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Case Report

Infective Endocarditis with Un Unusual Pathogen in A Patient Under Teriflunomide Therapy

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Abstract

Infective endocarditis (IE) is an uncommon infection with high mortality, most often caused by Gram-positive cocci (80-90%) or by bacteria from the HACEK group (2-4%). Klebsiella aerogenes is rarely implicated in IE, accounting for less than 2% of non-HACEK Gram-negative endocarditis cases.

We report a case of IE caused by Klebsiella aerogenes in a patient with multiple sclerosis (MS) undergoing treatment with teriflunomide. The patient presented in septic shock and was initially managed for presumed prostatitis. However, persistent neurological symptoms prompted further investigation, which revealed a large aortic valve vegetation. Urgent valve replacement was performed and cultures of the resected valve confirmed the final diagnosis of Klebsiella aerogenes endocarditis with embolic complications.

The absence of traditional risk factors and the recent initiation of teriflunomide raise concerns about potential immunosuppressive effects and vulnerability to rare infections. This case highlights the importance of vigilance for opportunistic infections in patients treated with teriflunomide.

Keywords: infective endocarditis; klebsiella aerogenes; teriflunomide

Introduction

Infective endocarditis (IE) is an uncommon but severe infection associated with high mortality. The majority of cases are caused by Gram-positive cocci, accounting for approximately 80–90% of infections [1,2], or by bacteria from the HACEK group in 2–4% of cases [2,3].

Non-HACEK Gram-negative infective endocarditis remains rare and is typically associated with nosocomial factors or significant comorbidities. Gram-negative IE carries a poor prognosis, with reported mortality rates exceeding 20% in the literature [2,3].

Klebsiella aerogenes, formerly known as Enterobacter aerogenes, is an infrequent causative agent of IE, likely due to its limited capacity for biofilm formation on native cardiac valves. In multiple large studies this pathogen was observed in less than 1% of the IE caused by non-HACEK gram-negative bacteria [4,5,6,7]. It is a nosocomial pathogen associated with a prolonged hospital stay, mechanic ventilation or stay at the intensive care unit [8].

Here we report a unique case of K. aerogenes IE in the absence of known predisposing cardiac or invasive risk factors, in a patient receiving teriflunomide monotherapy. This immunomodulatory drug is used in the treatment of multiple sclerosis and is associated with a low risk of severe infections. However, its role in predisposing patients to opportunistic infections like endocarditis remains unclear. We aim to highlight the potential immunosuppressive risks associated with teriflunomide therapy that may predispose patients to uncommon infections.

Case Presentation

A man in his early 60s was admitted with complaints of fever and confusion. His medical history included arterial hypertension, chronic renal insufficiency, and multiple sclerosis. Since his diagnosis of multiple sclerosis 12 years ago, he had remained clinically stable without relapses or evidence of ongoing inflammation. However, following the identification of

a new lesion on cerebral MRI, first-line immunomodulatory therapy with teriflunomide was initiated three months prior to admission.

Physical examination on admission revealed a patient with mottled skin and poor circulation in septic shock with hypotension, tachycardia, fever (38.9 °C) but no apparent clinical focus (normal heart- and lung auscultation, painless abdomen, normal neurological examination besides confusion, no dysuria). Blood analyses showed leukopenia with a white blood cell count (WBC) of 1.800/µL (reference 4000–11000/µL) with high C-reactive protein (CRP) 344 mg/L (reference <5mg/L) and elevated lactate 4.45 mmol/L (reference 0.67–2.47mmol/L). There were signs of secondary multi-organ failure with thrombopenia (13.000/µL, reference 150.000-450.000/µL), acute kidney insufficiency (creatinine 5.46 mg/dL, reference 0.7-1.2 mg/dL) and slightly perturbated liver tests (ALT 27 U/L (reference <41U/L), AST 61 U/L (reference <40U/L), GGT 49 U/L (reference 8-61U/L), total bilirubin 2.27 mg/dL (reference 0-1.2mg/dL)).

Further diagnostic evaluation showed a normal chest radiograph and no abnormalities on non-contrast abdominopelvic CT, apart from a mildly enlarged prostate. Mild pyuria was present in the urine (84 WBC/µL; reference <25/µL), without hematuria, and the prostate-specific antigen (PSA) level on admission was within normal limits (4 µg/L; reference range 0–4.1 µg/L).

Based on these findings, the working diagnosis of urosepsis as the source of septic shock was considered, and empirical antibiotic therapy with temocillin (2 × 2 g/day) was initiated. The patient was admitted to the intensive care unit with vasopressor support. Teriflunomide was discontinued upon admission.

Repeat measurement of PSA two days after admission showed a marked increase (16 µg/L, reference 0–4.1 µg/L) supporting the diagnosis of prostatitis. Blood and urine cultures obtained at admission grew Klebsiella aerogenes, which was susceptible to ciprofloxacin (minimal inhibitory concentration (MIC)≤0.25), piperacillin-tazobactam (MIC ≤ 4) and susceptible increased exposure to temocillin (MIC 8). Antibiotics were adjusted to ciprofloxacin (2*400 mg IV).

Day	Timeline
0	Admission in septic shock and multi-organ failure. Suspected urosepsis. Start temocillin (2*2g IV/d).
2	Blood cultures show growth of *Klebsiella aerogenes*. Diagnosis of prostatitis based on elevated PSA. Switch antibiotics to ciprofloxacine (2*400mg IV/d).
3	Persistent word-finding problems with minor stroke on CT. TEE shows a large vegetation on the native AV, probably endocarditis. Switch antibiotics to piperacillin-tazobactam (4*4g IV/d) and transfer to our hospital.
5	PET-scan suspicious for endocarditis at the level of the AV and a slightly increased FDG tracer uptake at the left prostatic lobe. Multiple recent infarctions of the brain on MRI.
6	Surgical AV replacement. Post-operative association of ciprofloxacine (2*400mg IV/d) to piperacillin-tazobactam as antimicrobial treatment on the intensive care unit. Culture of the resected AV showed growth of *Klebsiella aerogenes.*
9	Transfer to the ward for intravenous treatment and follow-up with weekly TTE. Transrectal ultrasound showed no abnormalities.
48	Stop antimicrobial treatment (6 weeks post cardiac surgery) and hospital discharge
62	Start of cardiac rehabilitation

Despite hemodynamic stabilization, with lactate clearance, improvement in renal function, and resolution of bacteremia, the patient continued to experience persistent word-finding difficulties. This prompted further investigation with a cranial CT scan, revealing recent areas of encephalomalacia and softening in the left frontal region. Given the presence of Klebsiella aerogenes bacteremia and the findings of a minor ischemic cerebrovascular event (CVA), an urgent transesophageal echocardiography (TEE) was conducted. This revealed a large vegetation of 3 cm on the aortic valve (AV), located on the left coronary cusp and non-coronary cusp, leading to severe stenosis (Pmax 90 mmHg, Pmean 55 mmHg, AVA 0.8 cm2) with a moderate central regurgitation, and also suspicion of an abscess in the aortic root (figure 1). The patient was subsequently transferred to our institution for further evaluation and management.

A cerebral MRI showed multiple recent infarctions supra- and infratentorial, probably emboligenic (figure 2). Given the suspicion of endocarditis, a PET-CT was also performed, which showed findings suggestive of endocarditis at the posterior part of the aortic valve (figure 3).

Multidisciplinary consultation of cardiologists, cardiovascular specialists and microbiologists withheld IE of the AV as the most plausible diagnosis, with aortic valve thrombosis being the next most likely possibility. Given the patient's thrombocytopenia and recent ischemic cerebrovascular event (CVA), thrombolysis was not considered a viable option, and the decision was made to proceed with urgent aortic valve replacement.

Peroperatively a thrombus-like mass measuring 3 cm on the AV was observed that bulged along the aortic and ventricular sides of the valve, with least involvement of the right coronary cusp (figure 4). The mass and valve cusps were excised and sent for microbiological and histological examination. At the commissure between the left and non-coronary cusps, a superficial laceration was observed, accompanied by wall-adherent thrombus material and a small quantity of white pus beneath it (figure 5). Following thorough irrigation and disinfection of the tissues, a bioprosthetic valve type Carpentier Edward Magna Ease 23 was implanted.

Final cultures of the perioperatively collected pus and valvular tissue were positive for Klebsiella aerogenes, confirming the diagnosis of emboligenic infective endocarditis (IE).

Histological analysis showed a sclerosed aortic valve with acute bacterial endocarditis and important infiltration with neutrophils in the thrombotic material, again confirming this final diagnosis.

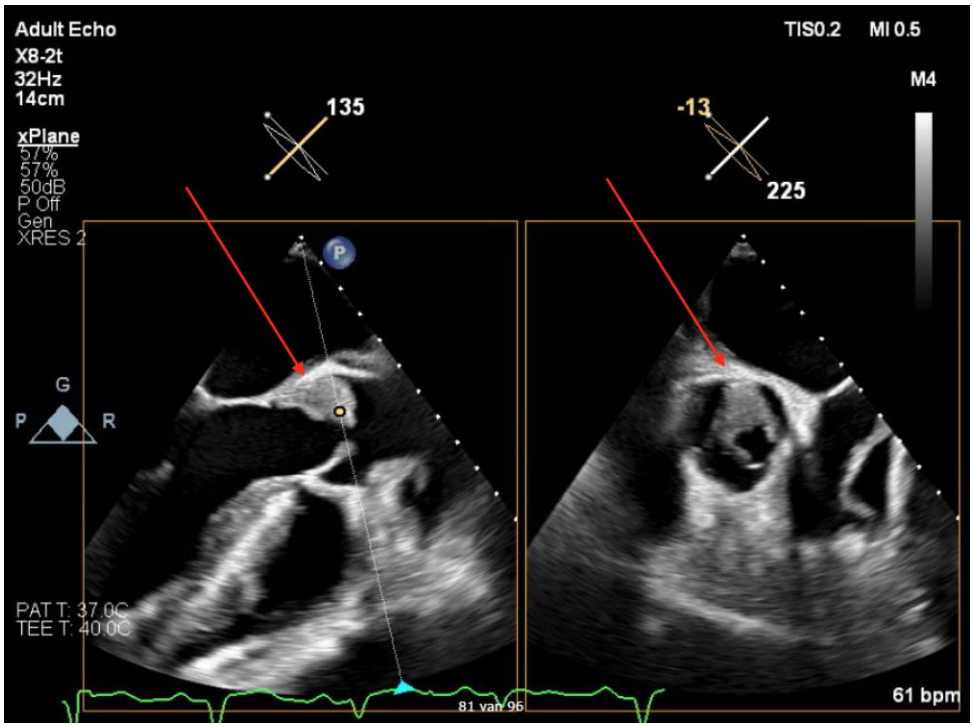

Figure 1: TEE showing a large vegetation of 3 cm on the aortic valve (AV), located on the left coronary cusp and non-coronary cusp, leading to severe stenosis with a moderate central regurgitation. Also suspicion of an abscess in the aortic root

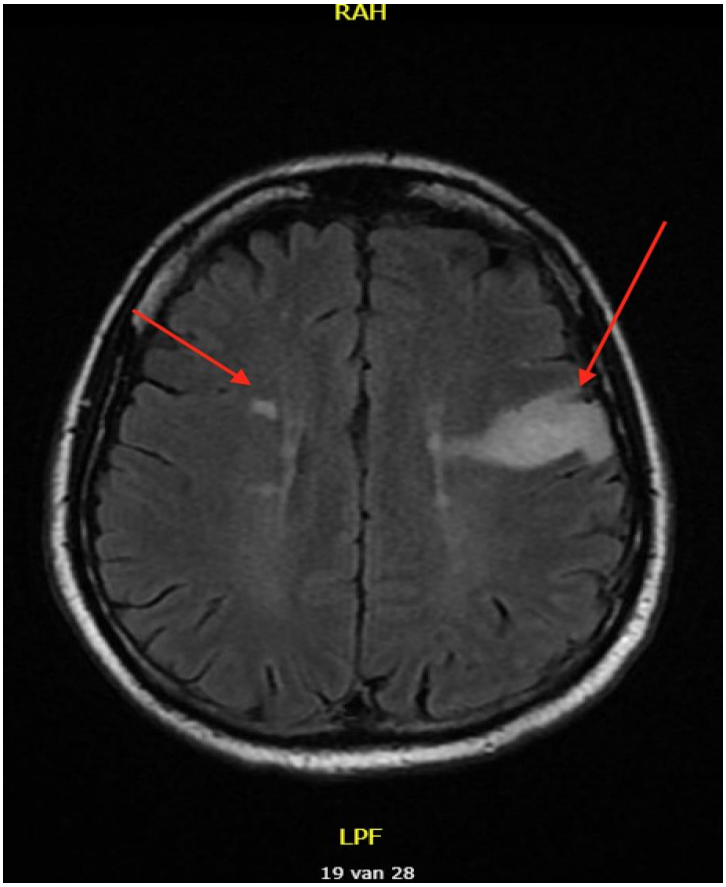

Figure 2: Cerebral MRI showing multiple recent infarctions supra- and infratentorial, probably emboligenic

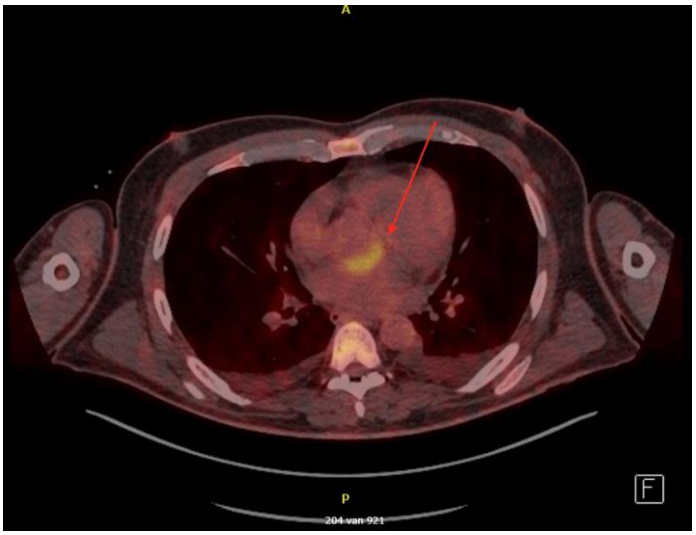

Figure 3: PET-CT showing findings suggestive of endocarditis at the posterior part of the aortic valve

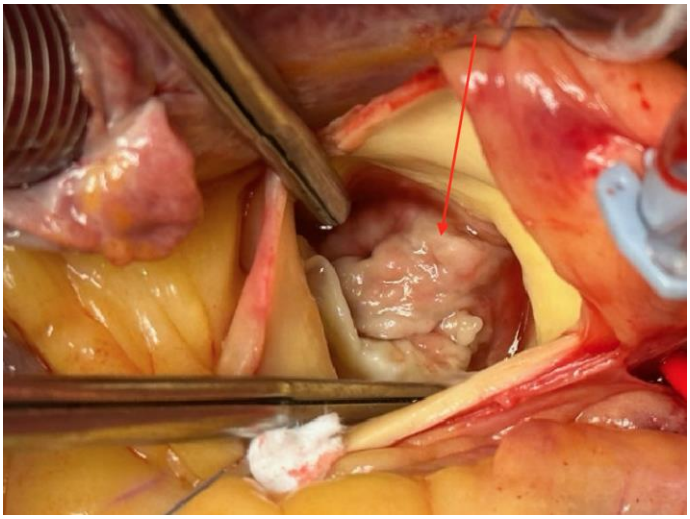

Figure 4: Peroperative image of a thrombus-like mass measuring 3 cm on the AV was observed that bulged along the aortic and ventricular sides of the valve, with least involvement of the right coronary cusp

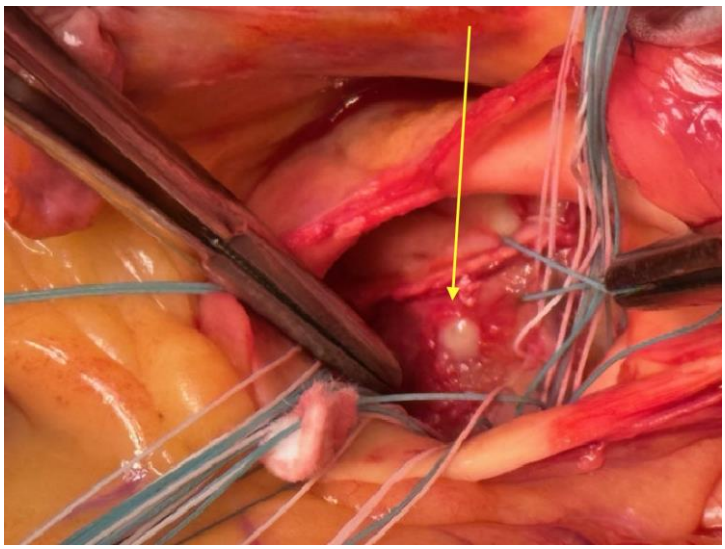

Figure 5: Peroperative image of superficial laceration at the commissure between the left and non-coronary cusps, accompanied by wall-adherent thrombus material and a small quantity of white pus beneath it

Treatment

The postoperative course was uncomplicated, with prolonged hospitalization due to need of intravenous combination of ciprofloxacine (2*400mg) and piperacillin-tazobactam (4*4g) for a total duration of 6 weeks after valve replacement.

Outcome And Follow-Up

The inflammatory markers rapidly decreased after surgery and initiation of antibiotic therapy.

Weekly transthoracic echocardiography (TTE) showed normal left ventricular ejection fraction and good function of the AV. The therapy with teriflunomide remained discontinued at the discharge. The patient was able to leave the hospital in good general condition after six weeks of treatment and started cardiac rehabilitation.

Discussion

Non-HACEK gram-negative IE is most frequently caused by Enterobacterales (25%) (E. coli, K. pneumoniae,) or P. aeruginosa (25%) (5,6). The mortality rate for non-HACEK Gram-negative endocarditis ranges from 17% to 30% (6,9,10), which is comparable to the mortality associated with endocarditis caused by other pathogens [1].

Additionally, a high rate of therapy failure (10%) has been reported [9], often associated with underlying comorbidities or the absence of surgical intervention [11]. In a large cohort study of non-HACEK gram-negative endocarditis more than half of the patients had health-care associated infections [5]. Predisposing factors such as prosthetic materials, catheters or underlying structural heart disease can facilitate the development of IE [4]. Our patient had undergone a TTE a few months prior to admission, which showed no abnormalities.

The European Society of Cardiology advises to treat non-HACEK gram-negative endocarditis with early surgery followed by prolonged (six weeks) therapy with bactericidal combinations of beta-lactams and aminoglycosides, sometimes with additional quinolones or cotrimoxazole. Due to the rarity of such cases, management should always involve discussion by an endocarditis team [7]. However, other literature presents conflicting results regarding the use of combination therapy and its associated benefits [6,9,10,15]. In this case, early surgery was followed by combination therapy with a beta-lactam antibiotic and a quinolone, rather than an aminoglycoside, to optimize tissue penetration and minimize renal toxicity, given the patient's pre-existing renal impairment and the prolonged duration of therapy. Ambiguities in treatment regimens along with high mortality and therapy failure rates highlight the complexity of managing patients with non-HACEK gram-negative endocarditis.

This case of Klebsiella aerogenes infective endocarditis is striking not only because of the pathogen's rarity in native valve IE, but also due to the absence of traditional risk factors such as structural heart disease, indwelling catheters, or recent hospitalization. The only noteworthy immunological vulnerability was the recent initiation of teriflunomide, a disease-modifying treatment for MS that selectively inhibits pyrimidine synthesis, thereby suppressing T- and B-lymphocyte proliferation involved in inflammatory respons [12]. Although teriflunomide is generally considered to confer a moderate immunosuppressive burden compared to other MS therapies, it has been associated with an increased risk of infections [13,14].

Nevertheless, to our knowledge, no cases of infective endocarditis have been reported in association with teriflunomide therapy in either clinical trials or post-marketing surveillance. The temporal proximity between drug initiation and the onset of severe infection in this case suggest a potential causal relationship.

Given the novelty of this case, further pharmacovigilance and registry data are needed to assess whether teriflunomide might confer a specific risk for hematogenous spread of rare organisms. This report underscores the importance of close monitoring for severe infections in patients receiving teriflunomide and suggests that clinicians should maintain a high index of suspicion for endocarditis, even when encountering atypical pathogens in such settings.

Conclusion

We present an unusual presentation of infective endocarditis caused by Klebsiella aerogenes in a patient receiving teriflunomide therapy for multiple sclerosis. In the absence of traditional risk factors such as structural heart disease or recent invasive procedures, this case raises the possibility of a link between teriflunomide-induced immunomodulation and susceptibility to opportunistic infections. It emphasizes the importance of maintaining a high index of suspicion for infective endocarditis in bacteremic patients with persistent or unexplained symptoms. Furthermore, it highlights the need for increased clinical awareness and vigilance for opportunistic infections in patients treated with teriflunomide.

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