



Heartbound Intruders: Deciphering a Case of *Klebsiella* Endocarditis

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Abstract

Gram-Negative Endocarditis (GNE) presents a formidable diagnostic and therapeutic challenge due to its intricate clinical manifestations, elusive etiology, and limited treatment options. Although rare, GNE typically manifests in patients with long-term catheters or cardiac devices, underlying structural heart disease, Immunosuppressive Conditions, Or Intravenous Drug Use (IVDU). We describe an unusual case of GNE secondary to *Klebsiella pneumoniae*, in a patient without known risk factors.

Introduction

Infective Endocarditis (IE) has an estimated annual incidence that ranges from 3 to 7 cases per 100,000 person-years [1]. GNE constitutes between 1% to 10% [cite] of these cases, but its prevalence increases among specific patient populations. Previously, GNE was thought to predominate amongst individuals with IVDU, but over the past 15 years, epidemiology has shifted towards a stronger association with older age, immunosuppression, and significant healthcare exposure [2]. GNE is rare as these bacteria usually exhibit lower adherence to heart valves and heightened susceptibility to antibiotics with bactericidal properties [3].

Conventionally, GNE is divided into two primary categories: those caused by HACEK Gram Negative Bacilli (GNB), which include *Haemophilus* sp., *Aggregatibacter* sp., *Cardiobacterium* sp., *Eikenella corrodens*, and *Kingella* sp.; and those caused by non-HACEK GNB. The latter are usually *Pseudomonas* sp. and members of the Enterobacteriaceae family. Both HACEK and non-HACEK GNE have similar incidences, but non-HACEK GNE carries a much higher mortality of 20% to 30% compared with HACEK GNE, which is only 2% [cite]. Here we present a unique case of a 60-year-old female who was found to have *Klebsiella pneumoniae* GNE of the tricuspid valve without the usual risk factors and without a known source.

OPEN ACCESS

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Received Date: 24 Mar 2024

Accepted Date: 10 Apr 2024

Published Date: 16 Apr 2024

Citation:

Allena N, Qasim A, Ravish S, Kasule SN, De La Cruz A. Heartbound Intruders: Deciphering a Case of *Klebsiella* Endocarditis. *Ann Infect Dis Epidemiol.* 2024; 8(1): 1071.

ISSN: 2475-5664

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Case Presentation

A 60-year-old female with a past medical history of type 2 diabetes mellitus, hypertension, cirrhosis complicated anemia and thrombocytopenia, and previous colonic angioectasia was initially hospitalized in September 2023 for diffuse arthralgia. She was diagnosed with Lyme disease, but later developed sepsis secondary to *Klebsiella pneumoniae* bacteremia, and a right upper extremity Deep Vein Thrombosis (DVT). Computed Tomography (CT) angiogram of her chest revealed several, sub-centimeter, right lobe ground glass opacities and a 2.5 cm × 0.9 cm, somewhat wedge-shaped, density in the right middle lobe. CT of the abdomen and pelvis was only notable for hepatosplenomegaly. Esophagogastroduodenoscopy and push-enteroscopy performed for anemia were unrevealing. Echocardiogram showed mild tricuspid regurgitation, severe pulmonary hypertension, and a normal ejection fraction. Urine cultures were negative. Though no source was found, she completed 10 days of antibiotics for the bacteremia and 28 days of doxycycline for the Lyme disease. The DVT resolved in six days without anti-coagulation. The lung findings were planned for outpatient follow-up.

In October, 2023 the patient was readmitted with a 2-week history of worsening shortness of breath and dull, retrosternal chest pain. She was hypotensive on arrival to 83/42, with a fever of 101.2°F, a heart rate of 137 beats per minute, and a respiratory rate of 26 breaths per minute. A chest

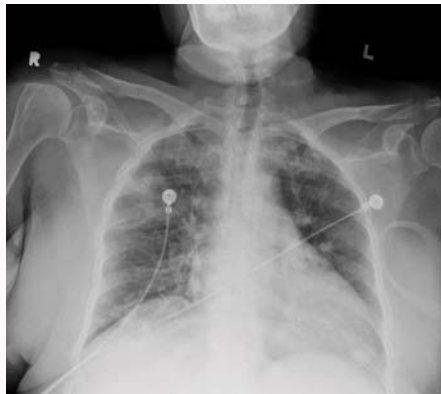


Figure 3: TEE showing the 1.6 cm x 0.9 cm vegetation on the tricuspid valve.



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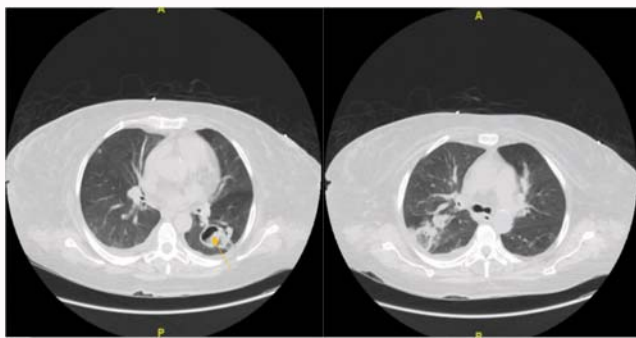


Figure 4: Doppler showing severe tricuspid regurgitation.



Figure 4: Doppler showing severe tricuspid regurgitation.

X-ray showed mild congestive failure alongside a superimposed right upper lobe pneumonia (Figure 1).

Initial laboratory results were concerning for lactic acidosis of 9.7 mmol/L (range 0.5–1.6), a neutrophil predominant leukocytosis of $19.7 \times 10^9/L$ (range $4.8\text{--}10.8 \times 10^9/L$), a hemoglobin of 6.4 grams/dL (range 12–16 g/dL), and a platelet count $63 \times 10^9/L$. Creatinine was 1.7 mg/dL (range 0.5–1.5), which was significantly increased compared to her baseline of 0.6 mg/dL.

Patient's hypotension remained refractory to fluid boluses and she was eventually transferred to the Medical Intensive Care Unit (MICU) for initiation norepinephrine. Vancomycin, piperacillin-tazobactam, and doxycycline were started empirically for pneumonia, with concern for Multi-Drug Resistant Organism (MDRO) and Methicillin Resistant Staphylococcus Aureus (MRSA) given her recent hospitalization. Blood cultures from admission grew *Klebsiella pneumoniae*, with an identical susceptibility profile to the *Klebsiella pneumoniae*, which grew in September 2023. The organism also grew from her urine cultures. Repeat blood cultures on day 2 and 3 of hospitalization also grew *Klebsiella pneumoniae*. Given concern for an invasive source of bacteremia, she underwent Computed Tomography (CT) chest, which revealed new cavitory lesions, including a 4 cm x 4.5 cm lesion in the right upper lobe and a 4 cm x 3 cm lesion in the upper aspect of the left lower lung, raising concerns of septic embolism (Figure 2).

Computed tomography of the abdomen and pelvis with and later without contrast was again unrevealing. TTE was negative for vegetations, but Transthoracic Echocardiogram (TEE) unveiled an erratically mobile structure measuring 1.6 cm x 0.9 cm attached to

the tricuspid valve (Figure 3) consistent with a vegetation and severe tricuspid regurgitation (Figure 4). Ophthalmology evaluation ruled out concurrent *Klebsiella pneumoniae* endophthalmitis.

By this time, patient had been stabilized and transferred out of the MICU to the general floors. Vancomycin and piperacillin-tazobactam were de-escalated to monotherapy with Ceftriaxone 2 grams daily. Following the results of the TEE ciprofloxacin 500 mg twice daily was added for combination therapy as recommended in the American Heart Association guidelines for non-HACEK gram negative endocarditis [cite]. Patient was transferred to a tertiary care center for possible catheter vegetectomy.

Discussion

Non-HACEK GNE is an infrequent yet severe infection, often acquired in a hospital setting, and primarily affecting elderly individuals. Cases attributed to *Enterobacterales* typically are typically community acquired, involve the mitral valve, and originate from genitourinary sources. Conversely, GNE cases caused by Non-Fermenting Non-Glucose-Fermenting Bacilli (NF-NGB), such as *Pseudomonas* sp., are more commonly associated with right valve involvement and central venous catheters. Historically, the connection of non-HACEK Gram-negative endocarditis with IVUD constrained the breadth of earlier investigations, potentially introducing reporting bias. The initial systematic review of GNE, which spanned from 1945 to 1977 only focused on individuals with IVUD, and revealed an incidence of IE in this group of 11% to 32%. GNE comprised 13% of cases [4]. The International Collaboration on Endocarditis conducted a prospective cohort study from 2000 to 2005, examining 2761 cases of infectious endocarditis. Gram-negative endocarditis constituted

approximately 1% to 10% of cases, primarily attributed to HACEK organisms. Non-HACEK Gram-negative organisms were identified in less than 1.8% of all endocarditis instances, with *Escherichia coli* and *Pseudomonas aeruginosa* being the most prevalent. Among these cases, 57% were associated with healthcare settings, often linked to implanted endovascular devices or intravenous drug misuse [9]. Endocarditis caused by *Klebsiella pneumoniae* represented only 10% of cases of non-HACEK GNE.

Our patient grew an atypical organism even for non-HACEK GNE and her only identifiable risk factor was her cirrhosis. She neither partook in IVDU nor had cardiac devices or significant central venous catheter use. We briefly considered whether her DVT had been a septic thrombophlebitis, but it self-resolved in such a short time, this seemed unlikely. Although difficult to prove, we propose that patient developed GNE sometime between her initial bacteremia in 9/2023 and her return 10/2023. Investigations for a primary source were ultimately negative. We do note her urine culture also grew *Klebsiella pneumoniae*, but patient had no urinary symptoms and her imaging of her kidney and bladders were negative. We believe the *Klebsiella* in her urine represented a descending infection.

Non-HACEK organisms constitute the majority of Gram-negative bacteremia, but the occurrence of hematogenous seeding of cardiac valves remains rare. Gram negative bacilli have heightened sensitivity to bactericidal antibiotics and a reduced tendency to adhere to impaired endothelium [cite]. Noteworthy exceptions to this typical pattern include *Salmonella*, possibly owing to its capacity to bind, invade, and proliferate in normal endothelium and lymphoid tissue; and *Pseudomonas*, which produces and thrives in a biofilm [12]. *Klebsiella* sp. usually produce transient infections, but they have the potential to metastasize to various organs, leading to septic complications even without concurrent endocarditis. Predisposing factors for invasive infection include liver cirrhosis, hepatobiliary disease, diabetes mellitus, asplenia or hyposplenia, neoplasia, chronic alcoholism, and the use of corticosteroids [15]. An analysis of 50 cases revealed when the heart is involved, the aortic valve is frequently affected, followed closely by the mitral valve [16]. The mortality rate in these instances exceeds 50%. It is interesting to note our patient's involved valve was the tricuspid, which is also atypical.

As with IE in gram positive organisms, echocardiogram is essential to the diagnosis of GNE. According to the ICE-PCS registry, intracardiac abscesses were documented in 25% of individuals with non-HACEK Gram-negative endocarditis, while paravalvular complications were observed in 31% of cases [19]. Transthoracic echocardiogram exhibits a lower sensitivity (50-70%) in detecting valve vegetation compared to transesophageal echocardiography (>90%) [20]. Consequently, in high-risk patients displaying an atypical clinical course, such as recurrent fever, coupled with persistent bacteremia of unidentified origin caused by common Gram-negative bacilli, it is advisable to consider transesophageal echocardiography, even if no vegetation is identified through transthoracic echocardiography. This was the case in our patient whose TTE in 10/2023 was relatively unchanged from her TTE in 9/2023, but whose TEE revealed her large vegetation. The management of infectious GNE involves a combination of antibiotics and surgery in approximately half of the cases. Antibiotic therapy includes a Third-Generation Cephalosporin (TGC) for four to six weeks combined with an aminoglycoside (gentamicin and amikacin) or a fluoroquinolone. In cases of TGC resistance, piperacillin-tazobactam is considered an alternative [21].

The choice between medical treatment alone and a combined medical and surgical approach should be tailored to each patient's specific circumstances. Still, cardiac surgery is typically advocated as a fundamental aspect of the treatment for non-HACEK endocarditis, particularly in cases involving *Pseudomonas*. This recommendation stems from the elevated mortality rates associated with conservative medical approaches. Individuals with TEE findings indicating valve perforation, rupture of chordae tendineae, intra-cardiac abscesses, or paravalvular extension of infection should be promptly referred for surgical evaluation. Furthermore, factors traditionally associated with indications for valve surgery, such as deteriorating heart failure, persistent positive blood cultures, recurrent emboli and the presence of multidrug-resistant Gram-negative bacteria, may also be considered as additional factors for cardiac surgery.

Ultimately, it was determined that our patient would be better managed at a tertiary center where she could be evaluated for possible surgery.

Conclusion

In conclusion, non-HACEK Gram-negative endocarditis, although infrequent, presents a formidable clinical challenge with potentially severe consequences. This complex infectious entity is often associated with healthcare settings, affecting individuals with significant comorbidities, and its incidence and characteristics may vary across demographics and geographical regions. Non-HACEK GNE requires a high index of suspicion, and collaboration among infectious disease specialists, cardiologists, and cardiothoracic surgeons. Ongoing research and a continual refinement of treatment strategies are crucial to improve outcomes and mitigate the impact of this life-threatening condition.

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