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Letter to the Editor

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Pulmonary nocardiosis after covid-19 infection: case report and literature review

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Sir,

An increasing number of opportunistic infections in COVID-19 patients are being described especially for patients with underlying diseases and those who received immunosuppressive therapy. Among these opportunistic infections, fungal infections account for most case reports in COVID-19 patients (mainly *Aspergillus*). Other associated pathogens are viral, protozoa, helminth, and bacterial infections. Regarding these last prospective cohort study in England, Scotland, and Wales analyzed data from COVID-19 inpatients showing that the most common pathogens causing early respiratory coinfections are *Staphylococcus aureus* and *Haemophilus influenzae*. Indeed *S. aureus* and Enterobacteriaceae are also the most common secondary respiratory infections [1].

Nocardia is a gram-positive, ubiquitous, soilborne bacterium that belongs to the family of aerobic actinomycetes that seem like branching, filamentous rods on microscopy. This genus *Nocardia* includes more than eighty species, thirty of which could affect humans. In retrospective studies, *N. asteroides* and *N. farcinica* have often been identified as the predominant species over the years [2].

Most patients with nocardial infection are immunocompromised with cell-mediated abnormalities. Their most common causes are malignancy, organ and hematopoietic stem cell transplantation, and HIV infection. Glucocorticoid therapy has traditionally been linked to nocardiosis. Recently a matched retrospective study conducted at a tertiary hospital in central Israel of sixty hospitalized consecutive adult patients with nocardiosis showed that systemic corticosteroid therapy was strongly associated with pulmonary nocardiosis (matched OR 4.69, 95% CI 2.45–8.99, $p < 0.001$) [3].

Immunosuppressive therapy has been used to alleviate hyperinflammation and cytokine storm syndrome in COVID-19 patients. In fact, a recent meta-analysis confirmed that systemic corticosteroids were associated with lower 28-day all-cause mortality compared with usual care or placebo in COVID-19 patients who received oxygen or invasive mechanical ventilation [4].

Other conditions that have been associated with nocardiosis include diabetes mellitus, alcoholism, chronic granulomatous disease, alveolar proteinosis, structural lung disease, tumor necrosis factor-alpha inhibitor (e.g., infliximab) therapy, inflammatory bowel disease, chronic obstructive pulmonary disease, and tuberculosis.

In one review of 1050 cases [5] main clinical presentations of nocardiosis were systemic (32 %); pulmonary (only) 39 %; CNS (only) 9 %, cutaneous or lymphocutaneous (8 %) and single site extrapulmonary (egg, eyes, bone) 12 %. The onset of pulmonary nocardiosis may be acute, subacute, or chronic and is not distinguished by any specific signs or symptoms. Fever, night sweats, fatigue, anorexia, weight loss, dyspnea, cough, hemoptysis, and pleuritic chest pain have all been described.

Here-in we report a case of a patient initially admitted and treated for COVID-19 pneumonia who was subsequently readmitted due to persistent worsening dyspnea. Pulmonary nocardiosis after further evaluation was diagnosed. An English literature review showed only other five reports of these associations. Data regarding these cases are shown [6-10].

An 86-year-old man infected with SARS-CoV-2 was admitted to the hospital for productive cough and dyspnea on minimal exertion. He was already suffering from multiple health conditions, including type 2 diabetes mellitus, hypertension, and atrial fibrillation treated with dabigatran. He was receiving corticosteroid therapy and daily oral cyclophosphamide because IgG lambda multiple myeloma. Among other medical conditions, a chronic kidney disease IIIB2A stage diabetic nephropathy and non-exacerbator COPD were remarkable features. The patient received acute inpatient care in a

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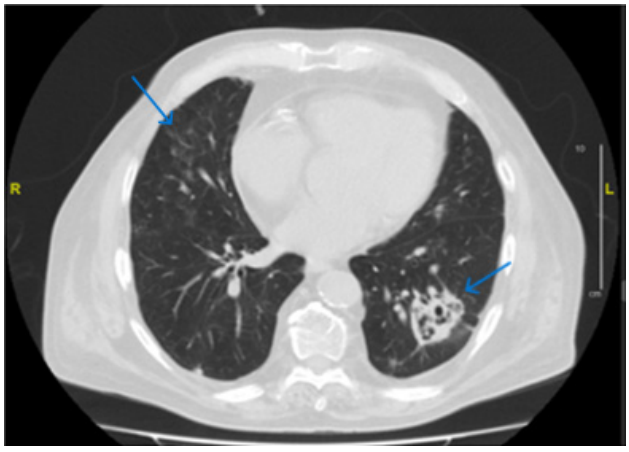

Figure 1 Multifocal and bilateral caviated condensations. Ground glass pattern areas and distal bronchial thickening.

Table 1 Risk factors and clinical characteristics of *Nocardia* COVID-19 coinfected patients.

Author (year) [reference]	Sex & Age	Risk factors	Days after COVID-19 diagnosis	Clinical picture	CT scan features
Colaneri (2021) [6]	Woman, 45 years	Untreated HIV/HCV IDU	5 days	Fever, coughing, dyspnea, fatigability (10 days). Oxygen saturation at room air: 94%	Multiple necrotic core lesions in both lungs, kidneys and soft tissues with peripheral contrast enhancement
Laplace (2021) [7]	Male, 86 years	Type 2 DM, COPD, Crohn´s disease	13 days	Acute dyspnea, fever, productive cough	Dense consolidation with air bronchograms in lower lung lobes
Atemnkeng (2021) [8]	Male, 63 years	Morbid obesity, Type 2 DM	32 days	Worsening shortness of breath. Oxygen saturation at room air: 77%	Near-complete opacification of the left hemithorax with minimal sparing of the apical region MRI: multiple bilateral ring-enhancing lesions in the brain
Arif (2021) [9]	Woman, 61 years	Type 2 DM, hypertension, HF	10 days	Dyspnea	Right upper lobe 3.3 x 3.2 cm mass and a left upper lobe 1.9 x 1.5 cm nodule
Driscoll (2022) [10]	Male, 16 years	Bronchiectasis Pseudomonas aeruginosa infection	6 days	Fever, dyspnea, cough, and lethargy	Left lower lobe opacification but no necrosis or pulmonary embolus
Ortiz (2023) [Present case]	Male, 86 years	Type 2 DM, hypertension, myeloma, COPD, atrial flutter, CKD	11 days	Increased productive cough, dyspnea Oxygen saturation at room air: 82%	Multifocal and bilateral cavitated condensations. Ground glass pattern areas and distal bronchial thickening

Type 2 DM: type 2 diabetes mellitus. COPD: Chronic obstructive pulmonary disease. CKD: Chronic kidney disease. HF: heart failure. HIV/HCV: chronic hepatitis C virus & HIV coinfected. IDU: Injecting drug user. SLE: Systemic lupus erythematosus.

hospital for ten days including high-flow oxygen, oral dexamethasone, and ceftriaxone. Oral cyclophosphamide was temporarily stopped.

The patient had been in his usual state of health until 5 days before this new admission (11 days after he was discharged), when fever developed. He noted shortness of breath at rest and dyspnea on exertion. He was brought to the emergency department of our hospital for further evaluation.

On examination, the temperature was 36.7°C, the blood pressure 107/62 mm Hg, the pulse 111 beats per minute, respiratory rate twenty-eight breaths per minute, and oxygen saturation 82% while the patient was breathing ambient air. Respiratory rate decreased to twenty-two breaths per minute and the oxygen saturation improved to 95% with the administration of supplemental oxygen through a nasal cannula at a rate of four liters per minute. Inspiratory crackles could be heard at the lung bases. The heart sounds were regular, with tachycardia but no murmur. There was no tenderness on palpation of the abdomen and no pitting edema were present in the legs.

Laboratory test results at admission were: leukocytes 8.9 10e9/l (3.5-12.0), lymphocytes 0.08 10e9/l (1.30-4.00); monocytes 1.70 10e9/l (0.20-1.00); hemoglobin 9.9 g/dl (13.5-17.5); hematocrit 29.5% (41- 53); platelets 119 10e9/l (140-450); neutrophils/lymphocytes ratio 89.00 (<3.13 covid-19 more favorable prognosis >3.13 COVID-19 less favorable prognosis); prothrombin time 17 sec (9.40-12.50); Quick index 57% (70.00-100.00); INR 1.4 ratio (0.5-1.5); D-dimer 2,171 ng/ml (0.00-500.00); urea 85 mg/dl (18-44); creatinine 1.67 mg/dl (0.53-1.18); albumin 2.89 g/dl (3.50-4.60); C-reactive protein 17.39 mg/dl (0.00-0.50); procalcitonin 0.91 ng/ml (0.00-0.50). His arterial blood gas analysis (ABG) revealed: arterial pH 7.495 pH (7.34 - 7.44); arterial pO2 50.1 mmHg (75.0-100.0); arterial HCO3- 26.7 mmol/l (22.0-26.0); arterial O2 saturation 86.3% (95.0 -98.0).

Chest x-ray revealed dense consolidations with air bronchograms in the lower lung lobes. Both SARS CoV-2 antigen and rT-PCR in nasopharyngeal sweep were positive (Ct = or < 30 expressing high viral load). The patient was started on empirical meropenem, oxygen supplementation through nasal prongs, and intravenous remdesivir.

A thoracic CT scan (Figure 1) revealed multifocal and bilateral cavitated condensations. Ground glass pattern areas and distal bronchial thickening. The sputum culture from day five showed abundant leukocytes and no acid-alcohol resistant Gram-positive branching rods in gram stain compatible with *Nocardia* species.

He was initially treated with broad-spectrum antibiotics (meropenem and vancomycin) and thereafter treatment was changed to intravenous imipenem for 4 weeks. We ruled out the use of cotrimoxazole or linezolid due to the foreseeable toxicity at the kidney and bone marrow level in this specific patient.

The patient was discharged home on oral minocycline 100 mg every 12 hours for 6 months.

While corticosteroids have been shown to have varying effects on T lymphocytes, high doses can cause a rapid depletion of circulating T cells by redistribution of circulating cells to other body compartments. In addition, they cause inhibition of interleukin (IL)-2, a cytokine that is essential for the function, differentiation, and proliferation of T-cells. They can also induce apoptosis of T-lymphocytes, which further depletes the total pool of mature functioning T-cells. All these mechanisms result in a profound immunosuppressive state that promotes the development of opportunistic infections.

It has been previously demonstrated that due to the downregulation of various proteins associated with immune function, the immune system is suppressed early during COVID-19 [11]. There is now a growing body of evidence that supports that COVID infection can lead to significant dysregulation of the immune system. Severe COVID infections have been characterized by lymphocytopenia, which is currently used as a prognostic indicator of clinical deterioration and poor outcomes.

We identified only five published case reports (6 overall including our case) of adult patients with a mean age of 59 years (16-86). Main risk factors and clinical characteristics of Nocardia COVID-19 coinfected patients are shown in table 1. Four patients were male (66%). Well-known risk factors were present in all six patients (type 2 diabetes as the main factor). Nocardia infection was diagnosed at a median of 13 days after diagnosis of Covid 19 (5-32 days). Main clinical features were acute o worsening dyspnea, acute respiratory failure, and productive cough. Radiological imaging tests showed mainly lobar or multilobar consolidation and lung cavitating lesions.

Table 2 summarizes microbiological and treatment features and outcomes of Nocardia COVID-19 coinfected patients. As described in the literature *Nocardia cryiacigeorgica*, *Nocardia asteroides* and *Nocardia farcinica* were predominating species. Patients received appropriate combined Nocardia treatment including trimethoprim/sulfamethoxazole, meropenem, linezolid or ceftriaxone. In hospital mortality was 33%.

Empiric antimicrobial treatment included intravenous administration of at least two agents that represent the first-line therapy (either amikacin, imipenem, or a third-generation cephalosporin) and should trimethoprim sulfamethoxazole [12]. After a minimum of 3 weeks of intravenous therapy, patients can be switched to oral treatment.

In summary, severe COVID-19 lung infection, SARS-CoV-2 induced dysregulation of the immune system and widespread use of steroids in COVID 19 can favor Nocardia as an opportunistic infection. We believe that these cases should serve as an example of potential threats of high steroid exposure in this patient population. We would like also to point out the relevance of early attention to opportunistic infections in patients with recent COVID infections.

Table 2 **Microbiological and treatment features and outcome of *Nocardia* COVID-19 coinfected patients.**

Author (year) [reference]	*Nocardia* species	Sample	COVID treatment	*Nocardia* treatment	Outcome
Colaneri (2021) [6]	*Nocardia cyriacigeorgica*	Blood culture	PIP/TAZ TMP/SMX	Linezolid, TMP/SMX and Ceftriaxone (one year)	Cure
Laplace (2021) [7]	*Nocardia cyriacigeorgica*	Sputum	DXM 6 mg/24h, enoxaparin, cefotaxime	Imipenem and TMP/SMX	In hospital death
Atemnkeng (2021) [8]	*Nocardia asteroides*	BAL	Azithromycin, ceftriaxone, REM, DXM y enoxaparin	Meropenem/linezolid TMP/SMX (one year)	Cure
Arif (2021) [9]	*Nocardia farcinica*	Lung biopsy	DXM 4mg oral	TMP/SMX Meropenem/linezolid	Discharged
Driscoll (2022) [10]	*Nocardia farcinica*	Bronchial secretion	Tobramycin, ceftazidime DXM	Linezolid	In hospital death
Ortiz (2023) [Present case]	*Nocardia* spp	Sputum	REM (10 días), ceftriaxone DXM	Imipenem Ceftriaxone	Discharged

COVID-19: Coronavirus disease 2019. PIP/TAZ: Piperacillin/tazobactam. TMP/SMX: Trimethoprim/sulfamethoxazole. DXM: dexamethasone. BAL: bronchoalveolar lavage. CSF: Cerebrospinal fluid. REM: remdesivir.

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CONFLICT OF INTEREST

Authors declare no have conflict of interest.

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