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Atypical presentation of infective endocarditis complicated by dietary-induced warfarin resistance

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Abstract. Infective endocarditis (IE) is a life-threatening disease that often presents with non-specific symptoms, leading to delayed diagnosis.

We present the case of a 39-year-old male without significant comorbidities who presented with lower-limb pain, swelling, and systemic symptoms, initially misdiagnosed as pneumonia. Computed tomography (CT) angiography revealed a thrombus in the distal posterior tibial artery, but IE was suspected only after a new heart murmur was detected. Echocardiography showed vegetations on the aortic valve, mitral valve perforation, and severe aortic regurgitation. Blood cultures remained negative, likely due to prolonged prior antibiotic therapy. However, molecular analysis of excised valve tissue confirmed the presence of Streptococcus species. The patient underwent successful surgery with mechanical valve implantation and completed a six-week course of antibiotics. Postoperatively, International Normalized Ratio (INR) values remained subtherapeutic despite warfarin therapy. A detailed dietary assessment revealed excessive matcha intake (6 g/day), a source of vitamin K, which reduced warfarin efficacy. After limiting matcha to 2 g/day, the INR stabilized, and the patient was safely discharged on continued outpatient warfarin therapy.

This case highlights the diagnostic complexity of IE, especially in atypical presentations and blood culture-negative cases. It also underscores the importance of monitoring vitamin K intake in patients who have undergone mechanical valve implantation and are on warfarin anticoagulation. A multidisciplinary approach, including thorough dietary assessment, is crucial for optimal management of IE cases. Fig. 2, Tab. 2, Ref. 16, on-line full text (Free, PDF), www.cardiologyletters.sk

Keywords: infective endocarditis – bacterial embolism and thrombosis – warfarin – dietary supplements – drug interactions

Infective endocarditis (IE) is a life-threatening infection of the endocardial surface, most often affecting native or prosthetic heart valves and implanted cardiac devices (1). In 2019, its global incidence was estimated at 13.8 cases per 100 000 people per year, with in-hospital mortality reaching 15–30% (2).

Pathogenesis typically begins with endothelial injury, exposing subendothelial collagen and other matrix

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components, which promote platelet and fibrin deposition. This environment facilitates bacterial colonization, leading to vegetations (3).

Staphylococcus aureus causes ~30% of IE cases, streptococci ~30%, coagulase-negative staphylococci and Enterococcus faecalis ~10% each. HACEK (Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella) organisms, zoonotic bacteria, and fungi together account for <5% (4). Pathogens may enter via skin, oral, gastrointestinal, or genitourinary infections, intravenous drug use, or invasive procedures (2).

Clinical presentation is variable and often nonspecific, with symptoms such as fever, night sweats, fatigue, weight loss, and loss of appetite. It may involve cardiovascular (e.g., new or changing murmurs), nervous (e.g., stroke, intracranial haemorrhage, mycotic aneurysms, meningitis), renal (e.g., glomerulonephritis), skin (e.g., petechiae, Osler's nodes, Roth spots, J aneway lesions), and embolic manifestations (1–3, 5).

Diagnosis combines clinical, microbiological, and imaging data, with the modified Duke criteria as the standard (2). Echocardiography remains a cornerstone imaging modality (1-7), while computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine studies, are playing an increasingly important role (2).

Management requires prolonged antibiotics—two to six weeks for native valves, at least six weeks for prosthetic valves or intracardiac devices. In many cases, surgical intervention becomes essential. Its necessity and timing are highly individualized and should be evaluated by an experienced Endocarditis Team (2).

Patients who undergo implantation of a mechanical valve prosthesis require lifelong anticoagulation with vitamin K antagonists (8).

Table 1 Key laboratory results at the time of admission

Analyte	Patient value	Reference range	Units
HGB	10.5	13.7-17.5	g/dL
WBC	12.81	4.23-10.00	10^9/L
NEU	10.96	1.78-5,38	10^9/L
NEU	85.5	34.0-67.9	%
LYMPH	1.18	1.32-3.57	10^9/L
LYMPH	9.2	21.8-53.1	%
PLT	555	140-400	10^9/L
CRP	54.1	<5.0	mg/L
PCT	0.05	<0.5	ng/mL
Creatinine	0.83	0.80-1.20	mg/dL
D-dimer	1648	<500	ng/mL
Troponin I (1st)	44.6	0.0-34.2	pg/mL
Troponin I (2nd)	36.7	0.0-34.2	pg/mL
NT-pro-BNP	2545.30	0.00-125.00	pg/mL

HGB – Hemoglobin; WBC – White Blood Cell Count; NEU – Neutrophils, LYMPH – Lymphocytes; PLT – Platelet Count; CRP – C-reactive protein; PCT – Procalcitonin; NT-proBNP – N-terminal pro B-type natriuretic peptide

Case presentation

A 39-year-old man with no history of chronic diseases presented to the emergency department with progressive pain, redness, and swelling of the left lower leg, accompanied by cough, recurrent fever, and reduced exercise tolerance. He denied experiencing chest pain. The patient had been receiving antibiotic treatment prescribed by his primary care physician for an upper respiratory tract infection, which had persisted for more than a month. Following onset of leg pain, his physician prescribed low molecular weight heparin (LMWH), specifically enoxaparin, and advised hospital admission.

On physical examination at the time of admission, vesicular breath sounds were normal, although a few crackles were noted. No cardiac murmurs were auscultated. Peripheral pulses were intact except for an absent left posterior tibial pulse. The left medial ankle showed edema, erythema, and tenderness.

Laboratory tests were ordered, and the key parameters are presented in **Table 1**.

Computed Tomography (CT) angiography of the aorta and lower limb revealed a thrombus in the distal segment of the left posterior tibial artery, just below the medial malleolus.

To rule out pulmonary embolism, a CT pulmonary angiography was performed (**Figure 1**). No signs of embolism or right ventricular overload were detected. However, cardiac silhouette enlargement and bilateral pleural effusion were noted. In the pulmonary parenchyma, symmetrical perihilar irregular consolidations were observed, partially exhibiting a ground-glass pattern, with thickened interlobular septa. The radiologist suggested pulmonary oedema or inflammatory changes and recommended clinical correlation.

The patient was transferred to the Department of Internal Medicine, where a therapeutic dose of LMWH

(60 mg twice daily), intravenous furosemide, and empirical antibiotic therapy with ceftriaxone for suspected pneumonia were administered.

In the following days, inflammatory markers decreased. Tests for rheumatic diseases were negative. The vascular surgeon found no indication for surgical intervention and recommended modifying anticoagulant therapy to rivaroxaban (2.5 mg twice daily) and acetylsalicylic acid (ASA, 100 mg once daily). A Holter electrocardiogram (ECG) revealed no abnormalities.

Ten days after admission, the attending physician noted a heart murmur in the mitral and aortic valve auscultation areas. Consequently, transthoracic echocardiography (TTE) was performed (**Figure 2**), revealing the following significant abnormalities: perforation of the anterior leaflet of the mitral valve; vegetations on the anterior and posterior leaflet of the aortic valve; severe aortic regurgitation; and features of pulmonary hypertension and congestion. At that time, no significant pleural effusion was observed.

Based on these findings, infective endocarditis (IE) was suspected. Three blood culture sets were obtained, the microbiologist consulted, and empirical ampicillin–vancomycin therapy initiated. The cardiothoracic surgeon deemed the patient eligible for surgery.

Given the suspicion that the infection originated from the oral cavity, a preoperative dental evaluation and oral decontamination were carried out, including the extraction of infected teeth.

The following day, the patient underwent surgery involving the implantation of a mechanical aortic valve prosthesis and reconstruction of the anterior mitral leaflet, including excision of two perforations and closure of the defect using an autologous pericardial patch.

All blood cultures remained negative. However, genetic analysis of surgical valve tissue identified Streptococcus spp. As the pathogen was detected solely by molecular methods, susceptibility testing was not possible, and vancomycin–ampicillin therapy was continued.

Due to the need for prolonged intravenous therapy, a midline catheter was placed. Additionally, as a result of mechanical valve implantation, warfarin therapy was initiated under International Normalized Ratio (INR) monitoring.

Warfarin was initiated at 8 mg, achieving an INR of 2.7–2.94 with alternating 5–8 mg doses. Three weeks post-surgery, INR fell to 1.38, prompting addition of LMWH (60 mg twice daily). No medical or drug-related cause was identified.

Over the following days of hospitalization, the patient required increasing doses of warfarin alongside continued LMWH administration, as detailed in **Table 2**.

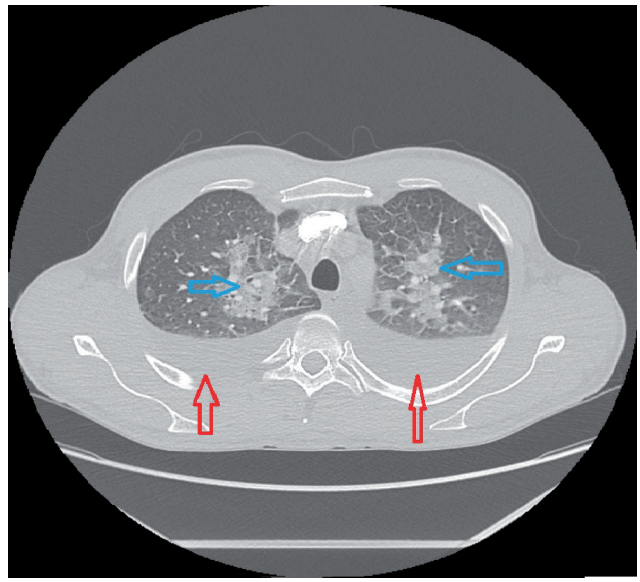

Figure 1 CT angiography illustrating bilateral pleural effusion (red arrows) and pulmonary parenchyma consolidations (blue arrows)
CT – Computed tomography

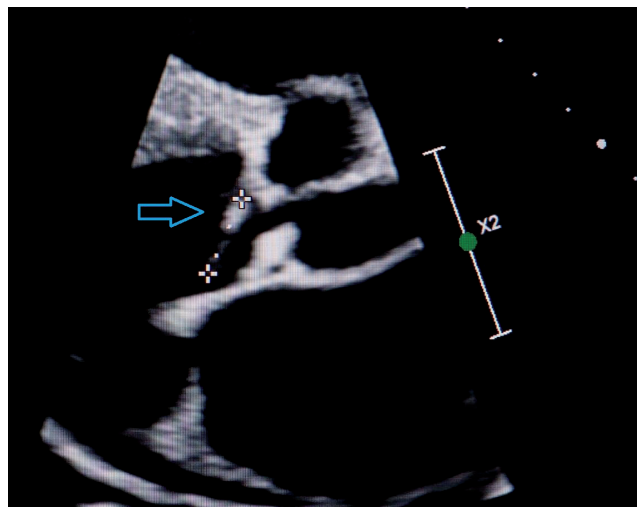

Figure 2 Echocardiography showing vegetation (blue arrow) on the aortic valve

Table 2 INR monitoring

Date	INR value	Matcha intake (g)	Warfarin dose (mg)
2.12.2024	1.38	6	8
3.12.2024	1.41	6	8
5.12.2024	1.6	6	8
7.12.2024	2.66	6	10
9.12.2024	1.88	6	10
10.12.2024	1.71	6	10
11.12.2024	2.78	2	13
12.12.2024	3.48	2	19
13.12.2024	3.13	2	8
16.12.2024	4.46	2	8
17.12.2024	4.0	2	8

INR – International Normalized Ratio

Retrospective analysis and a detailed patient interview revealed daily consumption of approximately 6 g of matcha (well above the usual 1–2 g) which likely reduced warfarin efficacy due to its high vitamin K content. After limiting intake to 2 g/day, the INR improved, allowing LMWH discontinuation and warfarin dose reduction to 8 mg.

In parallel, oral sanitation continued with extraction of two teeth. Moreover, surgical follow-up confirmed proper wound healing, suture removal, and normal prosthetic valve function.

After six weeks of antibiotics, the patient was discharged in stable condition.

Discussion

IE is a severe condition that often presents with nonspecific symptoms, making early diagnosis challenging. Delayed recognition and treatment increase the risk of complications and worsen outcomes (5, 9–11).

This patient had marked inflammation and elevated cardiac biomarkers before cardiac signs appeared, leading to initial misdiagnosis as pneumonia.

At an early stage of the diagnostic workup, a thrombus was identified in the tibial artery. Without comprehensive cardiac assessment, this embolic event was not linked to IE, which is a common mistake (12).

The diagnosis of IE was considered only after a new heart murmur was detected and echocardiography was performed, highlighting the pivotal role of early imaging in timely identification of the disease.

Blood cultures remained negative, most likely due to prior prolonged antibiotic therapy, the leading cause of blood culture-negative infective endocarditis (BCNIE) (2). Genetic analysis of excised valve tissue, likely via 16S rRNA polymerase chain reaction PCR, identified the causative pathogen, underscoring the value of molecular testing in BCNIE and the need for a multimodal diagnostic approach.

The probable source of bacteremia was the oral cavity. Poor oral hygiene is a well-established risk factor for IE, facilitating the entry of oral bacteria (commonly Streptococcus spp.) into the bloodstream, especially in the absence of proper dental care (13).

According to the 2023 ESC guidelines, the patient met the criteria for definite IE (2). One major criterion (typical echocardiographic findings) and several minor criteria—including fever, vascular phenomena (peripheral embolism), and microbiological evidence from genetic testing—were fulfilled.

Another notable aspect of this case was the difficulty in maintaining INR stability in a patient receiving warfarin therapy, despite adherence to standard dosing and monitoring protocols. While therapeutic INR levels were initially achieved, a significant decrease occurred during hospitalization, necessitating the concurrent use of low molecular weight heparin (LMWH).

After excluding medical error and drug interactions, a more detailed patient history revealed regular consumption of matcha—a powdered green tea product with a high vitamin K content (14). This likely contributed to the reduced INR values and the need for intensified anticoagulation, as vitamin K is essential for the synthesis of clotting factors, and excessive intake can counteract the effects of vitamin K antagonists such as warfarin (15, 16). Following a reduction in matcha consumption to a controlled dose, INR levels improved, enabling discontinuation of LMWH and continuation of warfarin monotherapy in the outpatient setting.

Conclusions

This case illustrates how the nonspecific presentation of infective endocarditis (IE) can delay diagnosis, while timely recognition of new signs—such as a heart murmur—enables comprehensive evaluation and prompt intervention. Early echocardiography, appropriate antibi-

otic therapy, and timely surgery are critical to improving outcomes.

It also emphasizes the importance of thorough dietary assessment in patients on vitamin K antagonists, as even healthy foods can significantly affect anticoagulation. Educating patients about potential food–drug interactions and encouraging them to report dietary changes, particularly those involving vitamin K-rich products, is essential to maintaining stable anticoagulation and ensuring treatment safety.

Authors' contribution:
Concept: Adrianna Perzanowska, Zuzanna Tomaszewska, Agata Antoniak, Klaudia Cierlicka.
Design: Adrianna Perzanowska, Zuzanna Tomaszewska, Agata Antoniak, Klaudia Cierlicka.
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Data interpretation: Adrianna Perzanowska, Zuzanna Tomaszewska, Agata Antoniak, Klaudia Cierlicka.
Drafting article: Adrianna Perzanowska, Zuzanna Tomaszewska, Agata Antoniak.
Critical revision of article: Klaudia Cierlicka.
Approval of article: Adrianna Perzanowska, Zuzanna Tomaszewska, Agata Antoniak, Klaudia Cierlicka.
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