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CASE REPORT
Other

Can chronic anti-tumour necrosing factor therapy and colic polyps overwhelm a normal functioning mitral valve? A case report of an endocarditis complicated by a ruptured intracranial mycotic aneurysm

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Background Rapid identification of endocarditis is challenging but also an important opportunity to change disease course. This is especially true when immunosuppression undermines diagnosis by mitigating symptoms that commonly accompany infectious disease, sometimes in the absence of predisposing heart valve disease as in this case presented here.

Case summary A middle-aged man with chronic etanercept treatment for ankylosing spondylitis, with previously well-documented normal cardiac valves, presented with afebrile chills, night sweating, weight loss, and a new mitral regurgitation at auscultation. This *Streptococcus bovis*-related endocarditis, in the presence of benign colic polyps, rapidly became complicated by a ruptured infectious intracranial mycotic aneurysm. The patient was successfully cured by endovascular embolization. Severe mitral regurgitation required an uneventful mitral annuloplasty 1 month thereafter.

Discussion Immunosuppression from etanercept treatment was likely responsible for this unspecific clinical presentation and potentially devastating intracranial mycotic aneurysm. This complication is infrequently reported within 6 months of anti-tumour necrosing factor therapy initiation but occurred after more than 11 years of therapy in our patient. This case is a timely reminder of the clinical challenges of endocarditis in immunosuppressed patients and highlights a potential long-term complication of etanercept.

Keywords *Streptococcus bovis* • Mitral endocarditis • Sub-arachnoid haemorrhage • Mycotic aneurysm • Etanercept • Case report

ESC Curriculum 2.2 Echocardiography • 2.1 Imaging modalities • 4.3 Mitral regurgitation • 4.11 Endocarditis

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Learning points

- Endocarditis in the presence of immunosuppression carries a risk of delayed diagnosis and poor prognosis.
- This remains a concern even after many years of antitumor necrosis factor therapy, as this case report of a *Streptococcus bovis*-mediated endocarditis in the presence colic polyps reveals.
- Neurological symptoms will require immediate imaging to detect intracranial infectious aneurysms and endovascular/surgical procedure if appropriate.

Introduction

Early infective endocarditis (IE) diagnosis is a challenge for clinicians due to the diversity in its clinical presentation. This is especially true for immunocompromised patients who may not present classical symptoms, have a higher risk for complications, and a worse prognosis.[1] Despite progress in disease diagnosis and management, intra-hospital IE mortality remains between 15% and 30%.[1] Complications which most impact mortality are acute heart failure and haematogenous dissemination of septic emboli, most of which are cerebral or abdominal. In terms of neurological complications, IE may lead to the formation of intracranial mycotic aneurysms, haemorrhage, or acute cerebral ischaemia. The diagnosis and management of such lesions are difficult because cerebral embolisms have an influence on treatment but 80% are asymptomatic.[1] We present the case of a 56-year-old patient treated by anti-tumour necrosis factor (TNF) therapy who developed sub-acute endocarditis from a *Streptococcus bovis* infection on a previously well-documented normal mitral valve, which became complicated by an acute sub-arachnoid haemorrhage from a ruptured mycotic aneurysm.

Timeline

Date	Events
2010	Ankylosing spondylitis treated by etanercept
18 October 2016	Methylprednisolone infiltration for painful left shoulder.
08 November 2016	The onset of the symptoms: chills and night sweating.
18 November 2016	Penicillin therapy against *Streptococcus bovis*-mediated sub-acute mitral endocarditis
22 November 2016	Severe headache due to sub-arachnoid Haemorrhage as a result of a ruptured intracranial mycotic aneurysm treated by endovascular embolization.
01 December 2016	Increase in vegetation size and mitral regurgitation.
5 December 2016	Colonoscopy: two benign hyperplasic sessile colic polyps
15 December 2016	Uneventful mitral annuloplasty
30 December 2016	Discharged from hospital and return home
17 January 2017	The patient complained of tiredness. A repeated echocardiogram showed a normal functional mitral valve

Case presentation

The patient complained about chills and night sweating for 10 days. Local corticoid infiltrations in relation to a shoulder tendinopathy had been administered 20 days prior to symptom onset. He also noticed a loss of 8 kg in 1 month with a mild diet. His medical history included treatment for ankylosing spondylitis by etanercept and a triple therapy for arterial hypertension: amlodipine 10 mg, lisinopril 20 mg, and nebivolol 5 mg once a day. He was also taking atorvastatin 20 mg once a day for a dyslipidaemia. The relevant elements of the physical examination were a regular tachycardia of 91 beats per minute, and a new left parasternal holosystolic murmur radiating to the back and the liver edge was palpable 2 cm below the costal margin. The patient was afebrile. There was no clinical sign of heart failure and the neurological exam was normal. A blood test showed normocytic anaemia and moderate inflammatory syndrome. An electrocardiogram showed sinus tachycardia. Cardiac transthoracic and transoesophageal echography showed an 8 mm vegetation on the anterior mitral commissure complicated by a moderate mitral insufficiency with an eccentric regurgitation jet, which was difficult to quantify. Left ventricular function remained preserved. Blood cultures indicated an ampicillin-sensitive *S. bovis* infection. A diagnosis of sub-acute endocarditis was retained, and 2 g of intravenous ampicillin was administrated six times per day starting from admission. Etanercept therapy was suspended. Digestive assessment by computed tomography (CT) scan, gastroscopy, and colonoscopy showed the presence of hepatomegaly and two benign colic polyps. Colonoscopy had not previously been performed. During the first few days of hospitalization, intravenous antibiotic therapy was accompanied by a favourable outcome, including resolution of the inflammatory syndrome and improvement of the symptoms. On the fourth day, the patient suddenly complained about headache without focal neurological sign. A cerebral CT scan showed significant sub-arachnoid haemorrhage (Fischer III) (*Figure 1*). Urgent cerebral arteriography demonstrated a ruptured intracranial mycotic aneurysm in the left cerebral posterior artery which was successfully treated by endovascular embolization. From discussion with the multi-disciplinary endocarditis team, it was decided to opt for a surgical treatment for the mitral endocarditis. However, in consideration of the high risk of haemorrhagic expansion due to the anticoagulation needed for cardiopulmonary bypass, the intervention was postponed.

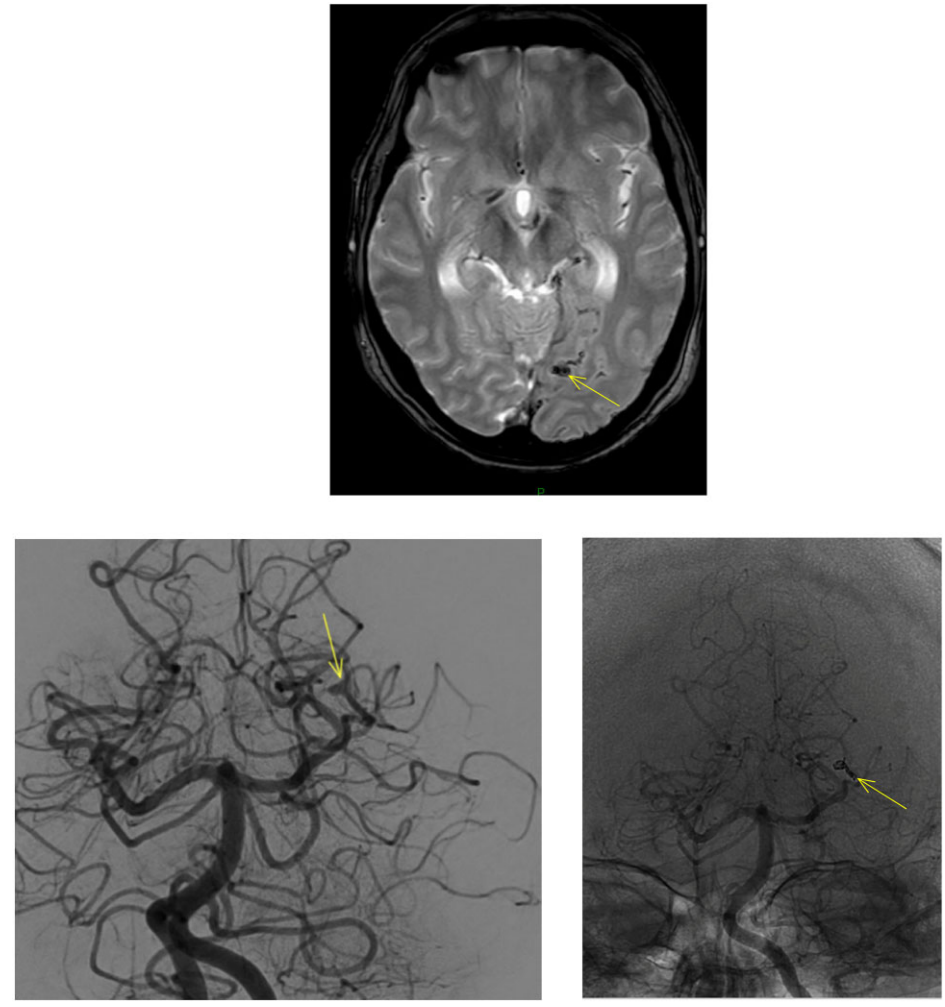


Figure 1 Brain magnetic resonance imaging showed in a T2-enhanced steady-state gradient echo sequences a left internal occipital sub-arachnoid haemorrhage (upper panel, indicated by the arrow) and cerebral angiography demonstrated a mycotic aneurysm of the left cerebral posterior artery before (lower left panel, aneurysm indicated by the arrow) and after endovascular coiling (lower right panel, coil indicated by the arrow).

The mitral vegetation size increased from 8 mm to 13 mm (*Figures 2* and *3* and *Video 1*) and transosophageal cardiac echography indicated a worsened mitral insufficiency (*Video 2*). Also, a moderate left atrium and ventricle dilatation appeared, with increased filling pressures. Three weeks after cerebral bleeding, haemorrhagic lesions decreased, and the mycotic aneurysm remained under control. Further echographic evidence of IE progression and clinical deterioration were noticed. The endocarditis team decided to proceed with surgical treatment on the 34th day of hospitalization which consisted in excision of the vegetations, partial leaflet resection, reconstruction by pericardial patch, and ring annuloplasty.

Post-surgical evolution was free of any complications, there was no valvular regurgitation (*Figure 4*), and the vegetation culture was negative. In total, the intravenous antibiotic treatment lasted 6 weeks and the patient then returned home.

A month later, the patient complained only of tiredness, there was no clinical sign of heart failure and the neurological exam was also normal. A repeated echocardiogram showed a normal functional mitral valve. Etanercept was restarted 3.5 months thereafter.

Discussion

Etanercept, along with infliximab and adalimumab, are anti-TNF treatments that are regularly used in rheumatology for their anti-inflammatory effects. However, inhibition of the inflammatory process exposes patients to increased risk of bacteraemia, reactivation of tuberculosis, opportunistic infections, and endocarditis. Although endocarditis is mentioned among complications of anti-TNF treatment, it occurs only rarely. Amongst a few reported cases, the organisms involved were *Listeria monocytogenes*,[2] *Staphylococcus aureus*,[3] as well as *Tropheryma whipplei*.[4] In those cases, the onset of endocarditis was mostly observed within 6 months following the initiation of anti-TNF therapy whereas in our case it occurred after 11 years of such

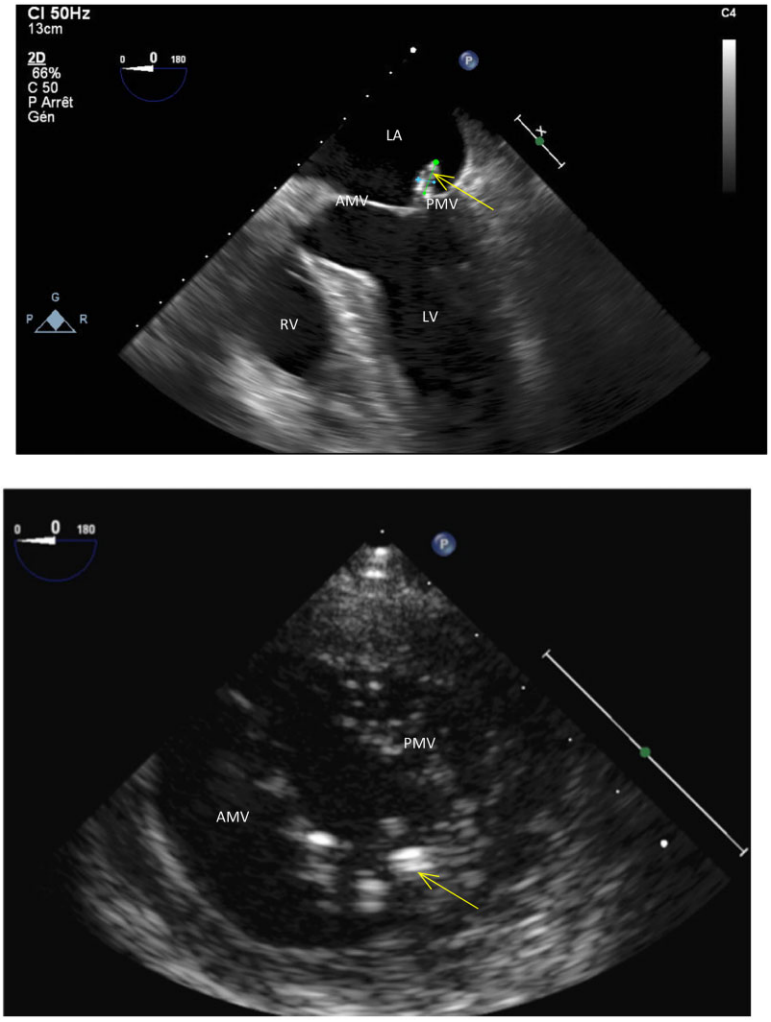


Figure 2 Transoesophageal echocardiography at J1: 8 mm vegetation on the anterior leaflet of the mitral valve in a zoom view at 0° (upper panel, vegetation indicated by the arrow) and in transgastric view (lower panel) showing the vegetation insertion point near the anterior commissure (indicated by the arrow). Anatomical landmarks: AMV, anterior mitral valve; LA, left atrium; LV, left ventricle; PMV, posterior mitral valve; RV, right ventricle.

therapy. The *S. bovis*-mediated endocarditis documented in our patient is typically associated with colon cancer and benign polyps,[5] the latter of which was documented in our patient. Ruptured mycotic aneurysms in *S. bovis*-mediated endocarditis are, however, rare. Our review on PubMed using the items 'aneurysm', 'mycotic', and '*S. bovis* endocarditis' found only 10 cases reporting a mycotic aneurysm in *S. bovis*-mediated endocarditis (*Table 1*). Most of these patients were middle-aged men. In addition, 36% of the patients were immunocompromised, as in our patient. The aneurysms were most frequently located in cerebral, abdominal, and peripheral arteries, respectively. Amongst the patients with an intracranial mycotic aneurysm, 83% presented ruptured aneurysm and mortality was 17%. The most common treatment was endovascular embolization followed by conservative treatment and neuro-surgery.

In conclusion, this is a unique case of *S. bovis*-mediated endocarditis complicated by a ruptured intracranial mycotic aneurysm in the presence of chronic anti-TNF therapy, possibly as a result of the appearance of colic polyps.

Given that more than half of patients with ankylosing spondylitis have colonoscopic evidence of at least occult inflammatory bowel disease,[16] performing a systematic colonoscopy in such patients may be helpful to identify potential portals of entry for IE and to prevent its complications. Also, this case illustrates the associated risk carried by such therapy on the emergence of endocarditis on normal native valves, followed by an unforeseen ruptured intracranial mycotic aneurysm. Clinicians should be aware of the occurrence of neurological complications in immunocompromised patients with endocarditis. Therefore, it is recommended to proceed to a multi-disciplinary management using cerebral imaging in this patient group.[1] However, due to the lack of randomized trials on the timing of cardiac surgery in patients with such complications, a case-by-case decision is necessary. An earlier intervention in this patient, when the intracranial

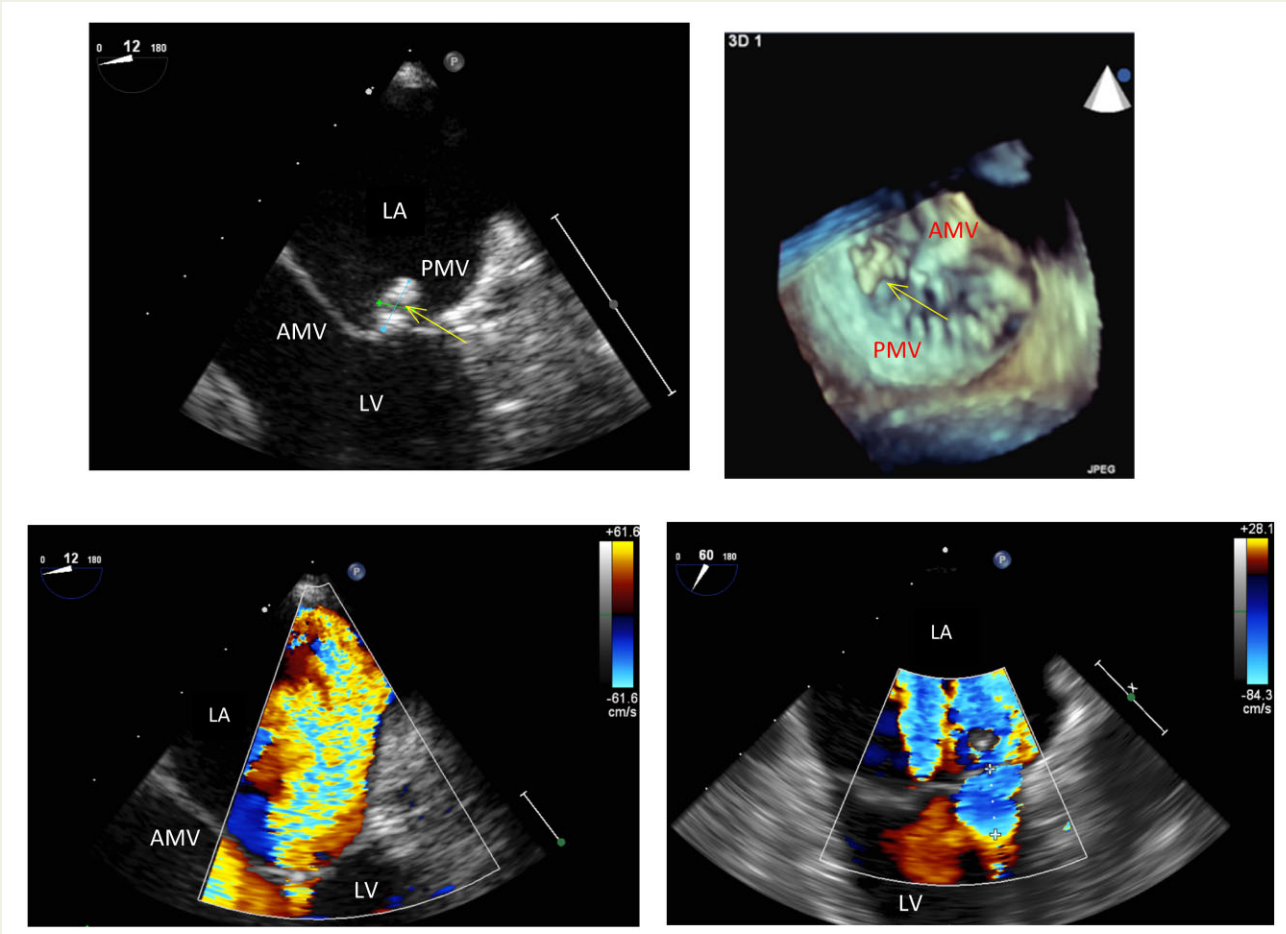
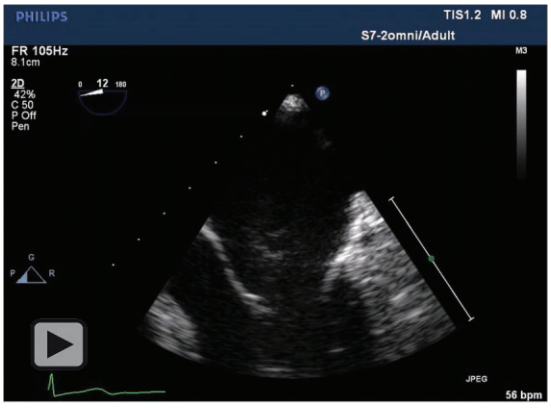
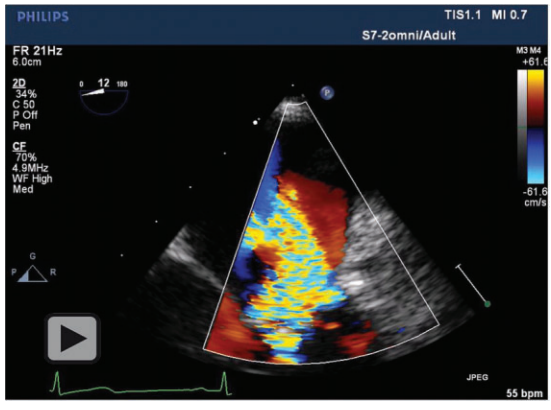


Figure 3 Transoesophageal echocardiography at J10 revealed a 13 mm vegetation on the anterior leaflet of the mitral valve in a commissural view 60° with a 3D reconstruction showing the insertion on the A1 segment near the anterior commissure (upper left and right panels, vegetation indicated by the arrow). Colour Doppler rayon PISA 14 mm in favour of severe mitral insufficiency (lower left and right panels). Anatomical landmarks: AMV, anterior mitral valve; LA, left atrium; LV, left ventricle; PMV, posterior mitral valve.



Video 1 Transoesophageal echocardiography mid-oesophageal incidence showing mitral vegetation.



Video 2 Transoesophageal echocardiography mid-oesophageal incidence showing severe mitral regurgitation.

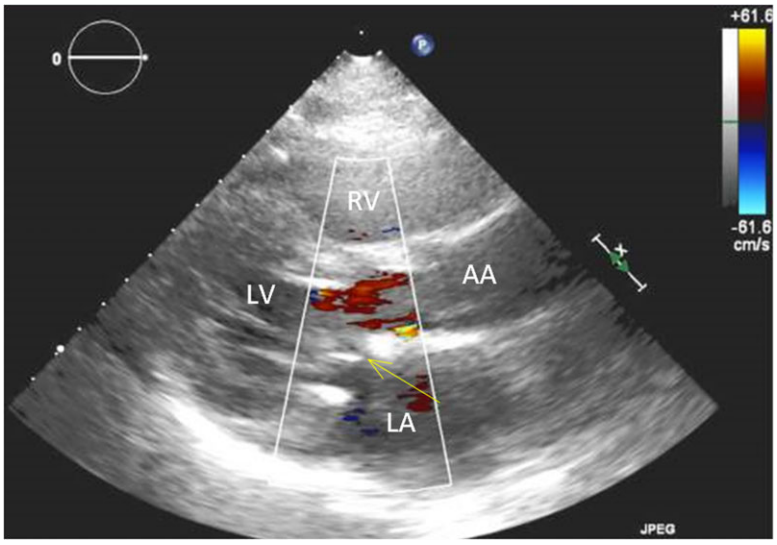


Figure 4 Longitudinal long-axis transthoracic echography after an uneventful vegetation excision, partial leaflet resection, and reconstruction by pericardial patch and ring annuloplasty (the latter is indicated by the arrow). Traces of colour Doppler flow in the left atrium indicates severe mitral regurgitation resolution after surgery. Anatomical landmarks: AA, ascending aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

Table 1 **Cases of mycotic aneurism in *Streptococcus bovis* endocarditis**

	Authors (years)	Age/sex	IC	Valve	MA location	Complication	Treatment	Dead/alive
1	Spring *et al.* (2020)[6]	44/M	Yes	MVN	Multiple intra and extra-abdominal vessels	/	Embolization	Alive
2	Poletti *et al.* (2000)[7]	47/M	Yes	MVN	Ileo-colic artery	Intra-abdominal bleeding	Embolization	Alive
3	Mittermayer *et al.* (1983)[8]	65/W	No	TVN & AVN	Left median cerebral artery	Cerebral bleeding	Conservative	Dead
4	Menanteau *et al.* (1995)[9]	78/M	No	NA	Postero-tibiale artery	/	Resection	Alive
5	Lobo *et al.* (2011)[10]	49/M	No	MVN	Brachial artery	/	Resection	Alive
6	Gonzalez *et al.* (2005)[11]	68/M	Yes	AVP	Cerebral artery	Parietal Haemorrhage	Conservative	Alive
7	Chai *et al.* (2010)[12]	46/M	No	MVN	Distal superior mesenteric artery	/	Resection	Alive
8	Boukobza *et al.* (2018)[13]	54/M	No	AVN	Distal right posterior cerebral artery	Subdural haematoma	Embolization	Alive
9	Attias *et al.* (2012)[14]	54/M	NA	AVN	Distal cerebral artery	/	Embolization	Alive
10	Almeida *et al.* (2016)[15]	65/W	No	MVN and BA	Left middle cerebral artery	Sub-arachnoid and intra-parenchymal Haemorrhage	Neuro-surgery	Alive
11	Our Case (2021)	56/M	Yes	MVN	Left cerebral posterior artery	Sub-arachnoid and intra-parenchymal Haemorrhage	Embolization	Alive

AVN, aortic valve native; AVP, aortic valve prosthetic; BA, brachial artery; F, female; M, male; MVN, mitral valve native; NA, not available.

mycotic aneurysm was asymptomatic, carried an unknown risk of a devastating rupture upon anticoagulation for cardiopulmonary bypass.

Lead author biography

My name is Karim Khadir. Originated from Morocco, I am a young resident in cardiology at 'Université Libre de Bruxelles' passioned about valvular disease, coronaropathy, and echocardiography.

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: The authors confirm that written consent for the submission and publication of this case, including images, has been obtained from the patient in line with COPE guidance. Institutional review board approval weas obtained under the number P2021/115. The data underlying this article are available in the article and in its online supplementary material.

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