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Infective endocarditis with metastatic infections in a renal transplant recipient: a case report

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Abstract

Background Infective endocarditis is an uncommon but well-known post-transplant complication with significant morbidity and mortality. It has been observed to be about 171 times more common in solid organ transplant patients than in the general population. With the increasing rate of end-stage kidney disease, the higher demand for kidney transplantation with better graft survival, and life expectancy rates, more transplant recipients may develop infective endocarditis as a late post-transplant complication. Prompt diagnosis of infective endocarditis is therefore necessary to avert graft loss and other life-threatening outcomes.

Case presentation We present a case of a 52-year-old African patient who had a live donor kidney transplant 18 months prior to presentation and had been on oral tacrolimus 5 mg every morning/4.5 mg every evening, mycophenolic acid (MPA) 720 mg twice daily, and oral prednisolone 10 mg daily as maintenance immunosuppressive medications. Regarding the above immunosuppressive medications, he had been in good health and had a functioning transplant graft. He presented with a resolving right thigh swelling, recurrence of fever, new onset left hemiplegia, and seizures. *Enterococcus faecalis* infective endocarditis was diagnosed with metastatic brain abscesses, which was treated with intravenous vancomycin and gentamycin for 5 weeks. There are very few reported cases of infective endocarditis due to *Enterococcus faecalis*, and this case is unique because the initial presentation was pyomyositis.

Conclusion Infective endocarditis with septic embolization to the brain should be considered in kidney transplant recipients with pyomyositis and multiple rim-enhancing lesions, especially in the late post-transplant period with Enterococcal spp. as an emerging cause of infective endocarditis in kidney transplant recipients. Clinicians will need to have a high index of suspicion to aid early diagnosis with appropriate treatment to prevent adverse outcomes.

Keywords Infective endocarditis, Kidney transplant, Immunosuppressive medications, Pyomyositis

Background

The burden of end-stage kidney disease (ESKD) appears to be increasing in developing countries [1]. Kidney transplantation provides the ideal treatment option for patients with ESKD, as it offers an increased life expectancy and increased quality of life [2]. Infections, however, remain the most common complications observed after the first year of transplantation, despite the lower but adequate chronic maintenance doses

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of immunosuppressants often given to maintain graft function.

Solid-organ transplantation has been associated with a 171-fold increased risk of infective endocarditis (IE) compared with the general population [3]. Although not commonly reported, IE carries a significant risk for hospitalization, graft loss, and death [4, 5]. A case of infective endocarditis (IE) in a kidney transplant recipient (KTR) is described. The patient initially presented with pyomyositis, and subsequent imaging examinations revealed the presence of metastatic brain abscesses. After examining the existing research, we highlighted the significance of retaining a strong sense of suspicion for infective endocarditis (IE), particularly in those who are taking long-term immunosuppressant medications and experience abrupt neurological symptoms.

Case presentation

A 52-year-old African living donor kidney transplant recipient in post-transplant month 18 presented to a private health facility with a week's history of painful right thigh swelling, fever, and general malaise. At that time, magnetic resonance imaging (MRI) of the right thigh revealed fluid collections too small for any surgical intervention or radiologically assisted percutaneous drainage. Following a week of medical treatment with intravenous vancomycin and intravenous meropenem, he experienced a significant reduction in right thigh swelling, pain, and fever, leading to his discharge home. However, 3 days following discharge, he experienced left-sided weakness of both upper and lower limbs, a recurrence of fever, and an episode of tonic–clonic seizures that aborted spontaneously. A contrast MRI of the brain was performed, which revealed multiple ovoid bilateral rim-enhancing lesions supratentorially located. At this point, he was referred to Korle-Bu Teaching Hospital (KBTH), a tertiary facility in Accra, Ghana.

At KBTH, the history from the patient's wife was negative for trauma to the right thigh, headaches, neck stiffness, confusion, photophobia, blurred vision, or slurred speech. There was also no history of cough, nasal congestion, nasal discharge, otalgia, dysuria, or diarrhea. Hypertension was the cause of his kidney failure, which necessitated a kidney transplant. He otherwise had no other comorbidities. Physical examination revealed high temperatures ranging between 37.8 °C and 39 °C, no digital clubbing or splinter hemorrhages, a pulse of 84 beats per minute, a blood pressure of 130/82 mmHg, and a displaced apex in the left sixth intercostal space mid-clavicular line. There were no murmurs. Respiratory and gastrointestinal exams were unremarkable. His central nervous system examination, however, revealed a state of unconsciousness, with a Glasgow coma scale (GCS) of 11/15, an upper motor neuron, left facial nerve palsy, and left hemiparesis. His neck was supple, Kernig's sign was negative, and he had equal, normal-sized (3 mm) pupils with an appropriate direct and consensual pupillary response. Fundoscopy was normal. The table below presents the results of his laboratory investigations.

The corresponding MRI report commented on multiple diffuse (12) roundish-ovoid T1 hypo-intense and T2/flair hyper-intense lesions of varying sizes at all levels of the brain (Figs. 1 and 2). We observed the lesions bilaterally in both the frontal lobes and the forceps minor. In the right hemisphere, we observed lesions in the right thalamus, right temporal lobe, right occipital lobe, and right cerebral peduncle. In the left hemisphere, there were lesions in the left centrum semi-ovale, the left body of the caudate nucleus, and the left corona radiata. The posterior parietal parasagittal region also displayed a lesion. There were no lesions seen in the cerebellum, pons, or medulla. Gadolinium contrast administration revealed perilesional edema with rim enhancement and a midline shift to the left.

A transthoracic echocardiogram showed vegetation measuring 0.7×0.9 cm on the non-coronary cusps of the aortic valve (Fig. 3).

He immediately began receiving intravenous vancomycin 1 g 12 hourly and intravenous meropenem 2 g 8 hourly as empirical antibiotic therapy after taking the blood cultures. We made a definite diagnosis of IE based on the modified Duke's criteria, which included a major criterion (vegetations on the aortic valve) and three minor criteria (fever, one positive blood culture with Enterococcus species, and multiple brain abscesses). After receiving the blood culture results, we reviewed the antibiotics and decided to administer an intravenous vancomycin infusion of 1 g over 2 hours every 12 hours and an intravenous gentamicin 1 mg/kg (80 mg) every 8 hours. We monitored the patient's urinalysis and kidney function weekly throughout the treatment.

His maintenance immunosuppressants before admission had been oral tacrolimus (5 mg every morning or 4.5 mg every evening), mycophenolic acid (MPA) 720 mg twice daily, and oral prednisolone (10 mg daily). On account of the infective endocarditis, intravenous hydrocortisone 50 mg 12 hours a day was initially substituted for the prednisolone, then changed back to the prednisolone at a dose of 40 mg daily due to the mass effect of the brain abscesses. The dose of prednisolone was subsequently tapered down with improvements in sensorium, left hemiplegia, and seizures. The ongoing active infection also necessitated the stopping of MPA, but tacrolimus was maintained and the dose was adjusted on the basis of the serum levels on admission.

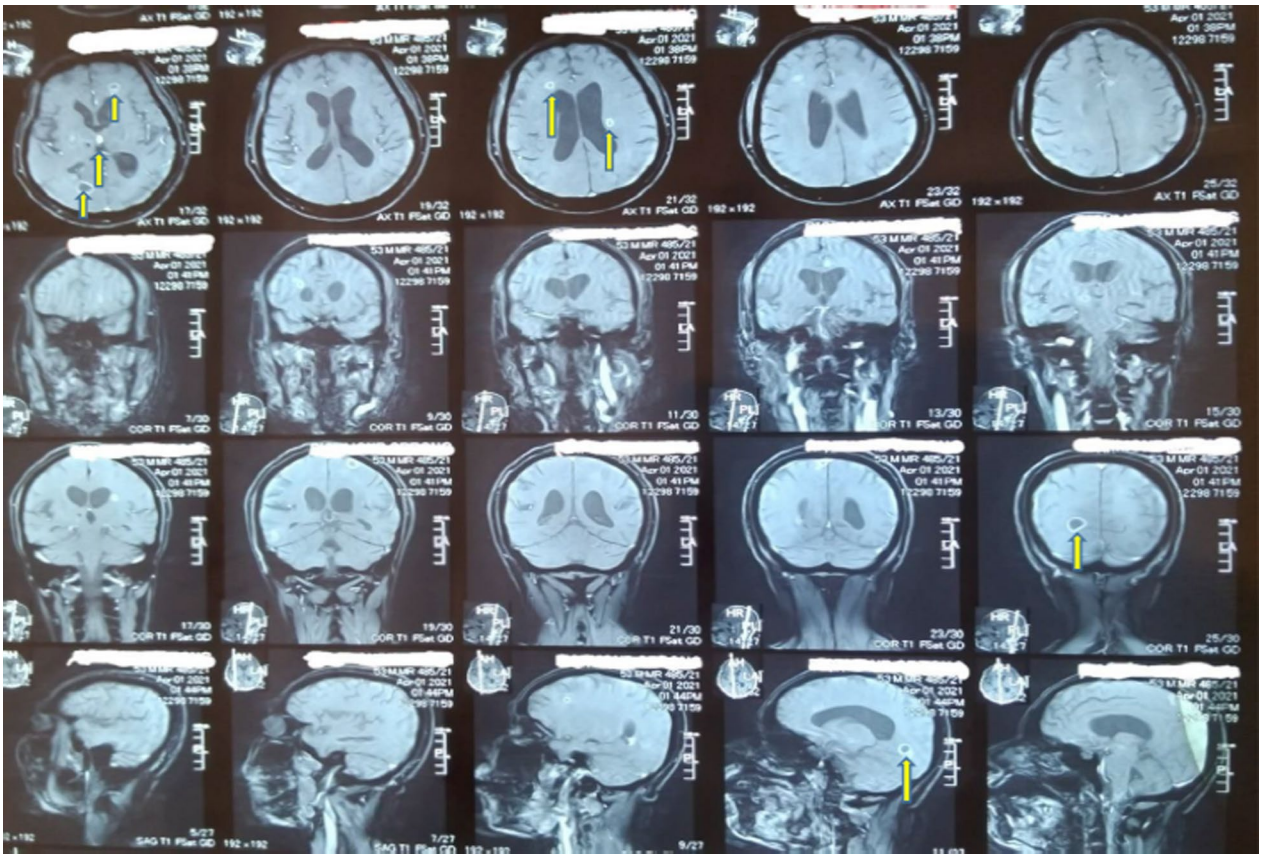

Fig. 1 T1 weighted axial, coronal, and sagittal magnetic resonance imaging of the brain showing multiple roundish-ovoid hypointense lesions of varying sizes (yellow arrows) diffusely distributed within the cerebrum with rim enhancement post-gadolinium and associated perilesional edema

We used oral anticonvulsants to manage his seizures. For the first 2 weeks after being admitted, he needed as much as 500 mg of oral levetiracetam twice a day and 400 mg of oral carbamazepine twice a day. Once the seizures were under better control, the dose of carbamazepine was lowered to avoid interactions with other drugs he was taking, especially tacrolimus, and to get a better picture of his sensorium.

After a total of 5 weeks of intravenous antibiotics (1 week of vancomycin and meropenem and 4 weeks of vancomycin and gentamicin), the patient was able to ambulate with a Zimmer frame. A repeat blood culture was negative for bacteremia, and a repeat transthoracic echocardiogram revealed vegetation measuring 0.4 × 0.4 cm on the non-coronary cusp of the aortic valve. The patient remained stable, mobilizing with the assistance of a Zimmer frame. A colonoscopy done prior to his discharge was normal.

Repeat MRI of the brain done 1 month after discharge revealed diffusely distributed, nonenhancing, roundish-ovoid, mostly supratentorial lesions suggestive of foci of microhemorrhage, but no mature abscess or any lesion suggestive of an active infective or inflammatory process. The plan is to follow up closely with him at the nephrology clinic and have periodic MRI scans of the brain until there is complete resolution or calcification of the brain abscesses.

Discussion

Infective endocarditis (IE) is more likely to be seen in KTRs than in the general population [3]. Following transplantation, the supratherapeutic levels of immunosuppressant medications such as tacrolimus used for the preservation of graft function have been associated with impaired phagocytic activity of resident tissue macrophages, particularly on *Staphylococcus aureus* resulting in staphylococcal bacteremia and infection [6]. Despite the above-described effect of immunosuppressant medications on the increased risk of infections among KTRs, individuals with end-stage renal disease receiving hemodialysis and peritoneal dialysis tend to have higher incidence rates of IE than KTRs, implying that kidney transplantation per se may not be a risk factor for IE but protective therapy may be [7]. Comparing

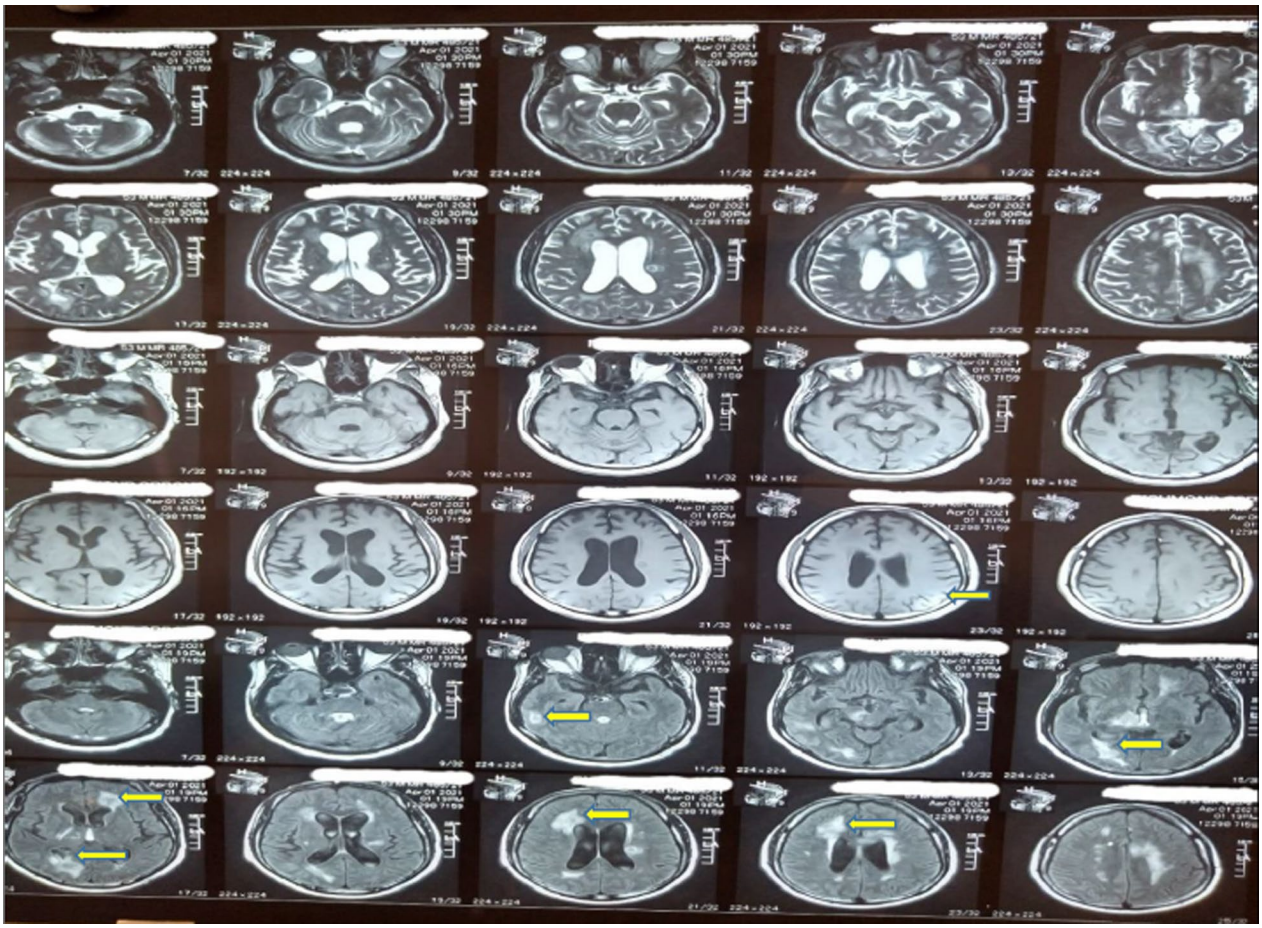

Fig. 2 T2/flair axial magnetic resonance imaging of the brain showing multiple roundish-ovoid hyperintense lesions (yellow arrows) of varying sizes diffusely distributed within the cerebrum with associated perilesional edema

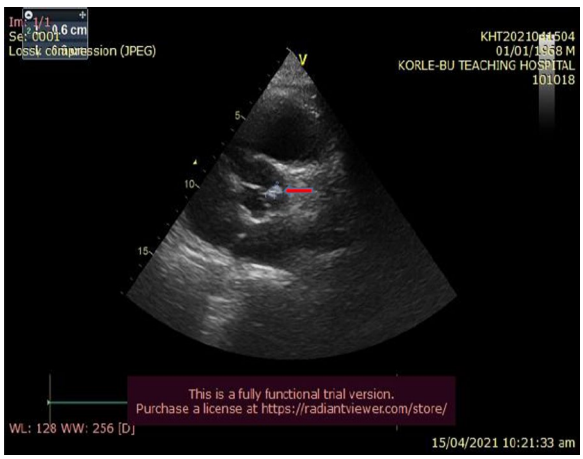

Fig. 3 Echocardiogram showing a 0.6 × 0.9 cm echogenic material (red arrow) on the non-coronary cusps of the aortic valve

the three modalities of renal replacement therapy (hemodialysis, peritoneal dialysis, or kidney transplantation), the absence of indwelling central venous catheters, cardiac devices, or prosthetic valves, as well as the absence of uremia-related immune response commonly seen in patients with ESKD, seem to outweigh the immunosuppressant-related risk of IE among KTRs [7, 8].

Specific types of infections occur at specific times in the post-transplant period, and the risk of a particular infection following solid organ transplant (SOT) is determined by the overall level of immunosuppression at a particular post-transplant period [9]. Provided there is no risk of kidney transplant rejection, the function of the transplanted kidney is maintained at lower doses of immunosuppressants beyond 6 months post-transplantation [9, 10]. Up to about 80% of KTRs in the late post-transplant period (> 12 months), have adequate graft function with no clinical signs of any chronic viral infection and a low immunosuppressive level. This category of people are typically at risk for community-acquired

infections and may occasionally acquire primary cytomegalovirus (CMV) infection through sexual contact [11]. A proportion of the remaining group of KTRs in the late post-transplant period may have chronic activation of endogenous viral infections, such as CMV, resulting in frequent episodes of rejection or chronic graft rejection. A smaller proportion of the latter group also may experience unfavorable graft function and may need intensification of immunosuppressant medication to improve graft function or prevent further graft deterioration [11]. CMV activation may directly and indirectly, through immunomodulation, suppress T-cell proliferation and cytotoxicity. Indirectly, CMV activation results in the inversion of the CD4/CD8 lymphocyte ratio and the suppression of cytotoxic T-cell specific antigen recognition, contributing to the development of opportunistic infections [12]. Consequently, a low absolute T-cell count results in the inability of the immune system to kill or contain new or reactivated infection [12]. It is worth noting that CMV gastrointestinal disease such as esophagitis, colitis, and neurological disease such as CMV meningoencephalitis may not have viremia. Given that our patient presented over 12 months post-kidney transplantation, had the negative serum CMV DNA, and no cytopenia, with particularly an absolute lymphocyte count of 2.06×10^9/L, a minimal net state of immunosuppression was implied. Therefore, a diagnosis of IE with metastatic brain abscesses was suspected in this case because of his neurological presentation with fever and multiple rim-enhancing lesions on MRI.

This led to the discovery of vegetations on the non-coronary cusps of the aortic valve. Left-sided IE is more common, with the aortic valve being the most frequently affected valve among KTRs with IE [4, 8, 13, 14]. In some studies, the mitral valve was reported to be the valve commonly affected [3, 15]. Fever on presentation has been found in more than 85% of cases [13, 14]. Other clinical presentations may include nonspecific symptoms such as headaches, vomiting, weakness, or seizures [13, 16]. A definite clinical diagnosis of IE was made in this patient using the modified Duke's Clinical criteria [17]. Therefore, the definite clinical diagnosis of IE complicated by metastatic brain abscesses and the response to therapy corroborated the least likelihood of opportunistic brain infections. The negative results on the workup of all these other differentials, as seen in Table 1, also made those differentials highly unlikely.

Regarding the microbiology of IE, data from the Spanish registry of patients who had IE between 2008 and 2018 found predominantly staphylococcal species (39.7%) and streptococcal species (25.9%) among non-transplant patients with IE versus a predominance of staphylococcal species (57.7%) and enterococcal species (16.5%) among solid organ transplant (SOT) recipients who had IE [15]. Staphylococcal and enterococcal species were the causative organisms in 67.8% and 16.1%, respectively, of IE among KTRs in that Spanish cohort [15]. Moshkani *et al.*, on the contrary, reported an enterococcal IE preponderance in the Iranian study between 2000 and 2010 [13].

Enterococcus bacteremia, which may be a complication of urinary tract infection (UTI) is a risk factor for endocarditis [9, 13, 18–20]. A normal colonoscopy and the absence of gastrointestinal (GI) symptoms make the GI a less likely source of the enterococcal bacteremia seen in this patient. Since UTI, symptomatic or asymptomatic, is the commonest infection among KTRs, we postulate that this patient might have had a community-acquired enterococcal UTI that might have caused bacteremia and then subsequently IE. Otherwise, being on immunosuppressants could have contributed to the enterococcal bacteremia seen in this case [21]. It should also be noted, however, that in the general population, a significant number of patients with enterococcal IE have an unknown portal of entry [21]. Among KTRs in the Swiss Transplant Cohort Study, certain risk factors for bacteremia were identified within the first year following transplantation. These risk factors, which include the recipient's age (an average of 58 years among cohort), deceased donor grafts, pre-transplant medical comorbidities such as diabetes mellitus, as well as post-transplant medical comorbidities such as hypertension, metabolic disorders, and cardiopulmonary diseases, may increase the risk of IE. Additional significant risk factors for bacteremia that were noted among the KTRs in the cohort included surgical site complications and other surgical complications such as vascular complications, anastomosis complications, bleeding, and graft rejection within the first year following transplantation [22].

A beta-lactam such as penicillin, ampicillin, or another type of cell-wall inhibitor such as vancomycin has been used as part of a combination therapy for enterococcal endocarditis [23]. These beta-lactams, however, exhibit differences in their antibacterial activity against enterococcus species, with ampicillin having the highest activity while cephalosporins, with the exception of newer generations such as ceftaroline, exhibit the lowest activity. However, the overall antibacterial activity of beta-lactams is generally poor, therefore, when administered as a monotherapy, result in failure to achieve a microbiological cure [24]. Microbiological killing and sterilization of vegetations in enterococcal IE therefore requires the addition of aminoglycosides for a synergistic killing action [17]. Thus, for several years, the synergistic action of penicillin and gentamicin combination has been the cornerstone of enterococcal IE treatment. Nonetheless, a study by Rafei *et al.* showed that a dual beta-lactam therapy of

Table 1 Summary of laboratory investigations

Parameter	31/03/2021	15/04/2021	22/04/2021
Hemoglobin	15 g/DL		
WBC	11.2×10^9/L		
Neutrophils	8.28×10^9/L		
Lymphocytes	2.06×10^9/L		
Platelets	161×10^9/L		
S-Na^+	135 mmol/L	138 mmol/L	136 mmol/L
S-K^+	3.5 mmol/L	4.9 mmol/L	4.5 mmol/L
S-Cl^-	110 mmol/L	101 mmol/L	100 mmol/L
S-HCO_3^-	24.5 mmol/L	24 mmol/L	
Urea	5.8 mmol/L	5.9 mmol/L	6.5 mmol/L
Creatinine	107 µmol/L	109 µmol/L	99 µmol/L
eGFR	68 mL/min/1.73 m^2	66 mL/min/1.73 m^2	88 mL/min/1.73 m^2
ESR	6 mm fall/h		
CRP	210 mg/L		
S-CrAg test	Negative		
Urinalysis	Proteinuria 1+, microscopic hematuria 2+, no WBC casts		
Fungitel assay	35 pg/mL (0–60)		
S-PCR for JC virus	Negative		
S-PCR for CMV	Negative		
HIV 1 & 2	Non-reactive		
S-Tacrolimus levels	4.6 ng/mL	7.9 ng/mL	
S-Toxo IgG & IgM	Negative		
Blood cultures and sensitivities	First: no bacterial growth after 5 days Second: Enterococcus faecalis Resistance—penicillin, ampicillin, ceftriaxone, and levofloxacin Sensitivity—vancomycin, gentamicin, and imipenem cilastatin		

S serum, *PCR* polymerase chain reaction, *Ig* immunoglobulin, *toxo* toxoplasmosis, *WBC* white blood cells, *Na^+* sodium, *K^+* potassium, *Cl^-* chloride, *HCO_3^-* bicarbonate, *eGFR* estimated glomerular filtration rate, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *CrAg* cryptococcal antigen test, *JC* John Cunningham, *CMV* cytomegalovirus; *HIV* human immunodeficiency virus

ampicillin-ceftriaxone combination is equally safe, efficacious, and associated with lower rates of nephrotoxicity [25]. This regimen was, however, not an option for our case since the isolated Enterococcus spp. was resistant to penicillin and ceftriaxone. The option of imipenem cilastatin was limited by the initial presentation of seizures our patient had and the initial high doses of anticonvulsive drugs the patient needed for seizure control. A study by Cannon *et al*. that showed that imipenem was associated with a higher risk of seizures when compared with other non-carbapenem antibiotics, which had an impact on the decision not to use imipenem [26].

According to multiple studies, prolonged gentamicin-based treatments for enterococcal bloodstream infections and IE have been associated with gentamicin toxicity, therefore, a 2-week course of therapy has been suggested [23]. International guidelines however, recommend a 6-week treatment with vancomycin and gentamicin combination therapy for patients who have penicillin-resistant enterococcus IE [17]. Vancomycin and gentamicin each cause ototoxicity and nephrotoxicity on their own, and the likelihood of these side effects increases when used combined. Despite the increased risk of toxicity of vancomycin–gentamicin combination therapy, we could barely compromise the 6 weeks of combination therapy since our patient had multiple brain abscesses complicating the penicillin-resistant enterococcal IE. The 6-week antibiotic therapy we gave to this patient conforms to the current consensus of treating multiple bacterial brain abscesses for a duration of 6–8 weeks. It is also recommended that brain abscesses complicating infective endocarditis, for which a blood-cultured microorganism has been identified, should be treated with antibiotics that are effective against the isolated microorganisms [27].

In view of a probable adrenal suppression due to the prolonged prednisolone intake, an abrupt withdrawal of the prednisolone in the setting of the acute IE might trigger adrenal insufficiency or the more dangerous acute adrenal crises. The dose of the chosen steroid is increased to mimic the body's natural stress response. In our patient, when an infection was suspected, prednisolone was initially substituted for hydrocortisone because of its similarity to the body's natural cortisol. In addition, despite being less potent than prednisone, it has the advantage of reducing the overall immunosuppressive effect while providing the necessary anti-inflammatory action [28]. However, the mass effect seen on the brain MRI and evidenced clinically by the seizures and decreased GCS necessitated a change back to prednisolone and to an even higher dose. Neither aspirations of the brain abscesses, abscess drainage, nor cardiac valve surgery were indicated or feasible [17].

Although IE is uncommonly reported in KTRs, it is associated with significant morbidity and mortality [4, 5]. Relapses are common after enterococcal endocarditis treatment. They are usually asymptomatic and can occur more than 6 months after the initial diagnosis of IE [29, 30]. According to a Spanish study by Pericàs *et al.*, relapse rates were significantly higher among individuals with enterococcal IE within a year of a possible or confirmed diagnosis of enterococcal endocarditis. A positive blood culture beyond 7 days of effective antibiotic therapy (persistent bacteremia) was identified as the only risk factor [31].

In the general population, mortality from neurological complications is substantially higher than mortality from non-neurological problems. Besides brain abscesses, other severe complications are meningitis, intracerebral haemorrhage (ICH), brain aneurysms, and ischemic strokes [30]. Pericàs *et al.*, in the Spanish study that was previously mentioned, observed some acute and long-term non-neurological complications. These complications included new onset of heart failure, septic shock, paravalvular complications, moderate–severe chronic renal disease, and moderate–severe liver disease, and predicted death within a year of a possible or confirmed diagnosis of enterococcal endocarditis [31].

It also poses a serious threat to the graft function [13]. Early kidney graft injury is associated with peripheral arterial diseases, diabetes mellitus, the use of more than one nephrotoxic drug, heart failure, and shock requiring inotrope administration [5]. Conversely, concomitant CMV infection is associated with a decline in the kidney graft function within 6 months after the initial diagnosis [13].

Conclusion

Infective endocarditis with septic embolization to the brain should be considered in KTRs with multiple rim-enhancing lesions, especially in the late post-transplant period on maintenance immunosuppressive therapy. Enterococcus spp. are an emerging cause of IE in KTRs. The microbiological cure of ampicillin-resistant enterococcal IE requires the synergistic combination of a cell wall active agent and an aminoglycoside over a prolonged period. This has the potential risk of ototoxicity and nephrotoxicity.

Abbreviations

CMV	Cytomegalovirus
ESKD	End-stage kidney disease
IE	Infective endocarditis
IV	Intravenous
KBTH	Korle-Bu Teaching Hospital
KTR	Kidney transplant recipient
MPA	Mycophenolic acid
MRI	Magnetic resonance imaging
UTI	Urinary tract infection

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Author contributions

IA, NMJ, and VB were involved in the conception, design, and drafting of the manuscript. EK, ML, and DA revised the manuscript critically for important intellectual content and approved the final version of the write-up. All authors read and approved the final manuscript.

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Availability of data and materials

All data and information related to the management of this patient is available at the Department of Medicine and Therapeutics in Korle-Bu Teaching Hospital and can be released upon request.

Declarations

Ethics approval and consent to participate

Not applicable in this section.

Consent for publications

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that no competing interests.

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