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Severe pneumonia caused by *Nocardia farcinica* and complicated by *Staphylococcus haemoliticus* superinfection

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Abstract. – It is reported the case of a subject 54 years old, painter, drinker and smoker who after an episode of cooling and the occurrence of widespread pain was taking its own initiative, cortisone and analgesics from approximately 30 days. The symptoms worsened and the patient was hospitalized. Chest X-ray and CT scan showed an extensive opacity in the left upper lobe with excavations in the context and also some nodular opacities excavated in the contralateral lung. In the first eight days after admission, the clinical picture despite empirical antibiotic therapy worsened towards adult respiratory distress syndrome (ARDS). On the ninth day after the admission, strains of *Nocardia farcinica* and *Staphylococcus haemoliticus* were isolated from the sputum. The targeted therapy (trimethoprim-sulfamethoxazole, amikacin, etc.) induced a rapid improvement of the clinical picture that was resolved in 6 months. Pneumonia caused by *Nocardia farcinica* is rare but its identification is necessary to set an appropriate therapy.

Key Words:

Nocardiosis, Pneumonia, ARDS, Infection, Molecular biology.

Introduction

Pulmonary nocardiosis is an uncommon and rare infection caused by *Nocardia (N.)* species including *N. asteroides, N. brasiliensis, N. farcinica,* etc. These aerobic actinomycetes can cause a severe clinical picture because of their aggressiveness, tendency to disseminate, difficulty to identify the bacteria and their resistance to antibiotics[1]. Predisposing conditions are immunocompromised host state, an underlying pulmonary disease or treatment with corticosteroids, but the infection can also affect healthy people[2]. Co-existing pathogens are mainly *Aspergillus* species. The mortality from pulmonary nocardiosis is still high and ranges between 14% and 40%, increasing significantly when there is dissemination to the central nervous system. In addition to pulmonary localization, cutaneous and sub-cutaneous spreading was often observed[3]. We describe a case of pulmonary nocardiosis caused by *Nocardia farcinica* and complicated by S*taphylococcus haemoliticus* superinfection.

Case Report

CP, male, aged 54, living in Rome, was admitted to the Emergency Department of our Hospital and then at Division of Pulmonology. He worked as painter, sculptor or cabinet maker. Furthermore, he had a smoking habit (30 packs/year) and drank about 1.5 lt. of wine a day. Thirty days before admission he had got cold during the work and he had developed cough, dyspnea and persistent chest pain in few hours. Initially he had ascribed his symptoms to an inflammation of the spinal column and he had taken betamethasone (1 mg t.i.d.), nimesulide (100 mg t.i.d), and omeprazole (20 mg once a day) with unsatisfactory results. In the same period, he reported scalding of his hands on work using acid-based products. On admission, he suffered from cough, yellow sputum, dyspnea at rest, continuous chest pain localized at the left side, fever (38°). The physical examination revealed general bad conditions, sweaty and pallid skin, tachypnea (28/min), increased rhythmic heart activity (130/min), arterial pression 90/60 mm Hg, body temperature 38°, transcutaneous oximetry (SpO_2) 90%, erythematous and vesicular lesions on the back of both hands. Hypophonesis was found on

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the left of the chest, both posteriorly and anteriorly, with crackles in the subclavear region and in the lower half of the hemithorax.

The chest radiograph revealed opacity in the entire left half of the chest, because of parenchymal consolidation, with nodular opacities in the right half. Computed tomography (CT), performed at the same time, confirmed the extended consolidation of the left upper lobe with signs of air bronchogram and cavitations in the context (Figure 1).

Multiple nodular lesions, most excavated, were also observed in the left lower lobe and right lung. Some of the injuries described were surrounded by halos of ground glass. Pleural effusion was present on the left and several lymph nodes, ranging from 5 mm to 20 mm in size, were visible in the mediastinic stations. No significant alterations were found in the abdomen and brain.

Among blood tests, the red blood cells (RBC) were 4.1×10^6 µL (normal range 4.4-6.0), haemoglobin (HGB) 13 g/dl (normal range 13-18), white blood cells (WBC) 1.8×10^3/µL (normal range 4.3-10.8; neutrophils 85%, lymphocytes 8%, monocytes 4%, eosinophils 2.3%), platelets 95×10^3/µL (normal range 140-400), AST 47 U/L (normal range 15-46), ALT 38 U/L (normal range 11-66), D-Dimer 845, pH 7.38, $PaCO_2$ 36 mmHg, PaO_2 63 mmHg.

The protein electrophoresis showed increase of acute phase proteins; total proteins were 4.56 gr/dl (albumin: 30.6%, alpha1 18.4%, alpha2 29.3%, beta 13.3%, gamma 8.4%) and A/G ratio 0.44.

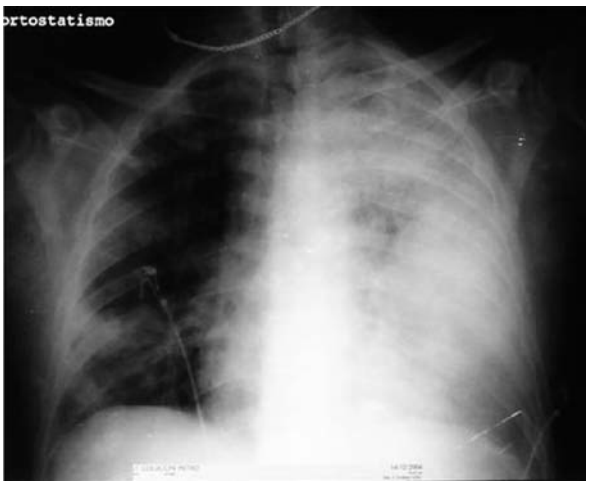

Figure 1. Chest X-ray upon admission.

The research for *Legionella pneumophila* urinary antigen was negative. The sputum culture for common bacteria highlighted the absence of pathogenic flora, while the electrocardiogram showed sinus tachycardia (130/min).

From the first day, were administered antibiotics (cefuroxime 2 g × 2 i.v., clindamycin 600 mg × 2 i.v., clarithromycin 500 mg × 2 i.v.), low molecular weight heparin, oxygen supplementation (Ventimask 50% with a 12 lt/min flow) and nutrition support therapy (omeprazole, ketorolac tromethamine, rehydration solutions).

On day 2, a strain of vancomycin-susceptible *Staphylococcus haemoliticus* was revealed on cultured sputum samples. On day 3, cefuroxime and clarithromycin have been replaced with meropenem (1 g t.i.d.) and vancomycin (500 mg b.i.d.), but the results were poor. On subsequent days, samples of blood and sputum continued to be sent to the laboratory for test bacterial overgrowth in an attempt to identify other bacteria.

Despite treatment, in the first eight days of hospitalization the patient had persistent cough with copious yellow sputum (100-150 cc), and, he had hemoptysis, fever 39-40°, persistent hypoxemia on room air (PaO_2 <45 mm Hg), leg edema, hepatomegaly, anemia, low number of platelets in the blood.

In the following days the patient's general condition deteriorated and he had onset of adult respiratory distress syndrome (ARDS). The patient underwent transfusion of red blood cells and platelets. The 3rd day after admission, the chest radiograph and high resolution CT (HRCT) showed an increase in left pulmonary opacity and multiple areas of parenchymal consolidation also on the right side. Excavations were present in the context of these areas and ground-glass opacities, consistent with intrapulmonary haemorrhage, were present in the remaining portions of the lungs.

Serological tests demonstrated the absence of IgG and IgM antibodies to *Chlamydia psittaci*, *Chlamydia trachomatis*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*; tests for HBsAg, HCV and HIV were negative.

On day 9 after admission, microscopic examination of sputum showed acid-alcohol resistant bacilli which grew rapidly on blood agar. The colonies were composed of filamentous microorganisms with branches at right angles to the main branch. Positive Gram stain, resistance to acids highlighted by staining for acid-alcohol resistant

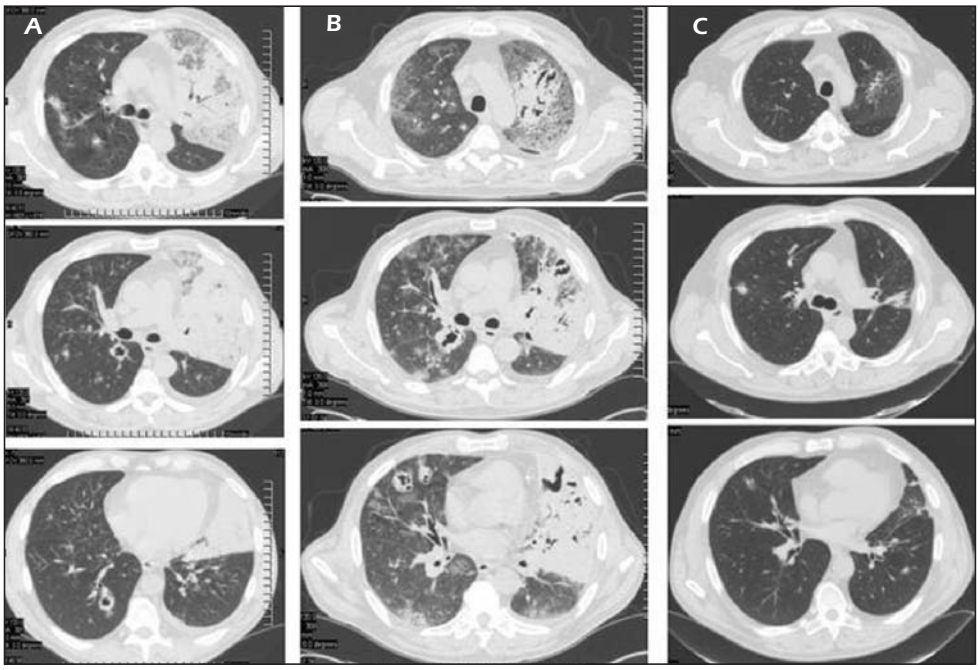

Figure 2. Chest CT at the time of admission ***(A)*** after 9 days of hospitalization ***(B)*** and 3 months after discharge ***(C)***,

microorganisms and rapid growth suggested a diagnosis of *Nocardia spp* as later demonstrated unequivocally with molecular biology.

The complete sequence of 16S rDNA of the isolated bacilli was determined after PCR amplification with universal primers (16SF, 5'-AGAGTTTGATCCTGGCTCAG; and 16SR, AGGAGGTGATCCAGCCGCA) and subsequent sequencing of the generated ca. 1400 bp PCR amplicon with the 16SF and 16SR primers.

BLAST analysis of the 16S rDNA sequence showed optimum alignment (>99% identity) with *Nocardia otitis discaviarium* and *Nocardia farcinica* strains (acc. nos. X80611 and X 80610 respectively). To unambiguously identify the isolated bacillus at species level, sequences signature of *Nocardia* genus present within variable regions of 16S rDNA were studied. The 16S rDNA sequence showed a perfect match with the signature of *Nocardia farcinica* published by Conville et al[4]. Moreover, the 16S rDNA bacterial sequence exhibited all 22 critical position described by Chun et al[5] that specifically characterized *N. farcinica* and differentiated it from closely related species of the *Nocardia* genus. These findings let us to conclude that the isolated bacillus had been unambiguously identified as *N. farcinica.*

In the light of the above result, antibiotic treatment was changed introducing fluconazole (200 b.i.d.), trimethoprim-sulfamethoxazole (TMX-SMP 5 amp t.i.d.), amikacin (500 mg b.i.d.), methylprednisolone (40 mg b.i.d.).

The clinical picture quickly improved, the peripheral oedemas and the left pleural effusion disappeared, the pulmonary lesions on the right were reabsorbed and the upper left lobe lesions decreased in size, inducing a rapid and progressive improvement of the patient's respiratory failure and blood tests (Table I).

After 15 days of the above therapy, the HRCT confirmed the improvement with the reduction of the opacity and of the excavated lesions in the upper left lobe, the initial retraction of this lobe, remarkable reduction of the ground glass opacities in the right lung and on the left lower, volumetric reduction of bilateral nodular excavated lesions, absence of pleural effusions, volumetric reduction of the lymph nodes.

The patient was discharged thirty-five days after admission and he was invited to take TMX-SMP for six months. Subsequent checks have shown a slow but steady improvement, with resolution of infection eight months after discharge from Hospital.

Table I. Trend of the main blood tests in our patient during hospitalization.

	Day 0	Day 1	Day 3	Day 9	Day 17
WBC × 10^3/μL	1.8	3.6	8.7	7.8	10.8
Granulocytes	85%	90%	92%	79%	70%
Lymphocytes	8%	5%	7.9%	17%	15%
Monocytes	5%	2%	0.1%	3%	10%
Eosinophils	2%	3%	0%	1%	5%
Platelets × 10^3/μL	95	79	60	465	449
AST U/L	47	44	50	22	22
ALT U/L	38	34	41	21	32
D Dimer	845	1277	869	1600	500
	R	**R**	**V50**	**V50**	**V50**
pH	7.38	7,39	7.47	7.48	7.42
$PaCO_2$	36	32	37	40	37
PaO_2	63	54	45	76	75
ESR	50	86	95	88	42

R = Room air; V50 = Ventimask 50%; WBC = white blood cells; ERS = erhytrocyte sedimentation rate.

Discussion

A case of *Nocardia farcinica* pneumonia with *Staphylococcus haemoliticus* superinfection is herein reported. The delayed admission to the Hospital and the delayed isolation of the bacteria caused a clinical picture complicated with an adult respiratory distress syndrome (ARDS). The identification of the *Nocardia* species and the administration of appropriate therapy improved the clinical picture up to the complete recovery.

Most cases (65%) of pulmonary nocardiosis are caused by *N. asteroides*[6]; more rarely by other *Nocardia* species. These pneumonia are usually observed in immunocompromised patients[7] but lately, human cases of nocardiosis from *N. farcinica* have been reported also in immunocompetent patients[8], probably for the improved diagnostic and isolation techniques[9,10]. Isolated cases of extrapulmonary nocardiosis have been also described[11].

The patient herein considered had a history of strong alcohol consumption and he was taking corticosteroids and nonsteroidal antinflammatory drugs for chest pain. These conditions, with the prolonged exposure to low temperatures in a dirty environment, might have fostered his *Nocardia* infection. At admission, his clinical and radiological conditions were severe, calling an immediate treatment, albeit empirical. Although samples for bacteriological testing had been collected from day 1, a microbiological diagnosis was formulated only on day 9. In the meantime, the patient presented an ARDS condition and severe respiratory failure corrected by oxygen therapy, corticosteroids and transfusions[12]. The *Staphylococcus haemoliticus* superinfection may be caused from the severe immunodepression of the patient in this phase. When treatment with amikacin and TMX-SMP began, the patient conditions quickly improved and he was discharged with home therapy. Complete remission and resolution of the radiological picture was achieved 8 months after discharge from the Hospital.

The diagnosis of pulmonary nocardiosis requires an early recognition of signs and symptoms, which, associated with a compatible radiological picture, may suggest the presence of nocardiosis and thus lead to the necessary diagnostic investigation as soon as possible.

Accurate and timely identification of these organisms by conventional methods is becoming more difficult due to the taxonomic evolution of the genus *Nocardia* in the last decade, the limited number of conventional tests available and the length of time required to complete the tests[9].

The 16S rDNA gene is known to be highly conserved among bacteria and, therefore, it is frequently used for the determination of organisms. However, variable regions may exist within the gene and some sequences are unique and suitable for the identification of bacterial species as members of the genus *Nocardia spp*[13].

Prompt action is required because actinomycetes cultures grow slowly and bacilli may initially escape routine detection[14].

Nocardia spp is a Gram-positive aerobic bacillus. The species of the *Nocardia* genus belong in the family Nocardiaceae from a homogeneous clusteramong Corynebacteriaceae, a suborder of the Actinomycetales order. Currently, the *Nocardia* genus contains more than 50 species and one half have been recognized as pathogens in human and/or animals; the aerosol route is the main portal of entry into the body and the lungs are the most common sites of infection. Species that produce pulmonary or disseminated infection include: *Nocardia asteroides, N. abscessus, N. farcinica, N. pseudobrasiliensis, N. transvalensis, N. nova, N. otitis discaviarium, N. africana, N. asiatica, N. beijingensis, N. cyriacigeorgica, N. higoensis, N. paucivorans and N. veterana*[7].

This infection is linked to a high mortality rate, due to the resistance to common first line antibiotics[15], and its presence is underestimated, because it is seldom recognized. All these conditions lead to a delay in the formulation of the correct diagnosis and treatment so that patients clinical picture got worse and complicated up to death.

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