

A Woman with a Lung Infiltrate and Brain Abscesses: Case Discussion from the University of Louisville Hospital

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Presentation of Case

Dr. Veronica Corcino (Infectious Diseases fellow): A 61-year-old female with no history of systemic disease presented to an outlying hospital with a headache, seizure-like episode and progressive productive cough for one month who presented to the emergency room of an outlying hospital where two brain lesions were detected on a computerized tomography (CT) scan. She was transferred to this university hospital the same day. She initially complained of dry cough that progressed to be productive a month prior to admission, however she had refused to seek medical care. She lives in Grand Rapids, Michigan and decided to visit her daughter in rural Kentucky in the winter. Her family stated she had chills, fevers, generalized weakness and a poor appetite the day prior to admission. Eventually, her headache progressed and she developed a seizure-like episode with loss of consciousness, which prompted going to the hospital. On presentation, her temperature was 100.9° F, blood pressure 145/80 mm Hg, pulse 110 beats/minute, and respiratory rate 23 breaths/minute. Her oxygen saturation was 95% on ambient air. Admission laboratory tests, including blood cultures, were collected. (Table 1) A chest radiograph (Figure 1) and head CT were also obtained (Figure 2).

Table 1 Baseline laboratory values

Variable	Value	Reference Range
White blood cell count (cells/mm ³)	15.4	4,500-10,800
Neutrophils (%)	84%	34-69
Hemoglobin (g/dL)	9.7	11-15.7
Hematocrit (%)	29.7	34-44
Platelet Count (cells/mm ³)	1,013,000	140,000-370,000
Sodium (mg/dL)	135	135-143
Potassium (mg/dL)	3.5	3.5-4.8
Blood Urea Nitrogen (mg/dL)	13	6.0-20.0
Creatinine (mg/dL)	1.04	0.44-1.03
Glucose (mg/dL)	117	65-110
AST (U/L)	14	8.0-34.0
ALT (U/L)	9	10.0-50
Alkaline Phosphatase (U/L)	103	25.0-125
Procalcitonin (ng/mL)	0.17	0-0.05
Lactic Acid (mmol/L)	0.74	0.5-2.2
Albumin (g/dL)	2.5	3.3-4.5

Diagnostic Approach

Dr. Viswanathan Nagarajan (fellow): This makes me wonder, "Did the brain abscess come first then the pneumonia or did the pneumonia occur first with a secondary brain abscess?" The way she presented with chronic cough, sputum production and recent onset of chills, she could have had a recent viral infection and subsequent secondary bacterial infection with pneumonia that hematogenously spread to the brain. Or, she had a brain abscess, which caused her seizures with subsequent aspiration, and then pneumonia. I favor the first scenario. The location of the lung abscess is consistent with aspiration. Organisms include oro-pharyngeal pathogens which she aspirated to the lungs. Geographic fungi are a possibility as she is from the upper Midwest (Michigan) where *Blastomycosis dermatitidis* can be associated with pneumonia and a brain abscess. If any skin lesions are noted on physical exam, they could be biopsied to rule out blastomycosis. Bacterial etiologies, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Klebsiella pneumoniae*, causing necrotizing pneumonia should also be considered. Due to her subacute to chronic presentation of four weeks duration, *Mycobacterium tuberculosis* should be considered. If she is immunocompromised, the differential would include *Nocardia asteroides*, *Actinomyces israelii* and *Aspergillus fumigatus* [1]. I would expect that whatever pathogen is defined in the lung is also in the brain. Finally, noninfectious causes include malignancies with metastatic lesions in the brain. She was exposed to secondhand smoke. Lung cancer could cause an obstructive pneumonia.

Dr. Julio Ramirez (Chief, Infectious Diseases): You reviewed the causes of pulmonary infections complicated by brain abscess. Based on this chest radiograph, do you think that there may be a cavity?

Dr. Viswanathan: There may be a cavity, but not an abscess because there is no air-fluid level. It is either a post-obstructive pneumonia, aspiration pneumonia or a necrotizing pneumonia.

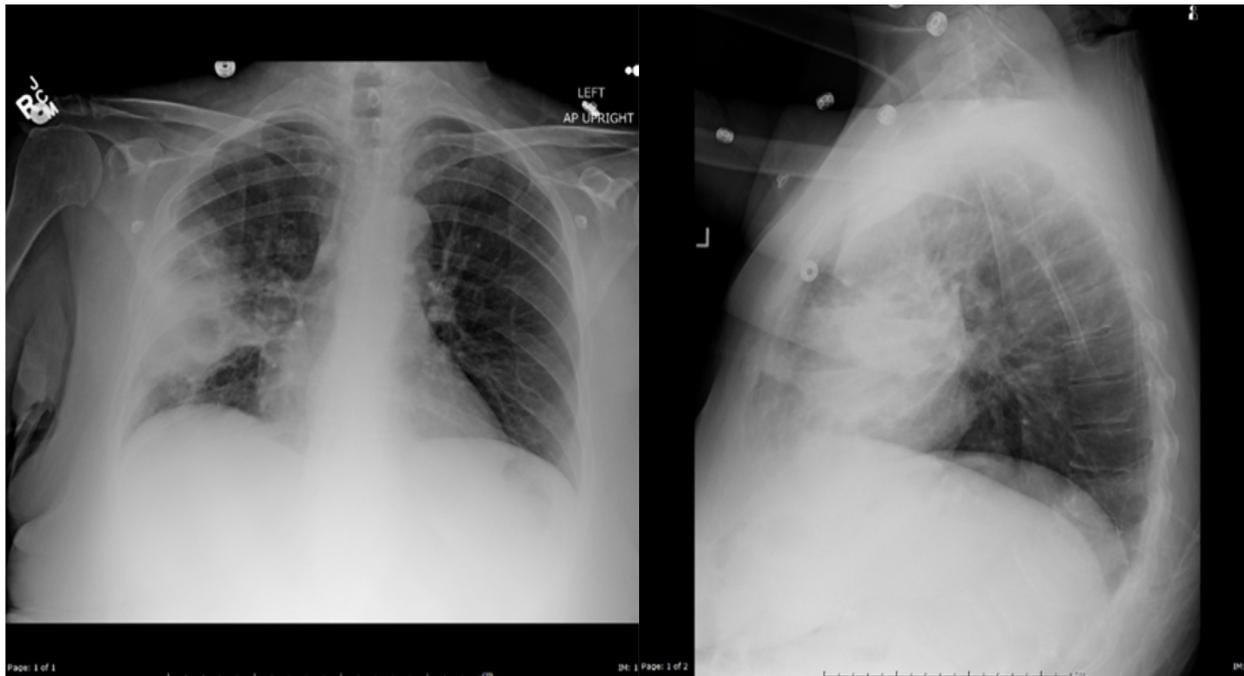


Figure 1 Chest radiograph from the day of admission shows right sided dense infiltrate with possible cavities.

Dr. Ramirez: What are the most likely pathogens you suspect after hearing this history and looking at this chest radiograph?

Dr. Viswanathan: The first is aspiration syndrome caused by anaerobic bacteria, the second is the fungus *B. dermatitidis*, and the third is MRSA.

Dr. Ramirez: I don't agree with any of your three choices. In which lobe is this infiltrate located?

Dr. Viswanathan: The lower part of the upper lobe.

Dr. Ramirez: You can see the infiltrate and below it is the major fissure, so that appears to be in the anterior segment of the upper lobe. To have a pneumonia in the anterior segment of the upper lobe, one would have to aspirate facedown. That would be unusual. Typically, aspiration occurs in the upper segment of the lower lobe. I don't think she has an anaerobic infection due to aspiration because after four weeks, she does not have a productive cough with foul smelling sputum, and the pneumonia is not in the location that I would expect. I don't think this is due to Klebsiella for some of the same reasons.

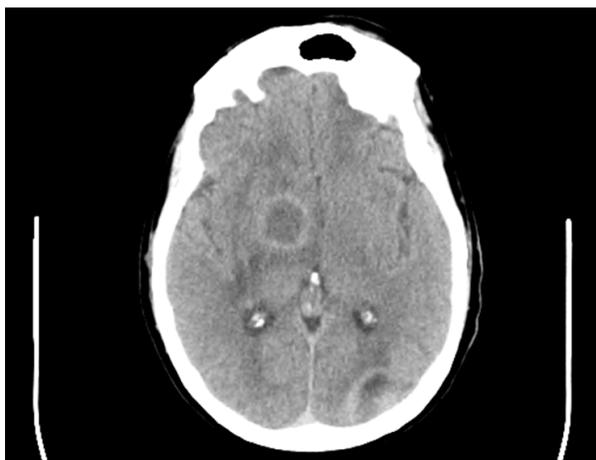


Figure 2 Computerized tomography of the head from the day of admission shows two lesions; one in the midbrain, and one in the left occipital lobe.

Dr. Martin Raff (ID faculty): People with *K. pneumoniae* also tend to be alcoholic and have very severe pneumonia. This patient has neither.

Dr. Ramirez: The location also makes tuberculosis less likely. Paragonimiasis [caused by the parasite *Paragonimus westermani*] can result in a lung abscess and a brain abscess, but this patient has no history of travel. When I consider the most likely pathogens, even though you said that this patient was not immunocompromised, I first consider Nocardia. It would certainly be at the top of the list if the patient had had a solid organ transplant, but *N. asteroides* may also affect immunocompetent patients as well.

Second, I consider *Streptococcus anginosus*, which we have seen cause severe abscesses in multiple organs of the body.

Third, one thing to note to consider malignancy is that she has over one million platelets. We see reactive thrombocytosis frequently in infections, but not usually that high. This patient has leukocytosis with increased neutrophils, though no bands, and anemia consistent with chronic disease, so she may have lung cancer with metastasis to the brain. A diagnosis of cancer would actually increase the likelihood of this being *N. asteroides* as well.

Dr. Anupama Raguram (ID faculty): We have a case of pneumonia with concomitant brain lesions. There are several etiologies to be considered. Regarding bacteria, if the patient's symptoms were more acute, I would favor *Streptococcus pneumoniae*. However, the duration of the cough being four weeks fits more with the *S. anginosus* group. **(Box 1)** Other bacterial etiologies to be considered include Nocardia, *M. tuberculosis*, *S. aureus* and *K. pneumoniae* - which have been mentioned. Legionella causes Pontiac fever and was interestingly described in Michigan, where this patient lives. You may see altered mental status with that pneumonia, but not usually focal brain lesions. Listeria may cause cerebritis, which infrequently progresses to a brain abscess, and pneumonia is not usually a manifestation of this infection. *Brucella melitensis* may cause pneumonia in approximately 7% of cases, but

Viridans streptococci
<i>Streptococci milleri</i> (<i>Streptococci anginosus</i>) group
<i>Streptococcus anginosus</i>
subspecies <i>anginosus</i>
subspecies <i>whileyi</i>
<i>Streptococcus intermedius</i>
<i>Streptococcus constellatus</i>
subspecies <i>constellatus</i>
subspecies <i>pharyngis</i>
subspecies <i>viborgensis</i>

Box 1 Nomenclature of Viridans streptococci with the ability to form abscesses

brain involvement is not seen [2]. *Coxiella burnetii* may cause pneumonia, hepatitis, and endocarditis, but not usually brain pathology. And thrombocytopenia tends to be associated with coxiella, not thrombocytosis. Zoonotic exposure for either Brucella or Coxiella is absent in this patient.

Regarding fungi, invasive aspergillosis or mucormycosis, could cause this presentation in an immunocompromised patient. Cryptococcal infection and disseminated histoplasmosis could be responsible for this presentation. Disseminated blastomycosis was mentioned as a possibility, but brain lesions tend to be cerebellar. Determining the patient's HIV status is very important because it may predispose to some of these fungal infections.

Primary pulmonary malignancy with brain metastasis could be a possibility. In my opinion, the top differential diagnosis should include the *S. anginosus* group and *N. asteroides*.

Dr. Raff: It strikes me that she has two abscesses in her brain. It is unusual under this circumstance for her infection. I suspect that it spread hematogenously or she has something like cerebral toxoplasmosis that has been reactivated by immunosuppression.

Dr. Ramirez: It goes without saying that this patient should have a rapid HIV test. If she were to have newly diagnosed HIV, it would expand the differential. She may have cryptococcal disease or cerebral toxoplasmosis, which can both cause lesions in the lung and brain. These two infections should be considered in an HIV patient.

Dr. Raff: Another question is, if we are considering *S. anginosus*, where did it come from?

Dr. Viswanathan: Aspiration?

Dr. Ramirez: No, let me tell you. Are you going to say that 99% of what is in the lung of this patient got there by aspiration? Consider the pathogenesis of pneumonia. Granted, 99% of the bacteria that are in the lung arrive by aspiration, but it is by microaspiration, which is different than what we call aspiration pneumonia. For that, we refer to large groups of anaerobes in the mouth getting into the lung and producing pneumoniaby macro-aspiration.

There are pneumonias that are transmitted via an exception to either type of aspiration. You get Legionella by breathing in, and you get tuberculosis by breathing in, but most bacterial pneumonia you do not get by breathing in. They get stuck in your oropharynx and you aspirate them. So, if you're going to say *S. anginosus* is present due to aspiration based on the pathogenesis I just described, then you are always right. But, we want to limit the term aspiration pneumonia to represent macro-aspiration of anaerobic bacteria, not micro-aspiration. And for this reason, sputum is often contaminated with pathogens that may or may not be significant because they may or may not be causing pneumonia. A bronchoscopy with a protected brush specimen and a brain biopsy will give us the best information. Now what would be your empiric antibiotic therapy?

Dr. Viswanathan: I would cover with vancomycin for MRSA, clindamycin for anaerobes and ceftriaxone for gram-negative pathogens.

Dr. Ramirez: I agree with what you're covering for, but clindamycin does not cross the blood-brain barrier well. Metronidazole would be a better option. Vancomycin is good for MRSA and since she does not have risk factors for multidrug resistant gram-negatives, ceftriaxone is adequate.

Clinical Diagnosis

Abscesses in the lung and brain due to Nocardia or *Streptococcus anginosus* group.

Hospital Course

Dr. Corcino: Her HIV test was negative. Urine was negative for pneumococcal, Histoplasma and Legionella antigens. The admission chest X-Ray performed on the admission showed a right middle lobe opacity. Heart size was normal. The chest CT scan showed a right middle lung cavitation. A bronchoalveolar lavage (BAL) was performed. In her BAL, she had 2505 white blood cells (72% neutrophils, 18% lymphocytes). A Gram's stain was performed. (**Figure 3**) A respiratory viral panel was negative. A magnetic resonance imaging (MRI) of her brain showed two lesions; one in the posterior limb of the right internal capsule and globus pallidus, and one in the left occipital lobe. (**Figure 4**) Neurosurgery was asked to perform a brain biopsy.

Microbiological and Pathological Discussion

Dr. Corcino: Neurosurgery performed a stereotactic brain biopsy. Tissue was collected for microbiology, but it did not make it there. A sample did make it to pathology where they reported mucopurulent exudate and gliotic reaction consistent with a brain abscess. Gomori Methenamine Silver (GMS) stain was positive for a spiral microorganism morphology consistent with spirochetes species (**Figure 5**). AFB stain was negative for a mycobacterial organism (and culture was eventually negative after six weeks).

Dr. Carmen Sciortino (Microbiology): These look like streptococci but there is a clostridium, *Clostridium ramosum*, that will form unique structures that I see on the slide of the brain biopsy from pathology, such as circles and half circles. Sometimes the half circles even look like a spiral as we see here [3]. Sometimes they are polychromatic not staining evenly, and look like cocci. The slide of the bronchoscopy from microbiology looked like streptococci, and I am in favor of streptococci.

Dr. Ramirez: The question here is, “Are these small cocci in chains or a single large bacterium?” The initial Gram’s stain from the lung seemed to me to be cocci in chains. The subsequent GMS stain from the brain seemed to me, and to the pathologist, to be a single large spirochete.

Dr Sciortino: The measurement bar at the lower right corner is 100 μm indicating that the organisms shown are big. If those are single bacteria, then they are large, much larger than you would see with streptococci. *C. ramosum* is large; approximately 2-3 μm by 20-30 μm . The largest spirochete is *Borrelia burgdorferi* [the cause of Lyme disease] and is 0.5 μm by 30-60 μm . To my knowledge, *Treponema* and *Leptospira* do not bend and overlap making “character” shapes microscopically, such as the letter “C”, whereas *Borrelia* may do so. The problem with declaring both organisms seen in the lung and brain as treponemes is that the slide from the lung was a Gram’s stain, and treponemes are not visible with Gram’s stain. The silver stain used in the brain biopsy may show them, but not Gram’s stain.

I have never seen a treponeme make a circle, and I don’t see how this is possible since spirochetes have a rigid axial filament that forms their linear posture. I have seen leptospirae in broth that are motile by flexing head to toe, so it is possible that one could capture this morphology in a stain, but that would be very rare, especially in a tissue biopsy.

Dr. Raghuram: We know we have nonpathogenic treponema in the oral flora. I am just having a hard time coming up with a syphilitic or treponemal pneumonia.

Dr. Forest Arnold (ID faculty): In the same way, we could not reason that other spirochetes made sense. *Helicobacter pylori* and *Leptospira* don’t cause lung or brain abscesses. Abscess formation is also a non-entity for *B. burgdorferi* that cause Lyme disease, and for other *Borrelia* species that cause tick or louse borne relapsing fever. The closest explanation we could reason was the gummatous lesions of tertiary stage *Treponema pallidum* subspecies *pallidum* (venereal syphilis) or *Treponema pallidum* subspecies *pertenue* (yaws). Yaws certainly did not fit with her social history, and her rapid plasma reagin (RPR) was negative.

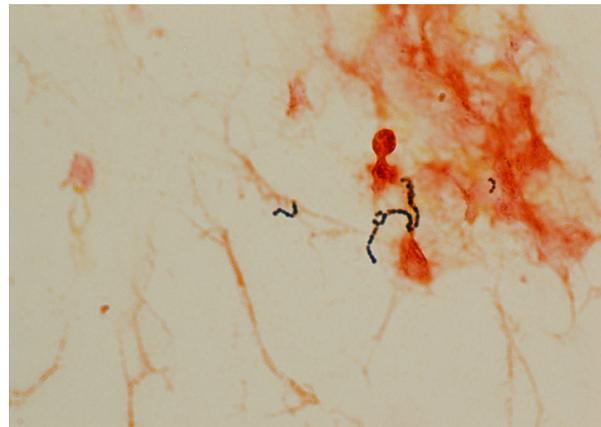


Figure 3 Gram’s stain of bronchoalveolar lavage.

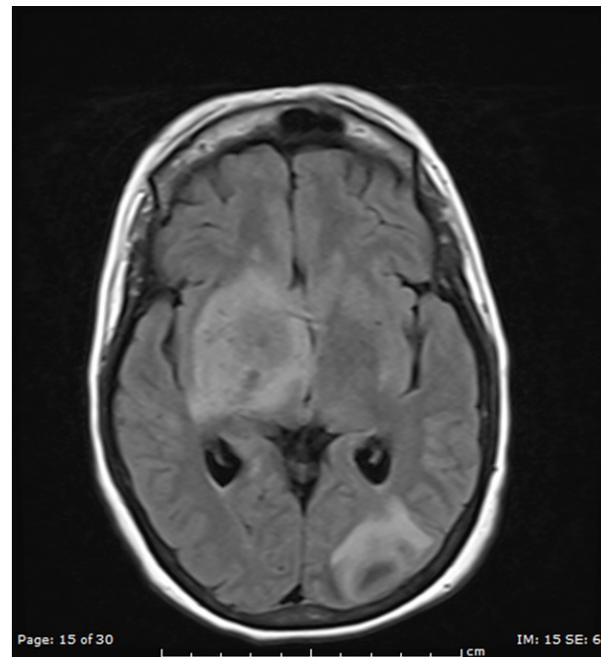


Figure 4 Magnetic resonance imaging of the brain performed after lesions seen on a computerized tomography scan shows two lesions; one in the posterior limb of the right internal capsule and globus pallidus, and one in the left occipital lobe.

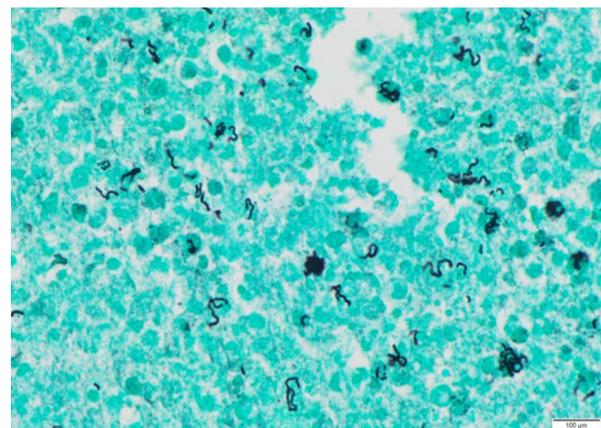


Figure 5 Gomori methenamine silver (GMS) stain of brain biopsy.

Dr. Ramirez: Do we have bacteria that look like a spirochete?

Dr. Sciortino: Yes, there is *Spirillum minus*, which is where it gets its name, and *Streptobacillus moniliformis*. Both cause rat bite fever in different geographic regions. These are big. They are probably 5 µm wide and 100 µm long. The spirochetes are large, which is why pathology is saying these are spirochetes.

Dr. Ramirez: Were the bacteria large that were in the BAL? And what was the Gram's stain of the brain?

Dr. Corcino: The bacteria seen on the BAL sample were under 100 power and were not large. There was no Gram's stain or culture from the brain specimen due to an error. To maximize information from pathology, they made new slides of the brain biopsy specimen. In the meantime, the patient's repeat MRI worsened necessitating another surgical drainage providing new samples for microbiology and pathology. The new samples did make it to both laboratories.

The first brain Bx was on day 10. The second brain Bx was on day 25. Empiric vancomycin, cefepime and metronidazole were changed to penicillin G on hospital day 13. The repeated pathology of the first brain Bx was not interpreted as spirochetes, but rather a mix of cocci and bacilli morphologies (no spirochetes). The second brain Bx pathology was read as histologic sections showing mostly chronic inflammatory infiltrates with patchy aggregates of macrophages, plasma cells and benign fibroblastic proliferation; consistent with an evolving chronic abscess. The Gram's stain of the brain did not show bacteria, and the culture did not have growth, which is unsurprising after more than three weeks of antibiotics.

Management

Dr. Ramirez: So, the patient is on penicillin G for streptococcal brain and lung abscesses. How long are you going to treat?

Dr. Corcino: The plan is to give eight weeks of antibiotics, reimage and then reevaluate the duration of therapy.

Anatomical Diagnosis

Streptococcal lung and brain abscesses, likely caused by *Streptococcus anginosus* group.

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