

# Nosocomial Pneumonia from *Neisseria subflava*: Case Report

## *Neisseria subflava*'nın Neden Olduğu Nozokomiyal Pnömoni

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Geliş Tarihi/Received: 12.09.2008  
Kabul Tarihi/Accepted: 02.03.2009

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**ABSTRACT** *Neisseria subflava* is a microaerophilic, gram negative diplococcus and a natural inhabitant of the upper respiratory tract. It has been known to cause endocarditis, meningitis, septic arthritis, endophthalmitis and septicemia. We report a case of a 28-year-old immunocompetent male, who was hospitalized with pulmonary thromboembolism. On day three he developed fever, new right-sided pleural effusion and worsening consolidation. He continued to spike high grade fever despite broad spectrum antibiotics and bronchoscopy and bronchoalveolar lavage (BAL) were performed. BAL cultures grew heavy growth of "*Neisseria subflava*", sensitive to Ceftriaxone and resistant to meropenem and levofloxacin. Diagnosis of "*Neisseria subflava*" was established. The fever resolved within 24 hours of ceftriaxone and the patient continued clinical and radiographic improvement on the therapy. *Neisseria subflava* has seldom been reported to cause lower respiratory tract infection, yet it should be included in the differential diagnosis of nosocomial pneumonia not responding to appropriate treatment. BAL may help to establish the diagnosis.

**Key Words:** Pneumonia; neisseriaceae infections; pulmonary embolism

**ÖZET** *Neisseria subflava*, mikroaerofilik ve gram negatif bir diplokoktur ve normal üst havayolu florasında bulunur. Endokardit, menenjit, septik artrit, endoftalmit ve sepsisemiye neden olduğu bilinmektedir. Pulmoner tromboemboli (PTE) tanısı ile yatırılan, 28 yaşında immün yetmezliği olmayan bir olguyu sunmayı amaçladık. Olgunun üçüncü günde ateş, yeni gelişen sağ plevra sıvısı ve ilerleyen konsolidasyonu ortaya çıktı. Geniş spektrumlu antibiyotik tedavisine rağmen ateşi yükselmeye devam eden olguya bronkoskopi ve bronkoalveoler lavaj (BAL) yapıldı. BAL kültüründe seftriaksona duyarlı, meropenem ve levofloksasine dirençli yüksek miktarda *Neisseria subflava* ürettiği gözlemlendi. *Neisseria subflava* pnömonisi tanısı konuldu. Seftriaksonun 24. saatinde ateşi düşen hasta aynı tedavi altında klinik ve radyolojik düzelme göstermeye devam etti. *Neisseria subflava* alt solunum yolları enfeksiyonlarına neden olan ender görülen bir mikroorganizmadır, ancak tedaviye cevap vermeyen nozokomiyal pnömonide ayırıcı tanılar içerisinde olmalıdır. BAL tanının konulmasında yardımcı olur.

**Anahtar Kelimeler:** Pnömoni; neisseria enfeksiyonları; pulmoner emboli

**Türkiye Klinikleri J Med Sci 2010;30(1):425-9**

**N***isseria subflava*, a nonpathogenic member of *Neisseria* species, is a microaerophilic, gram negative diplococcus and a natural inhabitant of the upper respiratory tract. It is an opportunistic organism associated with endocarditis, meningitis, septic arthritis, endophthalmitis and septicemia.<sup>1-3</sup> This organism has also been reported to cause pneumonia in a neutropenic patient, yet has never been associated with a nosocomial pneumonia in an immunocompetent host.<sup>4-6</sup>

We report a first case of *N. Subflava* pneumonia associated with a pulmonary thromboembolism in an immunocompetent host.

## CASE REPORT

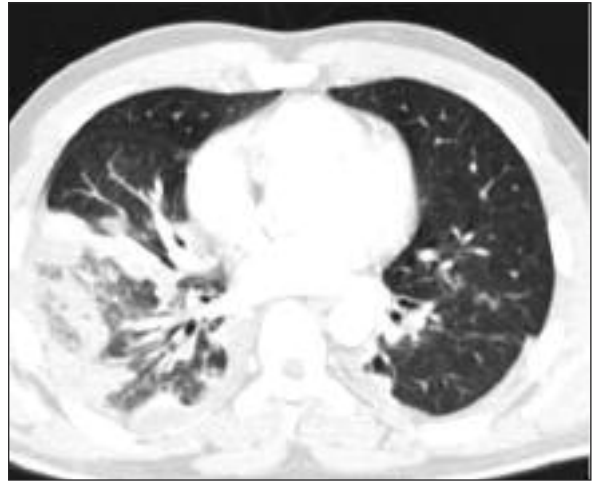
A 28-year-old male, 20 days post cholecystectomy, developed right-sided chest pain and shortness of breath and required hospitalization. On physical examination, his temperature was 37°C, pulse rate 104/min, respiratory rate 30/min and blood pressure 120/70mm-Hg. Fine crackles on the right base and bilateral rhonchi were detected on auscultation. There was no sinus tenderness, post-nasal drip or oro-pharyngeal inflammation.

On the laboratory findings, the white blood cell count was 12.700/uL with 76.4% neutrophils. C-reactive protein was 184.8 mg/L (N: 0-5mg/L) and D-dimer level of 20 µgr/ml (N: 0-0.5 µgr/ml). Chest X-ray (CXR) revealed right diaphragmatic elevation, bilateral hilar enlargement and right lower lobe (RLL) consolidation. Based on the clinical and laboratory findings a computed tomographic pulmonary angiography (CTPA) was performed which demonstrated thromboemboli at the trifurcation of both right and left pulmonary arteries (PA), complete occlusion of left upper lobe PA and partial filling defects in bilateral lower lobe segmental arteries (Figure 1). RLL consolidation was also noticed (Figure 2).

Screening for hypercoagulability status demonstrated normal protein S and protein C antigen lev-



**FIGURE 1:** Computed Tomographic Pulmonary Angiography demonstrated partial filling defect in left lower lobe segmental artery.



**FIGURE 2:** Computerized tomography of the chest revealing right lower lobe consolidation.

els and antithrombin III activity and negative lupus anticoagulant, factor V Leiden and prothrombin gene mutation. He had a decreased protein C activity of 57% (normal range 70-140%). On his ANA profile, anti-ds DNA activity, anti-neutrophil cytoplasmic antibody, anti-mitochondrial antibody, anti-nuclear antibody were all negative. His anti-factor Xa, factor VIII and IX levels were also normal. He had a normal lipoprotein A level and his folate level was 3.1; in the lower limits of normal range (3.1-17.5). Doppler ultrasound showed no evidence of lower limb deep venous thrombosis.

Diagnosis of pulmonary thromboembolism (PTE) was established and he was placed on enoxaparine (6000IU/0.6 ml) subcutaneously and levofloxacin 500 mg intravenously, twice daily. Next day his fever worsened to 39°C and meropenem 1 gram twice daily intravenously was added to the regimen. His dyspnea worsened even further. A repeat CXR revealed a new right-sided pleural effusion with progression of the consolidation. At thoracentesis serohemorrhagic exudative fluid was removed (LDH 960 IU/dl, cholesterol 70 mg/dl). Patients continued to spike high grade fever and developed productive cough. A flexible bronchoscopy was performed which revealed mucoid secretions and edematous mucosa involving the RLL.

Bronchoalveolar lavage (BAL) was obtained from the RLL by wedging an Olympus BF type

P20D bronchoscope under local anesthesia. No suction was used during the insertion of bronchoscope through the upper airways to minimize contamination of the working channel. For BAL, 20-mL aliquots of normal saline were instilled using a syringe attached to the suction port at room temperature. A total of 100 mL of saline were sequentially instilled and immediately retrieved manually. The resultant fluid was filtered through four layers of sterile gauze, pooled and immediately sent to the microbiology laboratory for the staining and culture.

Each sample was separately processed. BAL specimen was mixed and 5  $\mu$ L loopful samples were spread on 2 cm diameter area on the microscopy slides. The smears were allowed to dry, fixed and stained with Gram's stain and the number of bacteria/oil immersion field was reported. Semi-quantitative loop method was used for culture. Three mm (external) diameter loopful (2  $\mu$ L) sputum and for 10  $\mu$ L BAL were spread on Chocolate agar, sheep blood agar, EMB agar and Sabouraud-Dextrose-Agar plate and incubated at atmosphere of 10% CO<sub>2</sub>, 37 °C for 48 hours. Sputum and BAL cultures grew a gram negative diplococcus that was subsequently identified as *Neisseria subflava*. The organism grew aerobically on blood agar and Chocolate agar, as yellow-pigmented colonies. It fermented glucose, maltose, and sucrose, and was oxidase positive, nitrate negative, but nitrite positive. The organism was identified by colony morphology, standard biochemical reactions and Vitek 32 (bio-Merieux, France). *N. subflava* grew in sputum culture dominantly as well as in the BAL culture, more than 10.000 cfu/mL.

Disk diffusion susceptibility testing was performed by Clinical and Laboratory Standard Institute for Neisseria Gonorrhoeae. Isolated colonies suspended from an overnight culture on supplemented chocolate agar medium in 2.0 mL of Mueller-Hinton broth. We mixed the suspension thoroughly on a vortex mixer to break up clumps of growth. The turbidity of the cell suspension was adjusted by adding additional Mueller-Hinton broth or organisms, as required, until the turbidity of the suspension was equivalent to the turbidity

of a 0.5 McFarland standard. The sterile applicator swab was moistened in the standardized cell suspension, and expressed excess moisture by rotating the swab against the glass above the liquid in the tube. The entire surface of each plate was inoculated in three different directions to ensure uniform, confluent growth. Inoculated plates were placed at room temperature for 3 to 5 min to allow the absorption from the inoculums into the medium. When the surface of the medium was dry, we applied the disks of the selected antimicrobial agents to the surface of the medium and tamped them gently with a sterile loop or forceps to ensure that they were in complete contact with the agar surface. All disks were applied approximately the same distance from the edge of the plate and from each other. Then we inverted the inoculated plates (lid side down), and incubated them at 35° C to 36° C in 5% CO<sub>2</sub> for 20 to 24 hours. Zone diameters and interpretive standards for *N. gonorrhoeae* were used to determine susceptibility.

Both, the sputum and the BAL quantitative cultures showed heavy growth of "*Neisseria subflava*", resistant to meropenem and levofloxacin, but sensitive to ceftriaxone. Meropenem and levofloxacin were discontinued and ceftriaxone 2 grams daily, intravenously was resumed. His fever resolved within 24 hours and he remained afebrile throughout the hospitalization. He was discharged on the tenth day on cefixim 400mg/day orally for the next five days. He has been doing well for more than eight weeks after discharge.

## DISCUSSION

*N. subflava* is a member of the chromogenic and usually nonpathogenic group of *Neisseriae*. It is a natural inhabitant of the nasopharynx, saliva, sputum and mucous membranes of the respiratory tract.<sup>7</sup>

It is an opportunistic organism associated with endocarditis, meningitis, septic arthritis, endophthalmitis and septicemia.<sup>1-3</sup> *N. subflava* has seldom been reported to cause lower respiratory tract infection (LRTI). Review of the literature from the past five decades, revealed only one case of pneumonia with bacteremia in a neutropenic patient.<sup>6</sup>

As far as we know, we report the first case of *N. subflava* nosocomial pneumonia in an immunocompetent host. Correlation of the patient's clinical condition and the associated laboratory data is usually helpful in establishing the diagnosis of Neisseria infections. In the present case; his fever, productive cough, leukocytosis, consolidation in the RLL, bronchoscopic findings, quantitative culture results and prompt response to ceftriaxone were diagnostic of *N. subflava* pneumonia.

Certainly PTE can cause fever, yet it would not explain his culture results. Pleural effusion and the consolidation could be a part and partial of PTE and infarction. Hemoptysis is seen in 21% of the patients with infarction in PTE<sup>8</sup>, yet at no stage in the course of his illness our patient developed hemoptysis to suggest infarction. CXR revealed no evidence of "Hampton's Hump" to support infarction over the infection, yet it is seen in 36% of the patients with infarction in PTE.<sup>8,9</sup> Pleural effusions related with infarction may reveal eosinophilia,<sup>10</sup> which was also not the case in our patient.

Could this be a contamination of the specimen during its collection, transportation or laboratory processing? First, there were no signs of sinusitis or upper respiratory tract infection. Besides, we routinely perform sputum and BAL cultures in patients with consolidation whose fever do not resolve with empiric antibiotics and have never recovered heavy growth of *N. subflava*. The specimen was prepared and processed using a strict protocol as described above. Quantitative cultures were also performed and the number of colony forming units was in the range for high specificity and sensitivity. We also wondered if this could have been a "pseudo-infection" related to the procedure of bronchoscopy. Yet, we doubt, our bronchoscope was contaminated with the organism. Neisseria has neither been recovered, using the same instrument nor did any of our bronchos-

copy specimen collected during the same period grew the organism.<sup>11</sup>

We sincerely doubt that this was a drug fever as it would fail to explain consolidation, cough, sputum production and mucosal edema involving the endobronchial tree as well as the microbiological evidence. Extensive work-up also revealed no evidence to suggest immunocompromised state.

Thus, all facts considered, our patient suffered *N. subflava* pneumonia and recovered with appropriate management.

The most common portal for this organism into the circulation is considered to be the oropharynx, as the organism is a part of the normal upper respiratory tract flora;<sup>2-6</sup> which might also have been the case in our patient. We suspect that his recent hospitalization and intubation for the cholecystectomy contributed to the nosocomial nature of the incident. If his pulmonary embolism contributed to the emergence of the pneumonia; it remains a matter of speculation.

Although the majority of nonpathogenic *Neisseria*, including *N. subflava*, are sensitive to penicillin, initial empiric therapy should cover possible beta-lactamase-producing strains while further antimicrobial therapy is guided by the sensitivity results. In the present case, fever did not resolve with the empiric antibiotic therapy, therefore ceftriaxone was started according to the sensitivity results.

In summary, we present a case of nosocomial *N. subflava* pneumonia in an immunocompetent host. We suspect that the condition is under recognized with current practice of empiricism. *N. subflava* pneumonia should be included in the differential diagnosis nosocomial pneumonias not responding to conventional treatment. Quantitative cultures on BAL may support sputum studies to confirm the diagnosis and sensitivity studies should help select appropriate antibiotics regimen.

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