regurgitation (vena contracta ~5 mm).

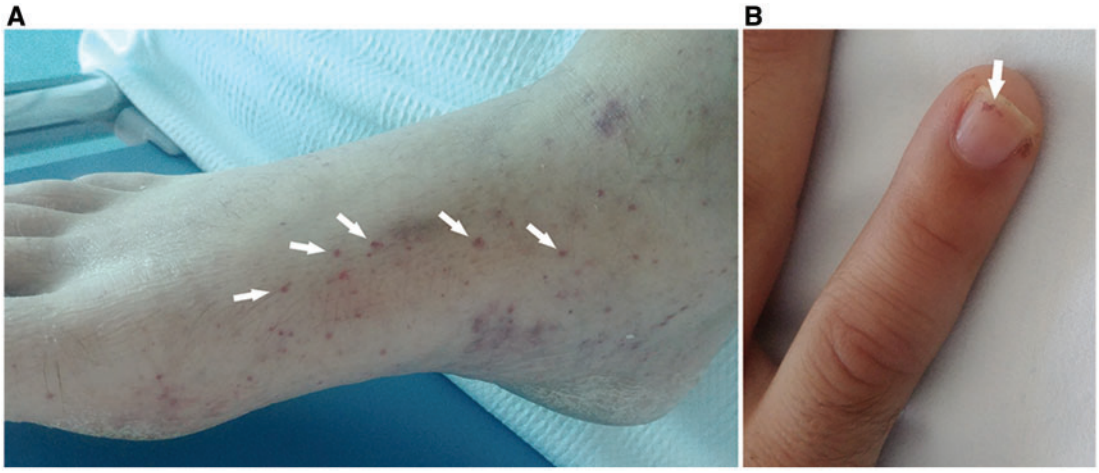


Figure 7 (*A*) Multiple petechiae (white arrows showing most representative ones) and (*B*) splinter haemorrhage (white arrow).

Patient 4

A 35-year-old male, with a history of intravenous drug abuse, presented to the ER due to persistent fever and fatigue commencing 3 weeks ago. On admission, the patient was haemodynamically stable and conscious. On physical examination, multiple petechiae of the lower extremities and splinter haemorrhages of the nail beds were observed (*Figure 7*). Cardiac auscultation revealed a diastolic murmur best heard at the Erb's point. The laboratory workup revealed elevated inflammation markers. Due to high suspicion of IE, a TOE was immediately performed revealing mobile vegetations (maximum diameter of 7 mm) on the aortic valve (*Figure 8A* and Supplementary material online, *Video S3*). The aortic valve was deformed and had severe regurgitation (VC ~6 mm, holodiastolic flow reversal in the descending aorta—*Figure 8B*). The LV was mildly dilated with normal EF. Blood cultures were positive for *S. aureus*. Despite the lack of specific symptoms, a whole-body CT demonstrated multiple cerebral and renal infarcts (*Figure 8C*). On Day 4 of his hospitalization, the patient complained of severe headache of abrupt onset that was followed by seizures. An urgent head CT revealed intracerebral haemorrhage likely due to haemorrhagic transformation of a septic embolus (*Figure 8D*). Despite these worrying findings on imaging the patient had a remarkably good neurological status and responded well to conservative treatment. The rest of his in-hospital course was uncomplicated. After 5 weeks of antimicrobial therapy, he underwent

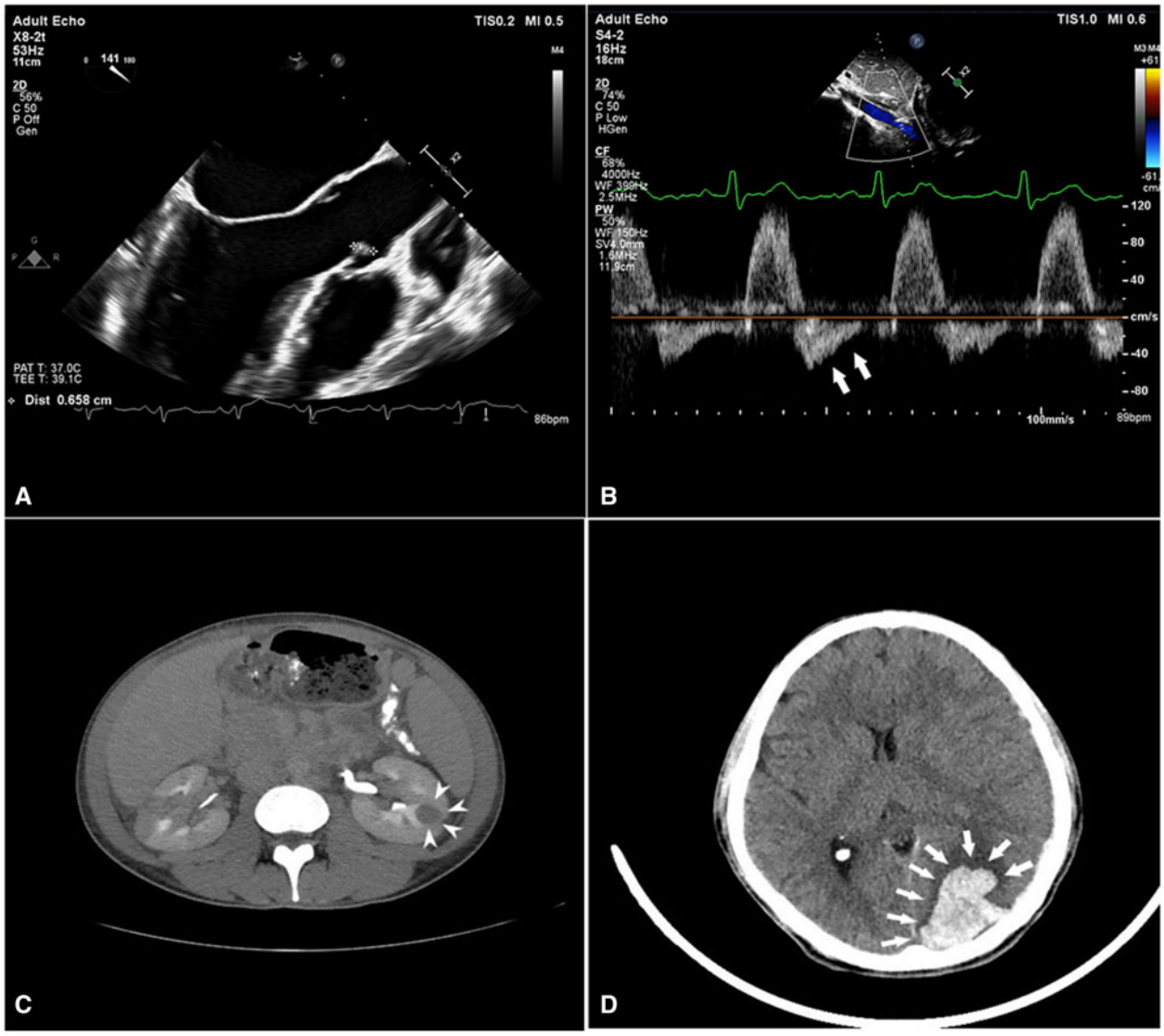


Figure 8 (*A*) Long-axis midoesophageal transoesophageal echocardiography view demonstrating vegetations on the aortic valve; (*B*) holodiastolic flow reversal in the abdominal aorta (white arrows) indicating severe aortic regurgitation; (*C*) left kidney infarct on abdominal computed tomography (white arrowheads); and (*D*) intracerebral haemorrhage on head computed tomography (white arrows).

successful replacement of his aortic valve with a mechanical prosthesis. At 3-month follow-up the patient was asymptomatic with good function of the aortic valve prosthesis.

Discussion

We report four cases of complicated IE hospitalized in our hospital within a 12-month period. All patients were young and had skin manifestations on initial presentation (mainly petechiae, splinter haemorrhages, and Janeway lesions) which in the appropriate clinical context (fever, cardiac murmur, neurological manifestations) led to a high clinical suspicion of IE that was subsequently readily diagnosed with echocardiography and positive blood cultures. Interestingly in the first patient failure to hear the murmur and detect the skin manifestations on admission led to a delay in diagnosis of IE only after an embolic stroke had occurred, underscoring the importance of thorough clinical examination in such patients. This is particularly important in the current era where the value of complete clinical examination has been largely replaced by the ease of ordering imaging tests.

Cutaneous manifestations of IE have been long described with petechiae and splinter haemorrhages seen in 20–40% of such patients.[3] These findings, however, are not specific for IE and can be

seen in a variety of other diseases.[4] On the other hand, Janeway lesions and Osler's nodes are relatively uncommon manifestations but highly suggestive of IE. Interestingly, in the pre-antibiotic era Osler's nodes were present in 40–90% of cases of endocarditis, whereas in the late 1980s they were seen in 10–23% of cases of endocarditis and in the contemporary era are encountered in <10% of patients with IE.[5] Similarly, the incidence of Janeway lesions in most recent studies range from 1.6% to 4.7% of all IE cases.[6,7] This reduction is most likely due to both use of antibiotics and earlier diagnosis of IE with advancement of imaging, which do not allow time for the cutaneous manifestations to develop. Missing skin lesions in IE patients due to degradation of doctors' clinical skills nowadays may have also played a role.

Janeway lesions were first described in 1899 by Janeway,[8] in the context of the differential diagnosis between IE and other infectious disorders. In 1906, Libman,[9] a student of Janeway, applied the eponym 'Janeway lesions'. These lesions usually present as erythematous, painless macules, and papules on the palms and soles. Osler's nodes on the other hand are tender subcutaneous violaceous nodules mostly on the pads of the fingers and toes, which may also occur on the thenar and hypothenar areas. Osler's nodes have an average diameter of 1–1.5 mm. The pain usually precedes nodule development, and they disappear in hours to days, leaving no sequelae.[5] Histologic reports suggest that both lesions are the result of septic microemboli, forming necrotic dermal microabscesses. Localized immune-mediated vasculitis has also been implicated in the pathogenesis of Osler's nodes.[10–12] Their appearance is often coincident with systemic embolization as seen in all of our patients. Both lesions overlap clinically and histologically and pain/tenderness is likely the most useful parameter to differentiate between the two.[13]

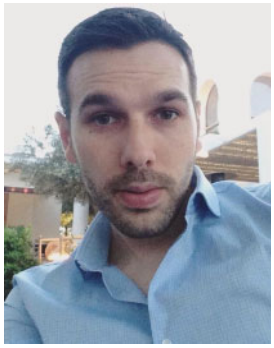
Rarely, cutaneous microembolism similar to Janeway lesion may be found in other diseases like systemic lupus erythematosus, eosinophilic endocarditis, non-bacterial thrombotic endocarditis, myxoma, and rheumatic fever.[14–18] In the majority of cases, differential diagnosis between IE and the above entities can be easily made based on clinical presentation, the presence of positive blood cultures, and imaging. The modified Duke criteria are the gold standard and can be helpful in establishing the diagnosis of IE. Of note, both Janeway lesions and Osler's nodes are considered a minor criterion in the modified Duke criteria.[19] Therefore, despite their rarity, when found they should prompt investigations towards a diagnosis of IE, as seen in all of our cases.

Skin manifestations may also carry prognostic implications. Limited data suggest that cutaneous manifestations are associated with higher rate of IE-related extracardiac complications which are known to adversely affect prognosis.[6,20] In our case series all patients had embolic phenomena and one died due to uncontrolled, complicated sepsis (Patient 3). The other three patients had a complicated course but they survived after being operated either on an urgent (Patient 2) or more elective basis (Patients 1 and 4).

Although no clear relationship has been established between specific IE skin lesions and a responsible microorganism, in all of our cases, blood cultures grew *S. aureus*. This is not surprising as it has been shown that *S. aureus* is associated with an increased risk of embolic events.[20]

In conclusion, clinicians should always assess for skin manifestations in patients with fever especially when suspicion of IE is high. Presence of Janeway lesions and Osler's nodes in this setting should prompt investigations for the diagnosis of IE with no further delay. Occurrence of skin lesions may also be associated with higher rate of complications.

Lead author biography



Christos Gogos is a Senior Resident, Cardiology Division, Papageorgiou Hospital, Thessaloniki, Greece

Supplementary material

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

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

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patients in line with COPE guidance.

Conflict of interest: None declared.
Funding: None declared.

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