CLINICAL REVIEW

Nocardiosis: An Unsuspected Cause of Pneumonia

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Nocardia are a group of bacteria found in soil and water that usually cause infection in patients with deficiencies in cell-mediated immunity but can also affect immunocompetent hosts. Infection, especially in immunocompetent individuals, are often sub-acute to chronic and present with non-specific symptoms making diagnosis challenging. Pulmonary involvement is the most frequent clinical presentation although disseminated disease is not uncommon. As infections caused by *Nocardia* species are infrequent and can mimic other infections and malignancy, delays in diagnosis and treatment are typical. A high index of suspicion is needed in patients with risk factors and common clinical findings of nocardiosis as early recognition and effective therapy are crucial to improve outcomes. I present an immunocompetent patient who was eventually diagnosed with nocardiosis after several months of illness and review the literature on *Nocardia* infections with a focus on pulmonary nocardiosis.

Case Report

A 73-year-old female complained of several months of persistent cough with clear sputum along with intermittent subjective fevers and night sweats. Twelve-weeks prior, the patient had the "flu" with cough, clear sputum production, and subjective fevers and chills. Nine-weeks prior, she saw her primary doctor for persistent cough and she was given a course of azithromycin. There was no improvement and two-weeks later she returned to her primary doctor and was diagnosed with 'acute sinusitis' and given a 14-day course of amoxicillin + clavulanate. Her symptoms did not improve, and she developed night sweats in addition to the persistent cough and she returned to her primary doctor four-weeks prior to admission and further evaluation was initiated. Vital signs were normal and pulmonary examination was described as unremarkable. Chest radiography (CXR) showed mild diffuse bronchial wall thickening concerning for airway inflammatory disease/ bronchitis with a bandlike opacity in the lingual compatible with atelectasis. No airspace consolidation or pleural effusion was seen (**Figure 1**). MTB-Quantiferon-Gold ELISA was positive. A 10-day course of levofloxacin was given for 'bronchitis' and a computed tomography (CT) scan of the chest was ordered for further evaluation. CT chest was done 1-day prior to admission and based on the results of this scan (see below) the patient was contacted and referred for hospital admission to 'rule out pulmonary tuberculosis'.

At the time of admission, additional history revealed that the patient grew up in Mexico and emigrated to the United States at the age of 30. She denied homelessness, incarceration, recent travel (last travel to Mexico was 2-years prior), birds or pets, sick contacts, or exposure to persons with active tuberculosis. She had previously worked at a dry-cleaning business many years ago and lived with her husband, who was well without cough. She was recently diagnosed with diabetes type 2 (hemoglobin A1C 6.5%), that was currently diet-controlled. Other past medical history included hypertension, gastro-esophageal reflux disease, spinal osteoarthritis, osteoporosis, hypothyroidism and essential tremor. She had never smoked cigarettes and there was no history of chronic lung disease. The patient noted mild improvement after recently taking levofloxacin, but cough was persistent. Physical examination showed a well-appearing elderly female speaking in full sentences with no respiratory distress. Vital signs were normal. Cardiac examination was normal. Pulmonary examination had no rales or wheezes and respiratory effort was normal. Her exam was otherwise unremarkable. Laboratory testing revealed a normal complete blood count (white blood cell 6.3 x 10^3/µL) and a normal basic metabolic panel except for mildly elevated glucose of 107 mg/dL. Procalcitonin level was < 0.10 µg/L. Repeat CXR showed a lingular opacity and persistent bilateral bronchial wall thickening (**Figure 2**). Chest CT scan showed multifocal regions of mucus plugging and airway secretions with ill-defined tree-in-bud opacities and clustered centrilobular pulmonary micronodules and nodules mainly in the posterior right upper lobe but also to a lesser extent in the bilateral upper lobes. In addition, focal nodular airspace consolidation with surrounding ground-glass attenuation and clustered micronodules were seen in the left lower lobe with focal airspace consolidation and clustered centrilobular micronodules in the lingula (**Figure 3**).

In the hospital, the patient was placed in respiratory isolation and induced sputum for acid fast bacterial (AFB) smear and mycobacterium tuberculosis complex PCR was obtained and negative on three occasions. Pulmonary and infectious disease (ID) consultations were obtained. Given diagnostic uncertainty, bronchoscopy with bronchoalveolar lavage (BAL) of the right upper and right middle lobe was performed. Cytology showed acute inflammation but was negative for malignant cells. Transbronchial biopsy of the right upper lobe showed scant fragments of necro-inflammatory debris, normal bronchial epithelium and alveolar tissue, no granulomas, viral inclusions or malignancy. AFB and GMS stains were negative

for mycobacteria and fungi, respectively. Bacterial culture initially grew a 'beaded gram-positive rod' that was later identified as a *Nocardia* species (confirmed by comparative 16s rDNA sequence analysis) susceptible to amikacin, ceftriaxone, cefotaxime, doxycycline, imipenem, linezolid, minocycline, and trimethroprim/sulfamethoxazole and resistant to amoxicillin + clavulanate, ciprofloxacin, and moxifloxacin. Pertinent negative or normal tests included B-type natriuretic peptide, human immunodeficiency virus (HIV) test, blood cultures, coccidioides antibodies, aspergillus antigen, sputum legionella and fungal cultures. Empiric treatment with cefepime was started and subsequently switched to trimethoprim/ sulfamethoxazole based on ID consultant recommendations and the patient was discharged with close follow-up.

Subsequent clinical course was complicated by trimethoprim/ sulfamethoxazole toxicity with leukopenia and hyperkalemia and the drug was discontinued and the patient was followed clinically. Subsequent chest CT scans showed persistent but stable multifocal areas of mucous plugging and airway impaction with clustered centrilobular pulmonary micronodules and nodules. Findings remained concerning for an ongoing indolent airway centered infection. As the patient's symptoms remained mild, clinical follow up off antibiotics with serial chest CT scans was pursued.

Discussion

In 1888, Edward Nocard first described bacteria that he isolated from cattle as bovine farcy.[1] Bovine farcy has two forms in cattle: a chronic suppurative granulomatous inflammation of the skin and lymphatics or a pulmonary form that closely resembles tuberculosis. We now know *Nocardia* as a genus of bacteria responsible for localized or disseminated disease in animals and humans. The first human case of nocardiosis was described in 1820.[2] Nocardiosis is a rare disease that can involve any organ with the lungs being the most common, followed by the skin and central nervous system (CNS).[3] Risk factors for disease are well described with depressed cellular immunity being the most common. Establishing a diagnosis of nocardiosis is often delayed as symptoms are nonspecific and presentation is similar to other infections or malignancy. Once a diagnosis is made, treatment typically involves a prolonged course of antimicrobial therapy depending on the site of disease and patient's immune status.[4]

Nocardia are a ubiquitous group of saprophytic bacteria that are found in dust, soil, decomposing vegetation, fresh water and marine water. More than 50 species of *Nocardia* can cause human infection. *Nocardia* are gram-positive, weakly acid-fast, filamentous bacteria. In contrast to mycobacteria, Nocardia has a 'beaded' acid-fast appearance on microscopy.[2-4] Nocardia infections are uncommon, with an estimated 500-1000 new cases each year in the US according the Centers for Disease Control and Prevention. A male preponderance is reported in many studies for unclear reasons. Clinicians tend to think of nocardiosis as an opportunistic infection affecting only immunocompromised hosts; however, immunocompetent hosts account for one-third of patients effected and can also experience life-threatening disease. The incidence of nocardiosis is thought to be increasing, presumably due to the higher number of immunosuppressed patients over the last several decades.[4-5] Nocardiosis has a marked tendency to recur so prolonged treatment with close clinical monitoring is necessary. Morbidity and mortality are high especially in immunocompromised patients with disseminated disease making early diagnosis and treatment important.[3]

Patients with depressed cell-mediated immunity are at particularly high risk for *Nocardia* infection. This group includes those with solid organ or hematopoietic stem cell transplants, HIV infection, malignancy receiving chemotherapy, and those receiving corticosteroid therapy.[3] Allogenic hematopoietic stem cell transplant recipients are at much higher risk than those with autologous transplants due to graft versus host disease and intensive immunosuppressive therapy. Lung transplant patients have the highest risk among solid organ transplant recipients. Prolonged treatment (beyond a few weeks) with systemic corticosteroids causes selective suppression of the Th-1 cellular immunity and is a major predisposing factor for pulmonary and disseminated nocardiosis. Chronic lung disease and alcoholism are also risk factors for pulmonary nocardiosis.[4] Nocardiosis may be seen in patients with chronic obstructive pulmonary disease (COPD). While this could be related to corticosteroid use for this condition, some suggest that in patients with COPD, bacterial colonization of the bronchus alters ciliary motility and causes damage of the epithelium which may facilitate the growth of Nocardia.[6] Patients with bronchiectasis and other structural lung abnormalities are also thought to be susceptible to *Nocardia* infections.[4]

Clinical presentation can be acute, sub-acute, or, more often chronic. The pace and chronicity of the disease are often related to the immune competence of the host. Immunocompetent patients often have a localized chronic infection, whereas immunocompromised host are at higher risk of hematogenous dissemination, and clinically more acute disease.[4] Various clinical presentations of nocardiosis are possible (**Table 1**). Symptoms and imaging findings are nonspecific and mimic other diseases leading to a broad differential diagnosis (**Table 2**). Pulmonary involvement is the most common site of infection because *Nocardia* organisms are readily aerosolized with dust and the main portal of entry is inhalation. Numerous *Nocardia* species can cause pulmonary disease and patients with structural lung disease are more susceptible to infection. Of note, there is no evidence of person-to-person transmission of *Nocardia* infections and isolation is not recommended.[2,4] *Nocardia* can disseminate to nearly any organ and has a particular predilection for the CNS. Up to 50% of all cases of pulmonary nocardiosis disseminate outside of the lungs, most commonly to the brain. Primary cutaneous infection can occur by direct inoculation into the skin and is caused mostly by *Nocardia brasiliensis*.[3-5]

Pulmonary nocardiosis is often a subacute to chronic infection with a tendency for remissions and exacerbations. Symptoms most commonly are fever and cough, but may also include dyspnea, hemoptysis, night sweats, weight loss, and fatigue. Patients with chronic infections often have a similar presentation to that of pulmonary tuberculosis.[3-4] A variety of imaging findings are possible on CXR and CT scan including lung consolidation (often multifocal), nodules (typically multiple of various size) and masses. Cavitation and pleural effusion may occur, both in approximately one third of patients. Mediastinal and hilar adenopathy are not unusual. Other CT findings, as a result of direct extension of infection, including pleural involvement with effusion or pleural thickening, may be seen. Extension to the chest wall to form an abscess or phlegmon occurs in a small number of patients.[7] As these radiologic findings are varied and non-specific, the differential diagnosis for pulmonary nocardiosis includes other infections, vasculitis, and malignancy. The correct diagnosis is often delayed as clinicians often initially suspect community or hospital-acquired pneumonia, tuberculosis, cancer or lung abscess of other etiology.[2-5]

Two observational case series in patients with pulmonary nocardiosis provide further insight regarding this disease. In a retrospective study of 17 patients with pulmonary nocardiosis at a single hospital from 2009-2013, the most common risk factors for disease were corticosteroid therapy (64%), diabetes mellitus (29%) and chronic lung disease (24%). Cough (94%) and fever (71%) were the most common presenting symptoms. The most frequent radiographic abnormalities were nodules or masses (82%) and consolidations (58%), with cavitation occurring most often within 2 weeks. Of significance, disease course was subacute in most patients and diagnosis was frequently difficult, with a median time to diagnosis of 25 days. Even after hospital admission, the median duration until diagnosis was 12 days. Disseminated disease occurred in 4 of 17 patients and the overall mortality rate was 19% and was higher in patients on immunosuppressive drugs. For those with dissemination and CNS involvement, the mortality rate was 50%. The authors concluded that a high clinical index of suspicion is necessary for early diagnosis and timely treatment in patients (especially those who are immunocompromised) who present with new lung nodules or masses that rapidly evolve into cavitation.[8]

Another observational study looked at risk factors and outcomes of pulmonary nocardiosis. Thirty-one cases were seen over a 13-year period at a single institution. Predisposing conditions included COPD (23%), organ transplantation (29%), HIV infection (19%), and alcoholism (6.5%). Corticosteroid therapy (65%) was also a common risk factor. The dose and duration of corticosteroid treatment prior to diagnosis of *Nocardia* ranged from 15 days to years of therapy. As in other studies, the median time to diagnosis was prolonged at 30 days and median duration of symptoms prior to hospital admission was 14 days. CXR findings included: an alveolar pattern (70%), nodules or masses (27%), cavitation (32%), and pleural effusion (36%). Mortality rate was high at 41% for pulmonary nocardiosis and 64% for disseminated disease. The authors noted that the illness tends to have a protracted course and diagnosis is often difficult. In an effort to reduce the delay in diagnosis and treatment, they emphasized that that testing for Nocardia species should be performed in patients with risk factors for pulmonary nocardiosis and pneumonia who have not responded to treatment.[6]

While nocardiosis often starts as a pulmonary infection, it can disseminate to virtually any organ. *Nocardia* infection should be suspected in any patient who presents with brain, soft tissue, or cutaneous lesions and a simultaneous or recent pulmonary infection. All patients with pulmonary disease should be carefully assessed for disseminated disease. While dissemination is possible in any patient, it is much more common in immunocompromised patients.[4] The most common sites for dissemination include the CNS, skin and subcutaneous tissues, kidneys, joints, bones, heart and eyes.[2] Pulmonary and disseminated disease can evolve slowly over a period of months until treatment is started. Dissemination worsens the prognosis, with mortality rates in patients with CNS disease being the highest.

CNS involvement occurs in approximately 20% of cases overall and in over 40% of those with disseminated disease. Abscesses are the hallmark of CNS disease and may present with fever, headache, meningeal signs, seizures, focal neurologic deficits or psychiatric disorders. However, clinical manifestations are often insidious in onset and neurological symptoms may develop gradually making the diagnosis difficult.[2] Some patients with CNS dissemination are asymptomatic and it is suggested that CNS involvement should always be excluded in high-risk patients (those who are immunocompromised and/or have severe pulmonary nocardiosis) even without neurological symptoms.[4,5] At times, when no infectious symptoms are present, nocardial brain abscesses may be mistaken for brain tumors or vascular infarcts prior to biopsy. Higher mortality is consistently reported in patients with CNS disease.[6,8]

Primary cutaneous and subcutaneous nocardiosis (25% of cases) is distinguished from other forms as it frequently develops in immunocompetent hosts after direct contact with the bacteria via cut or abraded skin. Agricultural work is an important risk factor. A superficial abscess or localized cellulitis may develop which is clinically indistinguishable from lesions produced by *Staphylococcus* or *Streptococcus* organisms.[2-3] In some patients, infection spreads to lymph nodes and produces lymphangitis and subcutaneous nodules and may have a similar presentation as sporotrichosis. At times, a chronic cutaneous infection progressing over months to years may result in a mycetoma. This can lead to progressive and disfiguring tissue destruction of the skin, subcutaneous tissues, muscles and bones following local trauma to the hand, foot, leg, or arm.[2] Treatment may require debridement or drainage in addition to antimicrobial therapy. Surgical wound infections from environmental contamination with *Nocardia* can also occur.

Bacteremia from Nocardia is only rarely reported even in severely immunocompromised patients with underlying malignancies. Bacteremia can be seen from central venous catheter (CVC) infection or associated with disseminated disease. CVCs can be the source of hospital-acquired *Nocardia* bacteremia. As with other catheter-associated bloodstream infections, patients typically respond well to catheter removal and antimicrobial therapy. Nocardia bacteremia associated with disseminated disease from a primary respiratory tract infection has a much poorer prognosis.[9]

A recent observational study on all adult patients at a tertiary care hospital with culture-proven Nocardia infection from 1994-2015 compared disease manifestations and outcomes in immunocompromised and immunocompetent patients. Of the 112 patients, 60% were immunocompromised (solid organ or hemopoietic cell transplant, malignancy treated with chemotherapy in the preceding 3 months, autoimmune disorders treated with immunosuppression, or high-dose corticosteroid treatment for at least 3 weeks) while 40% were immunocompetent. The most common immunocompromising condition was high-dose corticosteroid treatment, present in 61%. As in most other reported series, the lung was the most common site of infection in both groups. Pulmonary involvement occurred in 81% of the immunocompromised patients and was associated with corticosteroid treatment and allogenic stem cell transplant. In immunocompetent patients, 55% had pulmonary disease which was associated with chronic lung diseases including bronchiectasis and cigarette smoking. As might be expected, disseminated infection, most often to the CNS, was more common in the immunocompromised group. Interestingly, CNS infection which affected 12 patients was noted to be 'silent' in 3 patients and found only by MRI study.[5]

Clinical presentation was similar in both immunocompromised and immunocompetent patients with the majority of those with pulmonary nocardiosis presenting with cough with sputum production, dyspnea, and fever. Diagnoses was obtained by culture in all patients and the highest yield was from BAL fluid and/or sputum (71%). Radiological findings were similar in the two groups other than cavitation, which occurred only in immunocompromised patients, and bronchiectasis, which was present in more of the immunocompetent patients. Notably, infection was initially attributed to another entity in over half the patients, irrespective of their immune status. Of these patients, most were initially treated for typical community-acquired or hospital-acquired pneumonia. All-cause mortality at 1-year was much higher in the immunocompromised group (27% vs 7%).[5]

Diagnosis is consistently challenging as clinical and radiographic findings in nocardiosis are non-specific and may be mistaken for a variety of other conditions. Alertness to the possibility of nocardiosis in patients with lung, CNS, or skin and soft tissue involvement is key to arriving at the correct diagnosis. Pulmonary imaging including CXR and CT scan often show nodules and cavities. If the CNS is involved, brain imaging (CT or MRI) typically shows abscesses. These findings all provide clues to the diagnosis of nocardiosis but are non-specific. Definite diagnosis of *Nocardia* infection requires isolation and identification of organism from a clinal specimen. Organisms are most often isolated from respiratory samples, but since *Nocardia* species can disseminate to almost any organ, other samples include skin biopsies, aspirations from abscesses and cerebrospinal fluid, and surgical biopsy smears.[4]

A sputum sample is the most effective way to diagnose nocardiosis. Invasive methods, including BAL and percutaneous lung biopsy, are recommended to obtain a rapid diagnosis in patients who are unable to expectorate.[3,8] Smears may provide a rapid presumptive diagnosis and typically show Gram-positive, 'beaded', branching filaments that are weakly acid-fast. *Nocardia* species can grow on most non-selective media. However, growth may take from 48 hours to several weeks and the microbiology laboratory should be informed that *Nocardia* is suspected and cultures should be monitored for at least 30 days.[3,6] Nocardia colonies have a chalky white or 'cotton ball' appearance due to the abundant filaments. Multiple laboratory techniques can be used to differentiate the species. This is important as different species have different resistance profiles. Due to changing resistance patterns, susceptibility testing is crucial to guide final treatment decisions.[4]

Nocardia can be difficult to treat and tends to relapse or progress despite appropriate therapy. A delay in diagnosis, especially in immunocompromised patients, may be responsible for treatment failure and poor prognosis.[10] As nocardiosis is a rare disease, no randomized prospective clinical trials are availabe to guide treatment agent, route, or duration. Management must be individualized based on susceptibility patterns.[3,4] Important considerations for treatment included the organ involved, the antimicrobial sensitivity pattern of the isolated Nocardia species, and the use of combination antibiotic therapy.[11] Adjuvant surgical treatment may also be necessary depending on the involved body site and clinical scenario.

For the past 60 years, sulfonamides have been the agent of choice to treat nocardiosis. Trimethoprim-sulfamethoxazole (TMP-SMX) is the most commonly used sulfonamide in the United States. However, as resistance to TMP/SMX in the United States is reported in some studies to be 40-50%, initial combination therapy is crucial until antimicrobial sensitivity data is available.[3,8] Other antibiotics with activity against *Nocardia* include amikacin, imipenem, third-generation cephalosporins (ceftriaxone, cefotaxime), minocycline, levofloxacin, linezolid, and amoxicillin-clavulanic acid. Combination therapy, such as imipenem and TMP-SMX, amikacin and imipenem, or imipenem and cefotaxime, or even triple therapy with TMP/SMX, ceftriaxone, and imipenem is recommended initially. Consultation with an ID specialist is recommended.

Once clinical improvement occurs and *Nocardia* species and drug susceptibility information is confirmed, single-drug therapy may suffice. As relapse is not uncommon, a prolonged duration of treatment with close clinical monitoring is recommended. Duration of treatment depends on the site of the

lesion, the patient's immune status, and clinical monitoring of response. In general, primary cutaneous nocardiosis is treated for 1-3 months. Immunocompetent patients with pulmonary nocardiosis are often treated for 6-12 months. At least 12 months of treatment with clinical monitoring is recommended for immunosuppressed patients and those with CNS disease.[3,4] As the disease tends to recur and exacerbations can occur even during maintenance treatment if antibiotic concentrations are suboptimal, close monitoring of antibioitic levels and clinical improvement is important to encourage successful outcomes.[2]

Nocardiosis is a rare disease most commonly seen in immuno-compromised patients but can also occur in immunocompetent hosts. Disease course in pulmonary nocardiosis can be chronic and present with non-specific symptoms that mimic other respiratory infections. In addition, imaging findings are diverse making recognition of this disease difficult and often delayed. *Nocardia* infection should be suspected in patients with non-responding pneumonia, especially if risk-factors are present. Stain of sputum or aspirated material along with culture are necessary for diagnosis. Combination treatment is often given initially until antimicrobial susceptibilities are available. Treatment course is long, typically 6-12 months depending on infection site and immune status. Clinicians must have a high index of suspicion for *Nocardia* infections, especially in immunocompromised patients and those with chronic lung disease, as diagnosis is frequently challenging but early recognition and initiation of appropriate treatment remain crucial for successful outcomes. Due to medication toxicity and clinical stability with only mild symptoms, the patient we presented is being monitored closely off of treatment currently.

Table 1. **Clinical Features of Nocardiosis***

Clinical Presentation	Primary Cutaneous	Pulmonary Nocardiosis	Disseminated
Main Risk Group	Farm workers, Traumatic skin exposure	Chronic lung disease, Immunocompromised	Immunocompromised
Primary Features	Cellulitis or abscess, Lymphangitis, Mycetoma	Pneumonia, can be acute/ chronic, cavitation, nodular infiltrates, abscesses, effusions	Lung disease; hematogenous spread to any organ, CNS most common

*****adapted from reference 4.

Table 2. **Selected Differential Diagnosis of Nocardiosis***

A. Pulmonary Disease
   a. Primary or secondary lung malignancy
   b. Mycobacterial infections including tuberculosis
   c. Fungal infections
   d. Other bacterial infections such as actinomycosis
   e. Vasculitis

B. Cutaneous Disease
   a. Cellulitis due to staphylococcus or streptococcus
   b. Lymphcutaneous (e.g sporotrichosis)
   c. Mycetoma (e.g. actinomycosis, fungal)

C. CNS disease
   a. Bacterial abscess
   b. Primary or secondary malignancy
   c. Infarct due to vascular disease
   d. Other (fungal, tuberculosis, toxoplasmosis, cysticercosis)

***** adapted from reference 3.

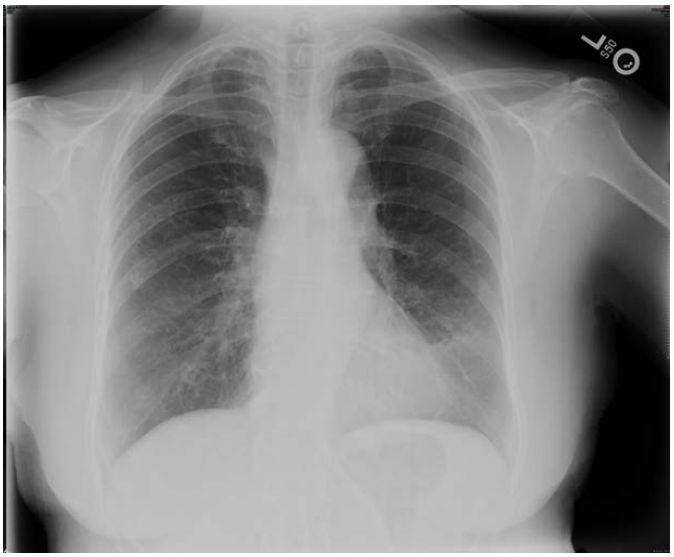

Figure 1. *CXR* – 3 weeks prior to admission.
Mild diffuse bronchial wall thickening concerning for airway inflammatory disease/bronchitis. Bandlike opacity within the lingula compatible with subsegmental atelectasis. No airspace consolidation, pleural effusion or clinically significant pneumothorax.

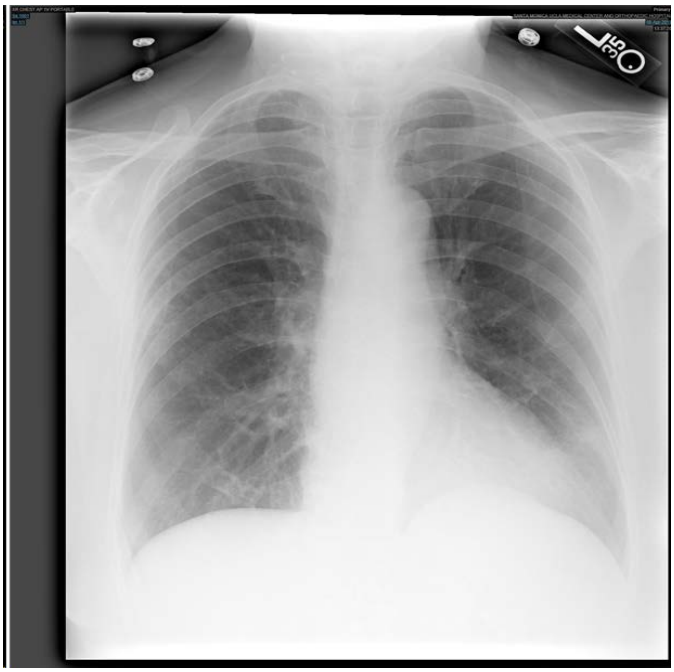

Figure 2. *CXR* – day of hospital admission.
Lingular opacity, corresponding to some of the nodularity opacities seen on CT chest performed on one day prior, suspicious for active airway centered infection including mycobacterial infection such as tuberculosis. Persistent bilateral bronchial wall thickening, which may represent reactive airway disease or viral/atypical pneumonia. No pleural effusion or pneumothorax.

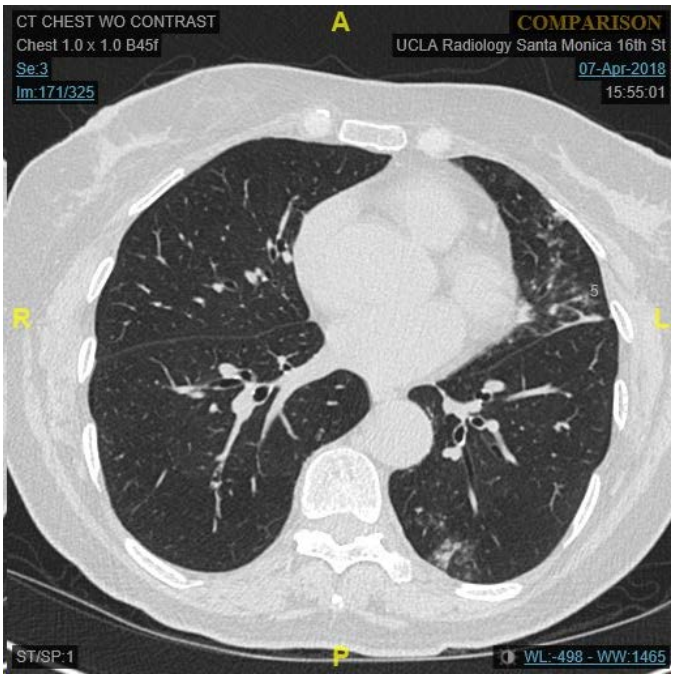

Figure 3. *Chest CT Scan* – day prior to hospital admission.
Focal nodular airspace consolidation with surrounding ground-glass attenuation and clustered micronodules in the left lower lobe (shown). There is focal airspace consolidation and clustered centrilobular micronodules in the lingula. In addition, ill-defined tree-in-bud and clustered centrilobular pulmonary micronodules and nodules within the posterior right upper lobe as well as to a lesser extent in other lobes. Findings concerning for active airway centered infection such as mycobacterial infection including tuberculosis.

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