CLINICAL VIGNETTE

Legionellosis in an Immunosuppressed Patient

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Introduction

Legionella pneumophilia, a gram-negative rod that lives in warm freshwater environments, infects humans when inhaled or aspirated.[1,2] It is not transmitted from person to person. It causes two clinical diseases: Legionnaires' disease and Pontiac fever. Legionnaire's disease, first described after an outbreak at the American Legion convention in Philadelphia in 1976,[3] produces symptoms of malaise, myalgias, and headache, followed by high fever, rigors, pleuritic chest pain, non-productive cough, dyspnea, and gastrointestinal symptoms including diarrhea.[4] Legionnaires' disease can range in severity from a mild respiratory illness to multisystem disease.[4,5] Pontiac fever is typically a flu-like illness.[1,6] We report a case of Legionnaires' disease in a 43-year-old male with history of idiopathic inflammatory ocular disease treated with prednisone and infliximab.

Case Report

A 43-year-old male with a history of idiopathic inflammatory ocular disease and chronic uveitis presented with four days of confusion, diarrhea, and subjective fevers. The patient was sent to the Emergency Department from the infusion center where he was scheduled to receive his second dose of infliximab. His last dose was given two weeks prior, and he was noted to be pale, diaphoretic, and tachypneic. The patient reported feeling "disoriented," which he described as waking up at night not knowing where he was and having poor balance. He had subjective fevers and chills, diarrhea, and shortness of breath; he took acetaminophen with no improvement. He had a poor appetite but reported drinking a half-gallon of water per day. He denied chest pain, vomiting, and abdominal pain, and he had no sick contacts or recent travel outside of California. He denied any direct exposure to air conditioning units or misting systems. He worked in finance in a modern building and swam at a local gym. He did not use the showers. He did not smoke, drink alcohol, or use illicit drugs. On exam, the patient was diaphoretic and tachypneic without accessory respiratory muscle use. His conjunctivae were pale and mucous membranes were moist. Heart exam was notable for tachycardia and lung auscultation revealed coarse rhonchi bilaterally with egophony. Abdomen was soft with normoactive bowel sounds and nontender. There were no skin rashes, and the neurologic exam was nonfocal.

While in the Emergency Department, he was febrile to 105.3 F with a heart rate ranging from 104-146 and respiratory rate of 40 breaths per minute. His oxygen saturation was 90% on room air, which improved to 94% on 4L nasal cannula. Labs were significant for a leukocytosis of 12.66 with 92.7% polymorphonuclear cells, hemoglobin of 12.3 with MCV 76.3, platelets of 127, sodium of 124, an anion gap of 16, delta gap of -2. A chest x-ray (Figure 1) showed airspace opacities within the right upper lobe, right infrahilar region, left perihilar region, and infrahilar region concerning for multifocal pneumonia without evidence of pleural effusions. Blood and sputum cultures were obtained, and a Legionella urinary antigen test was performed. The patient was empirically started on vancomycin, pipercillin-tazobactam, and azithromycin for treatment of health-care associated pneumonia (HCAP) with coverage for atypical organisms.

On the evening of admission, despite receiving antibiotics, the patient was persistently tachypneic and saturating 91-94% on 5 L nasal cannula. A venous blood gas (VBG) demonstrated a respiratory alkalosis with venous pH 7.43 and venous pCO2 27. The patient was started on high flow nasal cannula that was uptitrated to 20 L/min with a FiO2 of 60%. A repeat VBG showed venous pH 7.48 venous pCO2. The following morning, he developed worsening shortness of breath and was unable to speak in full sentences. He was transferred to the Intensive Care Unit for closer monitoring while increasing the FiO2 on high flow nasal cannula. That afternoon his test for the legionella urine antigen returned positive.

Over the following days, additional infectious work-up did not yield any other positive results. He was eventually transitioned to monotherapy with levofloxacin for a 21-day treatment course. He received one dose of vancomycin and cefepime when he spiked a fever to 38.5 F overnight while on levofloxacin, but the broad spectrum antibiotics were discontinued per recommendations from the consulting Infectious Disease team as this fever was considered part of the natural course of legionellosis as opposed to an additional infection. During the remainder of his hospitalization, he remained afebrile. His oxygen requirement slowly decreased to nasal cannula and eventually was discontinued prior to discharge from the hospital. At his follow-up after completing his antibiotics, he reported persistent dry cough when lying flat and gradual improvement in his dyspnea on exertion.

Discussion

Legionella is one of the top four most common causes of community-acquired pneumonia.[7] Risk factors for legionellosis include age, smoking, male sex, chronic lung disease, end-stage renal disease, lung, cancer, immunosuppression, and diabetes.[8] It has been suggested that treatment with TNF-alpha inhibitors such as infliximab is associated with a greater risk for infection with intracellular pathogens such as *Legionella*.[9] Compared to the other TNF-alpha inhibitors etanercept and adalimumab, infliximab was associated with a higher infection rate in patients being treated for rheumatoid arthritis.[10] Our patient's recent immunosuppression with infliximab put him at higher risk for legionellosis.

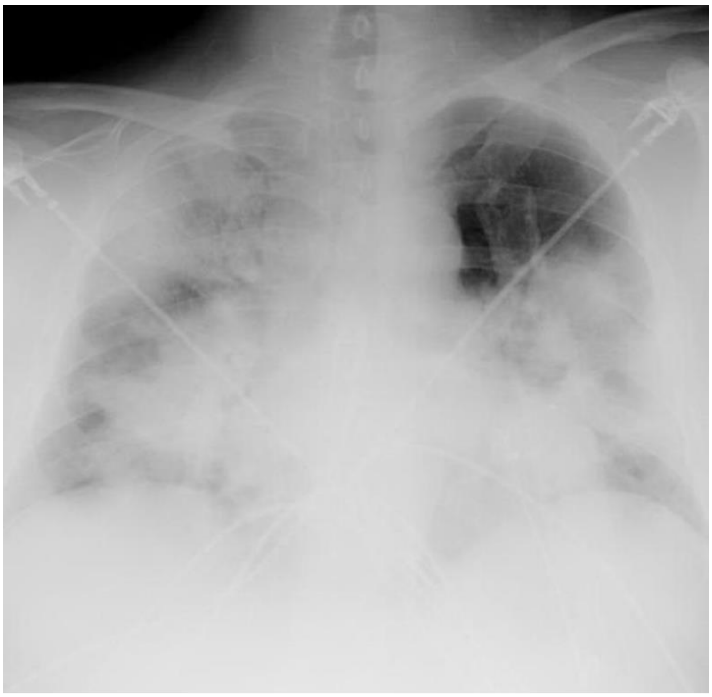
Diagnosing *Legionella* may be difficult as it does not grow easily in routine bacterial culture media.[7] The urine antigen test is routinely used as it allows for rapid diagnosis, and urinary antigens are detectable within a few days of the onset of illness. It can last up to several weeks even after starting treatment.[1] However, the urine antigen test only identifies *Legionella pneumophilia* serogroup 1, which causes roughly 80% of cases of Legionnaires' disease,[7] and does not detect the 14 other servovars of *Legionella pneumophilia*.[1] For serogroup 1, urinary antigen tests' sensitivities range from 70-100% and specificities are close to 100%.[11] It is estimated that reliance on this test alone may miss up to 40% of cases of Legionnaire's disease.[1] Radiographic features are not useful in differentiating *Legionella* pneumonia from other types of pneumonia.[12]

A number of prediction models have been created to try to identify patients with *Legionella* pneumonia. Haubitz et al[7] found that in patients with Legionnaires' disease, temperature, heart rate, C-reactive protein (CRP), and procalcitonin levels were significantly higher, and hyponatremia was more common compared to other causes of pneumonia.[7] Using the "*Legionella* score" developed by Fiumfreddo et al (2009)[13] in which 1 point was given for each of clinical criteria (CRP >187 mg/L, lactate dehydrogenase >225 U/L, platelet count <171 10^9/L, dry cough) a score of <2 points had a negative predictive value of 99.6%.[7]

Treatment of *Legionella* pneumonia consists of azithromycin or levofloxacin, although in the past erythromycin was the drug of choice.[1] In this patient's case, he was at high risk for HCAP given his recent immunosuppression. Empiric broad-spectrum antibiotic coverage with vancomycin and pipercillin-tazobactam does not provide adequate coverage for Legionnaire's disease. At our institution, it is recommended for patients who have suspected HCAP and are taking immunosuppressive medications or are neutropenic to add azithromycin for *Legionella* coverage as was done in this case.[14]

Figures

Figure 1. Chest x-ray showing airspace opacities.



REFERENCES

1. **Fields BS, Benson RF, Besser RE**. Legionella and Legionnaires' disease: 25 years of investigation. *Clin Microbiol Rev*. 2002 Jul;15(3):506-26. Review. PubMed PMID: 12097254; PubMed Central PMCID: MC118082.
2. **Kool JL, Carpenter JC, Fields BS**. Effect of monochloramine disinfection of municipal drinking water on risk of nosocomial Legionnaires' disease. *Lancet*. 1999 Jan 23;353(9149):272-7. PubMed PMID: 9929019.
3. **Brenner DJ, Steigerwalt AG, McDade JE**. Classification of the Legionnaires' disease bacterium: Legionella pneumophila, genus novum, species nova, of the family Legionellaceae, familia nova. *Ann Intern Med*. 1979 Apr;90(4):656-8. PubMed PMID: 434652.
4. **Fraser DW, Tsai TR, Orenstein W, Parkin WE, Beecham HJ, Sharrar RG, Harris J, Mallison GF, Martin SM, McDade JE, Shepard CC, Brachman PS**. Legionnaires' disease: description of an epidemic of pneumonia. *N Engl J Med*. 1977 Dec 1;297(22):1189-97. PubMed PMID: 335244.
5. **Tsai TF, Finn DR, Plikaytis BD, McCauley W, Martin SM, Fraser DW**. Legionnaires' disease: clinical features of the epidemic in Philadelphia. *Ann Intern Med*. 1979 Apr;90(4):509-17. PubMed PMID: 434627.
6. **Glick TH, Gregg MB, Berman B, Mallison G, Rhodes WW Jr, Kassanoff I**. Pontiac fever. An epidemic of unknown etiology in a health department: I. Clinical and epidemiologic aspects. *Am J Epidemiol*. 1978 Feb;107(2):149-60. PubMed PMID: 623097.

7. **Haubitz S, Hitz F, Graedel L, Batschwaroff M, Wiemken TL, Peyrani P, Ramirez JA, Fux CA, Mueller B, Schuetz P**. Ruling out Legionella in community-acquired pneumonia. *Am J Med*. 2014 Oct;127(10):1010.e11-9. doi: 10.1016/j.amjmed.2014.03.042. Epub 2014 May 6. PubMed PMID: 24813862.
8. **Marston BJ, Lipman HB, Breiman RF**. Surveillance for Legionnaires' disease. Risk factors for morbidity and mortality. *Arch Intern Med*. 1994 Nov 14;154(21):2417-22. PubMed PMID: 7979837.
9. **Morrison VA**. Immunosuppression associated with novel chemotherapy agents and monoclonal antibodies. *Clin Infect Dis*. 2014 Nov 15;59 Suppl 5:S360-4. doi: 10.1093/cid/ciu592. Review. PubMed PMID: 25352632.
10. **Curtis JR, Xie F, Chen L, Muntner P, Grijalva CG, Spettell C, Fernandes J, McMahan RM, Baddley JW, Saag KG, Beukelman T, Delzell E**. Use of a disease risk score to compare serious infections associated with anti-tumor necrosis factor therapy among high- versus lower-risk rheumatoid arthritis patients. *Arthritis Care Res* (Hoboken). 2012 Oct;64(10):1480-9. doi: 10.1002/acr.21805. PubMed PMID: 22833479; PubMed Central PMCID: PMC3687540.
11. **Reller LB, Weinstein MP, Murdoch DR**. Diagnosis of Legionella infection. *Clin Infect Dis*. 2003; 36(1):64-9.
12. **Macfarlane JT, Miller AC, Roderick Smith WH, Morris AH, Rose DH**. Comparative radiographic features of community acquired Legionnaires' disease, pneumococcal pneumonia, mycoplasma pneumonia, and psittacosis. *Thorax*. 1984 Jan;39(1):28-33. PubMed PMID: 6695350; PubMed Central PMCID: PMC459717.
13. **Fiumefreddo R, Zaborsky R, Haeuptle J, Christ-Crain M, Trampuz A, Steffen I, Frei R, Müller B, Schuetz P**. Clinical predictors for Legionella in patients presenting with community-acquired pneumonia to the emergency department. *BMC Pulm Med*. 2009 Jan 19;9:4. doi: 10.1186/1471-2466-9-4. PubMed PMID: 19152698; PubMed Central PMCID: PMC2636761.
14. **Antimicrobial Stewardship Program**. UCLA Health Antibiotic Guidebook. 2015. http://www.asp.mednet.ucla.edu.

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