

# Normal procalcitonin, C-reactive protein, and negative blood cultures in infective endocarditis with a massive residual vegetation: a case report

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## Background

Infective endocarditis (IE) is a serious infection with high morbidity and mortality that involves the endocardial lining of the heart. Most cases of IE are due to bacteria although other atypical micro-organisms can also be involved. Procalcitonin (PCT) is a biomarker that is used in the diagnosis of bacterial infections.

## Case summary

We present the case of a 54-year-old patient with bacterial endocarditis who has been regularly visiting his cardiologist for follow-up on a mitral valve prolapse and moderate mitral regurgitation (MR) for the last 11 years. During his last visit, transthoracic echocardiography (TTE) showed a previously non-existent structure on the posterior mitral valve leaflet with severe MR. Blood cultures were positive for *Streptococcus viridans*. On admission, he had elevated levels of PCT and C-reactive protein which returned to normal values after 4 weeks of intravenous antibiotic therapy. His follow-up blood cultures, taken after normalization of PCT, did not show bacterial growth; however, on TTE he had severe mitral regurgitation and a persistent vegetation which had slightly increased in size after completion of the full antibiotic course. He was referred for mitral valve replacement surgery.

## Discussion

Normalization of procalcitonin levels may correlate with negative blood cultures in cases of IE with residual vegetations. The optimal time for surgery in such patients is difficult to define but even in circumstances with less infective organisms such as *S. viridans* and late in the course of the disease residual vegetations remain a serious risk factor for embolic events. Randomized controlled clinical trials are needed in order to have better recommendations with solid evidence regarding prophylaxis and treatment in IE.

## Keywords

Endocarditis • Procalcitonin • Residual vegetation • Case report

## Learning points

- Procalcitonin levels, C-reactive protein, and erythrocyte sedimentation rate can be within reference ranges in cases of residual vegetations in infective endocarditis.
- Procalcitonin normalization may indicate an appropriate time to take follow-up blood cultures when the goal is to eradicate bacteraemia.
- The decision whether to operate in cases of residual vegetations should be individualized. However, enlarging vegetations, and those >10 mm are indicated for surgery.

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## Introduction

Infective endocarditis (IE) is a serious infection of the endocardial layer of the heart with high morbidity and mortality that most commonly involves the heart valves. More than 80% of cases of IE with an identifiable pathogen are due to Streptococci and Staphylococci.<sup>1</sup> Due to the bacterial nature of the infection, increased levels of procalcitonin are usually observed in IE along with an increase in other markers of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

## Timeline

Date	Events
2009	Posterior mitral valve leaflet prolapse and mild to moderate mitral regurgitation first detected on transthoracic echocardiography (TTE)
2011	Posterior ST-elevation myocardial infarction treated with aspiration thrombectomy
November 2019	Last dental procedure (filling) before symptom onset
January 2020	Low grade fever up to 37.5°C and symptomatic treatment
February 2020	Antibiotic treatment with cefuroxime 500 mg b.i.d. started due to persistent low-grade fever, cough, and malaise
March 2020	Second antibiotic treatment
April 2020	Third antibiotic treatment
May 2020	Fever up to 38.5°C with negative RT-PCR and Rapid IgM/IgG tests for COVID-19 and fourth course of antibiotic therapy with clarithromycin sedimentation rate 500 mg/day
2 June 2020	Visit to cardiologist and admission to hospital after a mobile structure is detected on TTE
June–July 2020	Intravenous antibiotic therapy with vancomycin and ceftriaxone
10 July 2020	Transient ischaemic attack
16 July 2020	Mitral valve replacement

## Case presentation

We present the case of a 54-year-old patient with bacterial endocarditis who has been regularly visiting his cardiologist for follow-up on a mitral valve prolapse and mild to moderate mitral regurgitation (MR) for the last 11 years. Although the patient was not at high risk of developing IE and the 2009 ESC Guidelines on the prevention, diagnosis, and treatment of infective endocarditis did not recommend antibiotic prophylaxis in the patient, he was advised by his cardiologist that he underwent antibiotic prophylaxis for invasive manipulations including dental procedures.<sup>2</sup> The patient generally followed this

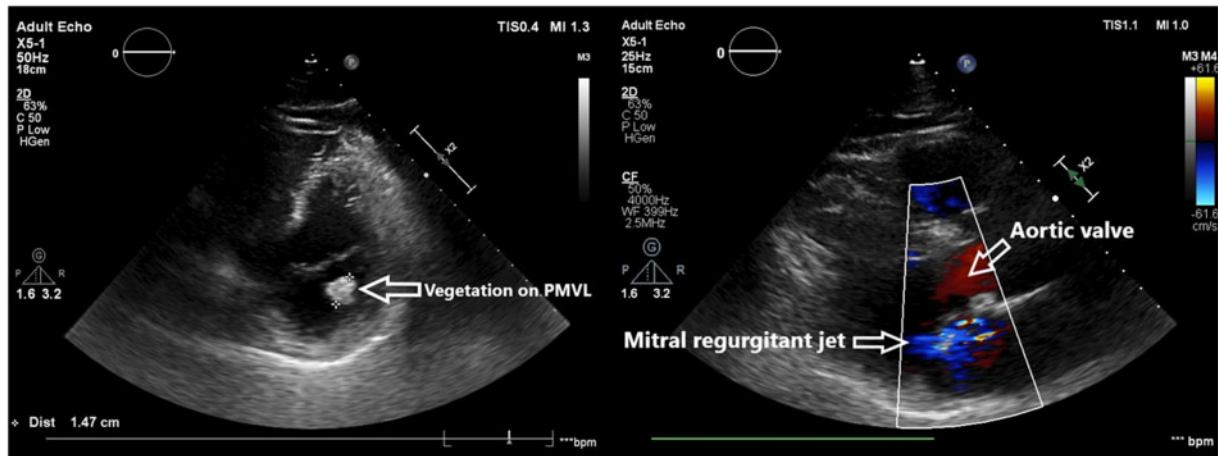
advice, and at the time of his current admission, his past medical history was insignificant except for a posterior ST-elevation myocardial infarction treated with aspiration thrombectomy in 2011. In November 2019, the patient visited his dentist for a dental procedure. Antibiotic prophylaxis was not used. In January 2020, the patient visited his primary care physician due to complaints of fever up to 37.5°C and cough. Symptomatic treatment was initiated with a reduction in temperature to around 36.9–37.0°C. In February, the patient made another visit to his primary care physician due to low-grade fever, persistent cough, and malaise. He was referred to a pulmonologist and antibiotic therapy with cefuroxime 500 mg b.i.d. was commenced with an initial positive effect. Due to relapse of symptoms in March and April, another two oral antibiotic courses were prescribed with little effect. In May 2020, after testing negative for COVID-19 in both Reverse transcription polymerase chain reaction (RT-PCR) and rapid IgM/IgG tests, he was prescribed his fourth course of antibiotic therapy with clarithromycin SR 500 mg/day. In the 2 weeks leading to the date of admission, his fever rose to 38.5°C and his cough became especially pronounced in the supine position which led his pulmonologist to refer him for a cardiology consult.

The patient was admitted to the intensive cardiac care unit after his transthoracic echocardiography (TTE) showed a previously non-existent structure on the posterior mitral valve leaflet (PMVL) with an increase in the severity of mitral regurgitation (see [Figure 1](#)). The patient did not report taking any medical therapy at the time of admission. His overall condition was satisfactory (see [Table 1](#)); his blood pressure was 125/81 mmHg and his heart rate 74 b.p.m. A pansystolic murmur could be heard at the apex with radiation to the left axilla. Peripheral oedema was not present. He was afebrile at first, and later during the day of admission, he developed a temperature of 37.7°C.

Three sets of blood cultures were taken and empiric antibiotic therapy was started with vancomycin and gentamicin in addition to intravenous furosemide. Five days later, the blood cultures came back positive for *Streptococcus viridans* which was sensitive to vancomycin and ceftriaxone but resistant to gentamicin. The patient had two major and two minor criteria (definite IE) according to the 2015 ESC Guidelines for the management of infective endocarditis.<sup>3</sup> On account of the large size of the vegetation, it was decided to continue the antibiotic therapy with both vancomycin and ceftriaxone. By the end of the first week, his fever and cough had subsided completely. Due to the size of the vegetation (approximately 15 mm × 10 mm), severe mitral regurgitation and the high risk of embolization assessed through TTE, it was recommended the patient underwent surgical mitral valve replacement (MVR) (Class IIa recommendation).<sup>3</sup> Nevertheless, the timing of surgery was decided to be elective (after completing a full antibiotic course), a decision based mainly on the positive therapeutic effect and the low risk of embolism (~7%) at 4 weeks after admission as assessed by using a symptomatic embolism risk calculator.<sup>4</sup>

After completing the 4-week antibiotic course, the patient's overall condition had improved which was also noticeable in the laboratory tests (see [Table 2](#)). The follow-up blood cultures, taken after normalization of PCT, did not show bacterial growth.

However, the surgical intervention was postponed for another 2 weeks due to a COVID-19 case in the department of cardiac surgery. While waiting for surgery the patient suffered a transient ischaemic



**Figure 1** Transthoracic echocardiography revealed a massive vegetation on the posterior mitral valve leaflet (PMVL) with a significant eccentric regurgitant jet (image on the left—parasternal short axis view; image on the right—parasternal long axis view). Transoesophageal echocardiogram was not performed since transthoracic echocardiography imaging was positive and diagnostic for infective endocarditis.

**Table 1** Blood work at admission

Marker	Reference range	Value
ESR	<30 mm/h	25
CRP	0–5 mg/L	49.5
PCT	<0.05 ng/mL	0.22
WBC	3.5–10.5 × 10 <sup>9</sup> /L	9.4

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; WBC, white blood cells.

**Table 2** Blood work after 4 weeks of intravenous antibiotic therapy

Marker	Reference range	Value
ESR	<30 mm/h	18
CRP	0–5 mg/L	5.7
PCT	<0.05 ng/mL	0.02
WBC	3.5–10.5 × 10 <sup>9</sup> /L	4.0

attack (TIA) with a short-lasting episode of dizziness, blurred vision, and vomiting. Diffusion-weighted MRI did not detect cerebral ischaemia and concerns about a septic embolization were cast aside after TTE did not show any change in the morphology of the vegetation (see [Figure 2](#) and [Videos S1](#) and [S2](#)).

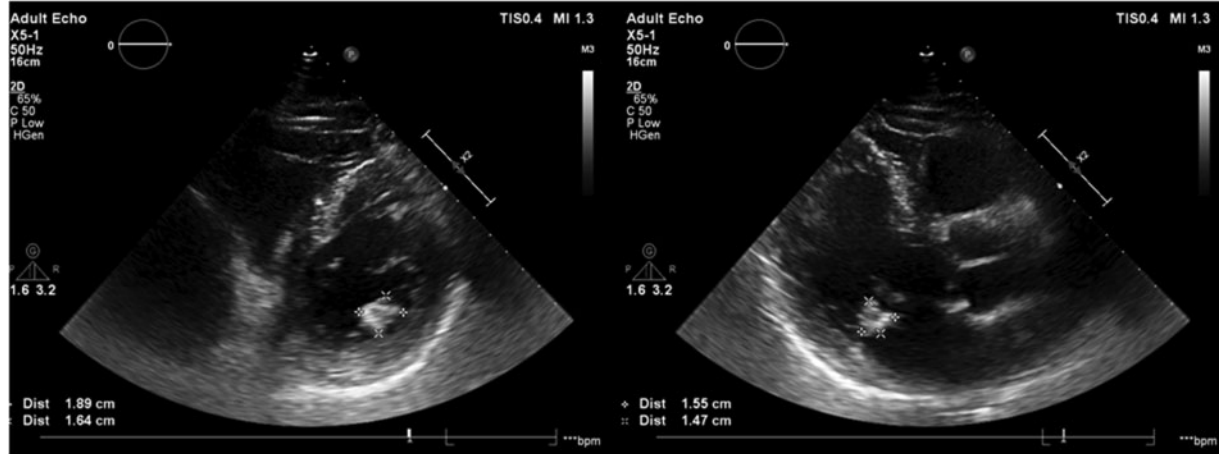
Subsequently, in July 2020, the patient underwent a successful MVR surgery with St. Jude Medical (SJM) No. 35 mechanical valve (Abbott Laboratories, Chicago, IL, USA) via a standard approach. His pre-operative markers of inflammation including PCT were within reference ranges (see [Table 3](#)).

At a 5-month follow-up in December 2020, the patient was feeling well with no signs of infection, had a normal functioning mechanical valve assessed by transthoracic echocardiography and a therapeutic international normalized ratio (INR).

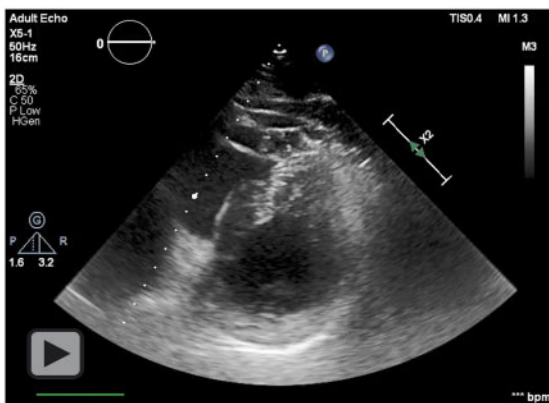
## Discussion

There are several important points to discuss regarding the presented case. First of all, the patient was initially diagnosed with mitral valve prolapse in 2009, and although he was not at high risk of developing IE, he was advised by his cardiologist that he underwent antibiotic prophylaxis for future invasive manipulations including dental procedures. This decision was based on personal experience and did not comply with the 2009 ESC guidelines on infective endocarditis, which does not mean that it was entirely wrong especially since most recommendations (including the current 2015 ESC guidelines on IE) regarding antibiotic prophylaxis are not evidence-based and reflect an expert consensus opinion.<sup>2,3</sup> That is why we believe that antibiotic prophylaxis is another area in IE management where future randomized controlled clinical trials would be of utmost importance for developing guidelines with recommendations with solid evidence that clinicians can rely on. Until then, whether or not the fact that the first and only time the patient did not use antibiotic prophylaxis during a dental procedure was related to the infective endocarditis that ensued will remain controversial.

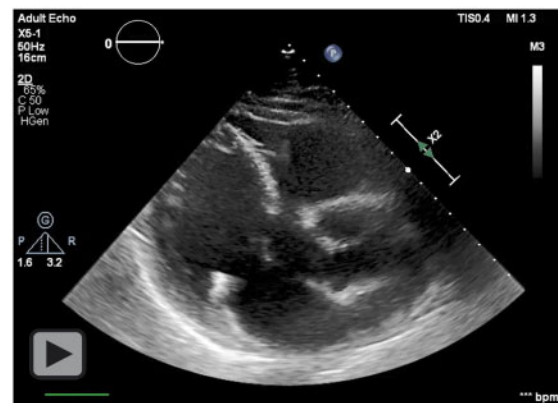
Secondly, ESR and CRP are widely used markers of inflammation that facilitate in the diagnosis of IE.<sup>5,6</sup> Procalcitonin is a less commonly used marker that is more specific to bacterial infections.<sup>7</sup> *Streptococcus viridans* infection could lead to generally less accurate PCT results when compared to *Staphylococcus aureus* and especially gram-negative infections.<sup>6,8–10</sup> Nonetheless, it is still a useful marker in IE management, especially for follow-up and can help reduce unnecessary blood cultures by providing an appropriate time to repeat samples.<sup>11</sup> Our experience shows that normal values of PCT



**Figure 2** Transthoracic echocardiography after transient ischaemic attack did not show any significant morphological change (image on the left—parasternal short-axis view; image on the right—parasternal long-axis view).



**Video 1** 2D echocardiography of the vegetation in parasternal short-axis view.



**Video 2** 2D echocardiography of the vegetation in parasternal long-axis view.

correlate well with negative blood cultures in patients treated with antibiotics, however significant residual vegetations might still be present in up to 71% of such cases.<sup>12</sup> It should be noted that depending solely on normalization of markers of inflammation such as ESR, CRP, and PCT can mislead the clinician into taking a more conservative approach in cases of residual vegetations. Yet, as our case shows even in circumstances with less infective organisms such as *S. viridans* and late in the course of the disease residual vegetations remain a serious risk factor for embolic stroke/TIA.

When it comes to surgical management, it is difficult to precise the timing for both elective and early surgery in infective endocarditis as data from randomized controlled trials are very limited. Elective surgery is defined by the 2015 ESC guidelines on IE as surgery performed at least after 1–2 weeks of antibiotic therapy.<sup>3</sup> On admission our patient had a large vegetation (>10 mm) which was associated with

**Table 3** Blood work after 6 weeks of intravenous antibiotic therapy

Marker	Reference range	Value
ESR	<30 mm/h	13
CRP	0–5 mg/L	4.2
PCT	<0.05 ng/mL	<0.02
WBC	3.5–10.5 × 10 <sup>9</sup> /L	5.9

severe mitral regurgitation, both of which were new findings. Since this is a Class IIa recommendation and the patient had acceptable tolerance of the valve lesion with no symptoms of heart failure and uncontrolled infection, the timing of surgery was decided to be elective,

i.e., after completing a full antibiotic course. In addition to the positive therapeutic effect, this decision was also supported by the low risk of embolism (~7%) at 4 weeks after admission as assessed by using a symptomatic embolism risk calculator.<sup>4</sup> The Embolic risk calculator, developed by Hubert *et al.*,<sup>4</sup> includes such criteria as vegetation size >10 mm, isolated micro-organism, age, diabetes, previous embolism, and atrial fibrillation. Based on the presented case, we would not recommend adding the evolution of biological markers into the calculator; rather, an initial high value of procalcitonin might be implemented as it was shown previously to be a useful predictor of poor outcome, i.e., death or serious infectious complications including embolic events.<sup>13</sup> Unfortunately, surgery in our patient had to be postponed several times due to anti-epidemic measures in the department of cardiac surgery, involving both patients and medical personnel, during which time the patient suffered TIA and the recommendation for surgery without delay became Class I (level of evidence B).<sup>3</sup> Hence, the authors recognize the undeniable impact the COVID-19 pandemic has had on patients, family members and medical personnel, noticed also in the late IE diagnosis although the patient was known to have a predisposing cardiac condition.

Finally, we would like to once again state that there are major gaps in evidence regarding IE. The guidelines mostly agree that vegetations larger than 10 mm at diagnosis should be a consideration for surgery, but the management of residual vegetations, especially those <10 mm, remains ambiguous.<sup>14,15</sup> We advocate for more focus in future guidelines on residual vegetations and the most appropriate way to handle them.

## Conclusion

Procalcitonin and blood cultures can be both negative in cases of large residual vegetations in IE with indications for surgery. Residual vegetations are a well-known but under-discussed phenomenon that should be addressed in the next ESC guidelines on IE.

## Lead author biography



Dzhem Farandzha, MD, is a third-year cardiology resident at University Hospital Lozenetz, Sofia, Bulgaria. Dr Farandzha completed his medical education at Sofia University St. Kliment Ohridski in 2017. His main research interests include management of native and prosthetic valve endocarditis, acute coronary syndromes and clinical pharmacology of cardiovascular drugs.

## 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 consent for submission and publication of this case report including the images, laboratory work and associated text has been obtained from the patient in line with COPE guidance.

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