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Native aortic valve *Staphylococcus warneri* endocarditis after COVID-19 infection: a case report and a review of literature

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We report a case of *Staphylococcus warneri* native valve endocarditis in an immunocompetent healthy adult, without known risk factors for infective endocarditis, two months following COVID-19 infection, who recovered with conservative treatment. Additionally, we reviewed previous cases of native valve endocarditis caused by *Staphylococcus warneri* and summarized the main clinical implications.

Key words: Native valve endocarditis; coagulase-negative staphylococcal infection; COVID-19.

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Native valve infective endocarditis (NVE) is an uncommon occurrence, with an incidence rate of 2–10 cases per 100,000 person-years [1]. *Staphylococcus warneri* is a coagulase-negative staphylococcus (CoNS) that is part of the normal skin flora, found mainly in the nares, head leg, and arms [2]. It is often considered a contaminant in clinical settings and therefore poses a diagnostic challenge in ascertaining its role as a pathogen. *Staphylococcus warneri* has occasionally been isolated in nosocomial bacteremia associated with immunocompromised or with the presence of prosthetic devices [2].

CoNS, a common cause of prosthetic valve endocarditis, are uncommon in NVE [3]. *Staphylococcus warneri* in particular is an extremely rare pathogen of NVE, and when occurs, is associated with predisposing factors. Herein, we present a case of NVE caused by *S. warneri* in a young healthy patient following a SARS-CoV-2 infection, with none of the classical risk factors.

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CASE PRESENTATION

A 19-year-old man presented to our hospital with four days of severe frontal headache and fever up to 39.5°C, accompanied by dry cough, nausea, vomiting, and anorexia. Two months prior to admission he suffered from a two-week febrile illness with a dry cough, which resolved spontaneously. Despite the fact that the patient resides in an ultraorthodox Jewish community which had a high prevalence of COVID-19 at that time, he was not tested for SARS-CoV-2. A detailed past medical history and review of systems were otherwise unremarkable.

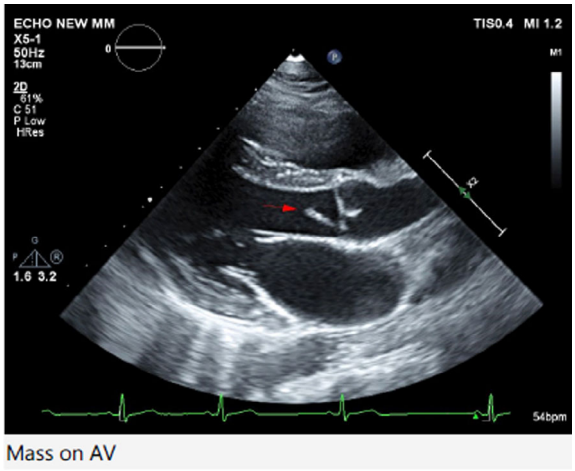
Upon admission, vital signs were normal, physical examination was unremarkable except for a systolic murmur heard best over the fifth intercostal

space at the left midclavicular line. Specifically, he had no wounds that could be a source of skin flora entry. Initial laboratory workup, showed elevated creatinine of 139 µmol/L (normal – 62–115 µmol/L), hypokalemia 2.8 mmol/L (normal – 3.5–5.1 mmol/L), normal white blood cell count of 7000 U/L (normal – 4,000–10,500 U/L) with lymphopenia of 500 U/L (normal – 1070–3120 U/L). The C-reactive protein (CRP) was elevated at 23.5 mg/dL (normal <0.5 mg/dL), erythrocyte sedimentation rate (ESR) was elevated at 38 (normal 1–20), and ferritin was also elevated at 588 ng/ml (normal 22–322 ng/ml). Liver enzymes were normal, as was the international normalized ratio (INR) and the D-dimer levels.

Electrocardiogram (ECG) showed normal sinus rhythm with a normal P-R interval and no signs of ischemia or myocarditis. Chest X-ray and computerized tomography scan of the head, chest, abdomen, and pelvis were unremarkable. A nasopharyngeal swab tested by RT-PCR for SARS-CoV-2 was negative ([N, Nsp2 genes], NeuMoDx™ SARS-CoV-2 assay, NeuMoDx Molecular, Inc).

Due to the aforementioned murmur, a transthoracic echocardiography (TTE) was performed and demonstrated a possible aortic valve vegetation (Figure 1). A transesophageal echocardiography (TEE) performed two days later revealed an oblong echogenic mobile mass, measuring up to 13 mm in length on the aortic valve, attached to the left coronary cusp on its ventricular aspect, and a second vegetation on the non-coronary cusp of the aortic valve measuring 8 mm in length. There was no aortic regurgitation or outflow obstruction.

Two sets of blood cultures, the first taken upon admission and the second drawn three days after, grew (time to positivity 13 h and 41 minutes) a coagulase-negative Staphylococcus that was identified by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) (VITEK® MS, bioMérieux) as *S. warneri* (99.9% confidence). The identification was verified by sequencing the 16S rDNA real-time PCR amplicon as previously described, sequencing results were analyzed with Geneious bioinformatics software and compared to the National Center for Biotechnology Information (NCBI) world database for bacterial species (International Nucleotide Sequence Database Collaboration) [4].



Mass on AV

Fig. 1. Mass on the aortic valve as seen on TTE (red arrow).

Following the CLSI breakpoints [5], the isolate was susceptible to oxacillin/methicillin (MIC ≤0.25 mcg/mL), gentamicin (≤0.5 mcg/mL), rifampicin (≤0.5 mcg/mL), clindamycin (≤0.25 mcg/mL), and trimethoprim-sulfamethoxazole (≤10 mcg/mL).

A SARS-CoV-2 IgG serological test (LIAISON® SARS-CoV-2 IgG, DiaSorin) was positive (45.7 AU/ml, positive value ≥15 AU/mL), thus confirming prior infection.

Immunologic studies included normal complement and rheumatoid factor levels and negative antinuclear antibody. HIV testing was negative.

A diagnosis of endocarditis with two major modified duke criteria [6] was made, and the patient was empirically treated with intravenous vancomycin and ceftriaxone. Upon receipt of susceptibility results, treatment was changed to cefazolin. The patient was discharged after 14 days and completed a six weeks treatment via a peripherally inserted central catheter. At follow-up, post-completion of the antibiotic course, the patient has recovered clinically. TTE performed at that time demonstrated unchanged vegetation upon the aortic valve.

DISCUSSION

Literature review

Staphylococcus warneri is a gram-positive bacterium, a member of the coagulase-negative staphylococci family. It is a part of the normal skin flora, present in approximately 50% of healthy adults [7]. Compared with other members of the coagulase-negative staphylococci, *S. warneri* is considered to be a weak pathogen, usually causing a disease in immunocompromised patients or in those with prosthetic devices [3]. The majority of patients with CoNS NVE undergo surgery, more than in patients with NVE due to *S. aureus* or viridans group streptococci [8].

A literature review of former cases describing NVE caused by *S. warneri*, yielded a total of 11 reports in adults as shown in Table 1.

Dan et al. [9] were the first to describe a case of *S. warneri* NVE in 1984 in a young patient who underwent vasectomy two weeks prior. The patient age

Table 1. A summarized review of previous cases reporting *Staphylococcus warneri* endocarditis

Age/ Sex	Predisposing factor	Valvular disease	Echocardiographic findings	Diagnosis	Dissemination	Treatment and outcome	Original article
32/ M	Vasectomy operation 2 weeks prior	None	Aortic vegetation with Insufficiency	Positive cultures from vegetations	Popliteal artery embolism	ABX—penicillin & gentamycin—4 weeks Intervention—AVR	Dan et al. 1984 [9]
66/ M	Hip replacement 1 year prior (remote possibility)	None	Mitral insufficiency and Aortic ring abscess	Duke's: 2 major criteria—Definitive Dx	Vertebral OM	ABX—vancomycin and gentamycin for 4 weeks, following vancomycin & rifampin for 2 weeks Intervention—AVR, MVR, and abscess debridement	Wood et al. 1989 [12]
64/ M	Cirrhosis	None	Mitral aortic and pulmonic vegetation (upon autopsy)	Bacteremia, emboli and vegetations on autopsy	Septic emboli to kidney, spleen	ABX—vancomycin &gentamycin for 14 days -> death	Kamath et al. 1992 [10]
48/ M	L4-5 Disc prosthesis 2 years prior	None	Aortic insufficiency	Duke's: 2 Major, 1 minor criteria—Definitive Dx	None	ABX—vancomycin and fusidic acid followed by rifampin and fusidic acid	Stollberger et al. 2006 [15]
78/F	None	Aortic sclerosis	Mitral insufficiency and atrial mobile echo density	Duke's: 2 major criteria—Definitive Dx.	None	ABX—nafcillin & gentamycin followed by nafcillin for 6 weeks	Kini et al. 2010 [3]
59/ M	Scalp sutures 2 weeks prior	None	Mitral vegetation	Duke's: 2 major criteria—Definitive Dx	None	ABX—nafcillin followed by cefazolin for 6 weeks	Bhardwaj et al. 2016 [32]
79/ M	None	Degenerative valvular disease requiring surgery	Aortic stenosis and Mitral insufficiency with mitral vegetation	Duke's: 1 Major and 2 minor criteria—Possible Dx	None	ABX—Vancomycin and gentamycin followed by oxacillin Intervention—refused by patient	Diaconu et al. 2019 [33]
28/F	None	None	Aortic insufficiency	Positive culture from Valve biopsy	Frontal micro-embolism	Not specified	El Nakadi et al. 2020 [13]
59/ M	Diabetes (insulin injections)	Severe aortic insufficiency +bicuspid valve	Mitral regurgitation with vegetation and Aortic vegetation	Duke's: 2 major and 1 minor criteria—Definitive Dx	None	ABX—ampicillin sulbactam & gentamycin followed by cefazolin Intervention—AVR and MVR	Yamamoto et al. 2020 [34]
50/ M	None	Mitral regurgitation	Not specified	Bacteremia and septic emboli	Cerebral aneurysm	ABX—treatment not specified	Taneda et al. 2021 [11]

Table 1 *(continued)*

Age/ Sex	Predisposing factor	Valvular disease	Echocardiographic findings	Diagnosis	Dissemination	Treatment and outcome	Original article
72/F	None	Mitral regurgitation	Mitral vegetation with regurgitation	Duke's: 2 major and 3 minor criteria—Definitive Dx	Discitis and cerebral septic emboli	ABX—Cefazolin followed by penicillin for 6 weeks than amoxicillin for 6 months	Kurihara et al. 2021 [35]

ABX, Antibiotics; OM, Osteomyelitis; AVR, Aortic valve replacement; MVR, Mitral valve replacement; Dx, diagnosis.

range in the cases reviewed was 28 to 79, with a male predominance—eight of the 11 cases. Interestingly, it appears that an increase in cases reported had occurred in the last two years, with five of the 11 cases taking place from the end of 2019 to this day.

Five of the previous cases have shown damage to more than one heart valve at the time of diagnosis, with three cases requiring a surgical intervention. Mortality occurred in only one case [10]. The rest of the cases ended with good clinical outcome, excluding one case in which the long-term outcome has not been specified [11].

Wood et al. [12] were the first to describe a patient with no discernable risk factors other than a hip replacement performed a year prior to the development of *S. warneri* NVE. Since then, with the exception of a single case report [13], in all previous cases, the patient had either a pre-existing degenerative valvular condition that made him susceptible to NVE, or a known risk factor for acquiring CoNS bacteremia such as intravascular devices [14], skin puncture, or immunocompromised state. In two cases, recent orthopedic prosthetic implants (prosthetic joint and a lumbar disc) were mentioned as possible source, and subsequently refuted because there was no evidence of prosthesis infection at the time of the endocarditis [12, 15].

Our case is unique in the sense that a young healthy patient without any signs of previous valvular condition, and without any known risk factors, developed *S. warneri* NVE, and fully recovered with conservative antibiotic treatment, without the need for surgical intervention.

SARS-CoV-2 as a potential predisposing factor for endocarditis

Non-bacterial thrombotic endocarditis (NBTE) is a form of non-infective endocarditis that can develop in patients with risk factors [16]. It is the result of fibrin and platelets deposition on the heart valves and is associated with different malignancies and inflammatory conditions that lead to a procoagulant state [17]. NBTE is an under-diagnosed condition, found mostly in autopsies, where its incidence is approximately 1–3.7% [18, 19]. The presumed pathophysiology of NBTE begins with inflammation causing endothelial damage, creating a thrombogenic surface and leading to thrombi on the valvular surface [20]. When transient bacteremia occurs in patients with NBTE, the bacteria may adhere to these deposits, where it multiplies and result in infective endocarditis [21].

The COVID-19 pandemic caused by SARS-CoV-2, created a dramatic impact on global health, affecting millions of people worldwide [22].

COVID-19 is known to cause hypercoagulable and hyperinflammatory states [23].

This hypercoagulable state may cause arterial and venous thrombi, as well as microthrombi, damaging the endothelium [24].

The combination of hypercoagulability, as well as increased inflammatory reaction, may give rise to NBTE, disposing patients to IE [25–27].

A large systemic review of autopsies done on patients with COVID-19 infection has shown the presence of endothelial inflammation, with a procoagulant state and tissue injury of the endothelial cells [28].

Our patient may possibly represent a "missing link" between COVID-19 followed by IE [29, 30].

Possibly, the low rate of TEE performed on COVID-19 patients, due to the hypothetical risk of disease transmission to other patients and healthcare workers [31], may hide the true incidence of this phenomenon.

SUMMARY

We have herein reported a case of native valve endocarditis caused by *S. warneri* occurring in a healthy nineteen-year-old man without any prosthesis, no history of skin puncture, no previous valvular condition, and no indication of immunocompromise. The patient was treated conservatively with antibiotics without indication for surgery and fully recovered.

This article points out that low-virulence bacteria can be the cause of NVE, as demonstrated by the increasing number of cases of *S. warneri* NVE being reported worldwide. Clinicians should have a high level of suspicion when CoNS grows in consecutive blood cultures.

Additionally, clinicians should be aware of the potential risk factor of NBTE that may arise from COVID-19 infection. COVID-19 patients may be at greater risk for these thrombotic complications, and therefore susceptible to IE. TEE and other diagnostic tests should not be avoided, when clinically indicated.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

All authors made a substantial contribution to the case report and approved the final version of the manuscript.

ETHICAL APPROVAL

Written informed consent was obtained from the patient for publication of this case report.

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