Case report

Infected endocarditis caused by *Neisseria mucosa* on a prosthetic pulmonary valve with false positive serology for *Coxiella burnetii* – The first described case

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**Abstract**

We present a case of infective endocarditis (IE) on a prosthetic pulmonary valve in a 36-year-old patient with tetralogy of Fallot (TOF). The patient underwent valve replacement surgery and active antibiotic treatment against Gram-negative cocci (Piperacillin Tazobactam then Ceftriaxone) for a total duration of 42 days with a favourable outcome. The causative agent was *Neisseria mucosa* which was identified on the infected valve by sequencing of 16S ribosomal RNA. To our knowledge, this is the first described case of a *N. mucosa* infective endocarditis on a pulmonary valve. Initially, serologies performed in clinical settings by immunofluorescence for *Coxiella burnetii* antibodies showed a major increase in phase I IgG titers at 1024 (normal values <16) corresponding with the diagnostic criteria for Q fever endocarditis. However, this diagnosis could not be confirmed by the National Reference Center, making it the first reported case of a false positive serology for *C. burnetii* during an infection due to *Neisseria* spp.

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**Background**

Infective endocarditis due to *Neisseria mucosa* is very rare. In 2014, a review of the literature reported a total of 21 cases and none of them concerned the pulmonary valve [1]. Here we describe the first case of infective endocarditis caused by *N. mucosa* on a pulmonary valve. *N. mucosa* is an aerobic Gram-negative diplococcus. It is a commensal bacterium of the human oral cavity but has also been found in other mammals [2]. Phylogenetic analyses show a very high homology between the 16S and 23S ribosomal RNA sequences of the species *N. mucosa*, *N. sicca* and *N. macacae*, suggesting a common designation of these three species as the *N. mucosa* group [3]. A recent study has moreover shown that identification by Matrix Assisted Laser Desorption Ionization - Time of Flight (MALDI-TOF) was excellent to identify the bacteria of the *Neisseria mucosa* group but insufficient to discriminate between the different species within this group [4].

**Case presentation**

We present the case of a 36-year-old patient whose only history was a tetralogy of Fallot, operated during the first year of life and re-operated at the age of 10 years due to pulmonary valvular insufficiency. The patient lived alone in a strict urban environment and had no contact with animals. He had not travelled outside Belgium during the last year and had never used intravenous drugs.

The patient presented to the emergency department with a recurrent fever for one month associated with cough. On admission, cardiac auscultation revealed aortic murmur, whereas the rest of the clinical examination was unremarkable. Laboratory workup showed hyperleukocytosis at 12,000 white blood cells per cubic millimeter and an inflammatory syndrome with increased C-reactive protein at 200 mg/l. The patient was hospitalized, the first aerobic blood culture (day 0) was carried out, showing the presence of *Neisseria* spp. after 18 h of incubation. The second aerobic blood culture (day 1) also showed the presence of *Neisseria* spp. after 19 h of incubation. Both bacteria were identified by MALDI-TOF with a moderate confidence index between 1.7 and 2 log. The formal identification of a species within the genus

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Neisseria was thus not possible. A thoracic computed tomography (CT) showed nodular-looking peripheral pulmonary parenchymal condensation in the right lower lobe. The patient was treated on from day 0 with ceftriaxone which had rapid favourable biological and clinical course. The diagnosis of bronchopneumonia involving Neisseria spp. was given and the patient was discharged on day 9 with a scheduled outpatient cardiac workup.

On Day 13, the patient re-presented to the hospital with yet again a recurrent fever. Several blood cultures were collected, and the patient was readmitted. Empirical treatment with Amikacin and Cefotaxime for 3 days was started. On day 17, a cardiac transthoracic echography showed a 20 × 6 mm mass on the side of the right ventricle compatible with vegetation and suggestive of endocarditis. In view of the patient’s condition and the negative blood cultures, the patient was put on empirical antibiotic treatment with Vancomycin/Gentamicin/Piperacillin-Tazobactam and serology workup was requested following a blood culture negative endocarditis protocol. On day 23, a chest angiography showed pulmonary emboils associated with a pulmonary infarction, while a trans-esophageal ultrasound showed a 20 mm vegetation on the pulmonary valve. Serology performed by immunofluorescence revealed Coxiella burnetii phase I IgG at titer of 1024 with normal values (NV) lower than 16. On the basis of this serology and the echocardiographic result, the diagnosis of C. burnetii infective endocarditis was withheld in accordance with the modified Duke criteria.

Based on this, the antibiotic therapy was switched to Ceftriaxone with the addition of Doxycycline and Hydroxychloroquine (HCQ). On day 32, the patient underwent pulmonary valve replacement surgery during which endocarditis with voluminous vegetation on the pulmonary valve was macroscopically visible. The cardiac valve was sent to the laboratory for conventional culture, but that did not reveal any bacteria. The clinical course was favourable and the patient was discharged on day 46 with the continuation of HCQ and Doxycycline orally and Ceftriaxone by outpatient parenteral antimicrobial therapy.

Polymerase Chain Reaction (PCR) for C. burnetii on the valve did not confirm initial suspicion as results were negative. Also, C. burnetii serology showed a surprisingly rapid decrease in phase I IgG from titer 1024 to 64 in less than 2 months. Based on these findings, Doxycycline and HCQ were terminated. Control of the serological results was carried out by the National Reference Center on collected sera from days 31 and 89. The results were negative for phase I and II IgG and phase I IgM antibodies in both samples and the titer of phase II IgM decreased from >256 to 64 (normal value <16), typically the pattern in case of a false positive IgM result. These results rendered C. burnetii highly unlikely as the cause of this infective endocarditis. A 16S ribosomal RNA amplification was carried out on the valve and showed the presence of a unique product of amplification with sequence corresponding to N. mucosa, which confirmed with certainty its involvement in this infective endocarditis. The patient continued the antibiotic treatment with Ceftriaxone until day 58, totaling six weeks of active antibiotic treatment on this Gram-negative coccus. Six months after the end of the treatment, the patient’s clinical course was strictly favourable and the patient was considered cured.

Discussion

Endocarditis involving N. mucosa is extremely rare. In 2014, a literature review identified 21 cases published between 1971 and 2014 [1]. We have not found any other published cases since then. Interestingly, the authors showed that endocarditis involving this organism occurred mostly in young patients (mean age of 40 years), half of whom were carriers of cardiac predisposition abnormalities, as was our patient. In this review, there were no cases of N. mucosa endocarditis involving the pulmonary valve [1]. Our literature search found no cases involving this species on a pulmonary valve, making it the first described case to our knowledge.

The risk of infective endocarditis in patients who have undergone surgery for tetralogy of Fallot is about 20 times higher than in the general population. The annual incidence varies from 0.13 to 0.6 % depending on the studies and the risk is mainly present during the first six months post-surgery [5]. A recent large retrospective study of 338 patients with prosthetic valves for TOF showed a 50 % mortality rate in patients with endocarditis. The authors conclude on the importance of educating these patients about the risk of prosthetic valve endocarditis. They insist on the need for a high index of suspicion in cases of systemic signs with the need for early multidisciplinary management for these high-risk patients [5].

C. burnetii serological results with positive IgG phase I and II and absence of phase II IgM antibodies coupled with the clinical and echocardiographic data, initially suggested a diagnosis of C. burnetii endocarditis, since the diagnostic criteria were met [6]. Serology control carried out two months later showed a very significant drop in these values. PCR performed on the cardiac valve was negative for C. burnetii. It is well established that C. burnetii IgG values gradually decline over several months but they usually remain positive for years [7,8]. Control of serology was therefore carried out in the National Reference Center and the results could not confirm a C. burnetii infection but yet false positive reaction of IgM. The precise reason for this false positive reaction is unknown. A study highlights that some proteins present in C. burnetii may react with sera of patients with Legionella pneumophila, rickettsial spotted fever and streptococcal pneumonia [9]. Positive results of IgM without seroconversion of IgG antibodies in a follow-up sample are not uncommon and should be interpreted with caution. False positive reactions to serological tests for Q fever have already been reported during infections caused by Legionella, Leishmania, Anaplasma and Rickettsia [10–14]. In the context of endocarditis, cross reactions have been reported several times with Bartonella [15,16]. To our knowledge, cross-reactivity between C. burnetii and Neisseria species has not been described previously. This case highlights the complementary importance of molecular diagnostics in the diagnosis of infective endocarditis.

Conclusion

Neisseria mucosa infective endocarditis on a prosthetic pulmonary valve in a patient with tetralogy of Fallot required valve replacement and six weeks of intravenous antibiotic therapy (Piperacillin Tazobactam followed by Ceftriaxone). The outcome was favourable. To our knowledge this is the first reported case of N. mucosa endocarditis on a pulmonary valve and also the first documented case of cross reactivity of Q fever serology during an infection due to Neisseria spp.

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Not applicable.

Author contributions

All authors were involved in patient care. AA performed material preparation, data collection and analysis. AA wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CRediT authorship contribution statement

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Declaration of Competing Interest

The authors report no declarations of interest.

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