An Unusual Etiology of Fluorodeoxyglucose Avid Intrathoracic Lymph Nodes

Alyssa Bonnier[1], Santu Saha[2], Adam Austin[3], Biplab K. Saha[3]

[1] Department of Critical Care Nursing, Goldfarb School of Nursing, Barnes Jewish College, Saint Louis, USA;
[2] Department of Medicine, Saha Clinic, Bangladesh;
[3] Department of Pulmonary, Critical Care and Sleep Medicine, University of Florida, Gainesville, USA

Received November 24, 2022; Accepted January 30, 2024.

Key words: Tularemia – Pneumonia – Lymph nodes – PET-CT

Abstract: A middle-aged man in his 50s, active smoker, presented to the pulmonary office for lung cancer evaluation. On a low-dose computed tomography for lung cancer screening, he was found to have an 8 mm endobronchial lesion in the right main stem bronchus. A PET-CT revealed no endobronchial lesion, but incidentally, fluorodeoxyglucose (FDG) avidity was present in the right hilar (SUV 13.2) and paratracheal lymph nodes (LNs). He underwent bronchoscopy and EBUS-TBNA of station 7 and 10 R LNs. The fine needle aspiration (FNA) revealed necrotizing epithelioid granuloma. The acid-fast bacilli (AFB) and Grocott methenamine silver (GMS) stains were negative. He had suffered from pneumonic tularemia 13 months ago and immunohistochemical staining for *Francisella tularensis* on FNA samples at Center for Disease Control and Prevention was negative. The intense positron emission tomography (PET) avidity was attributed to prior tularemic intrathoracic lymphadenitis without active tularemia, a rare occurrence. To the best of our knowledge, PET-positive intrathoracic lymph node beyond one year without evidence of active tularemia has not been previously reported.

Mailing Address: Biplab K. Saha, MD., FCCP, Department of Pulmonary, Critical Care and Sleep Medicine, Medical Sciences Building, Room #M-452, University of Florida, 1600 SW Archer Road, Gainesville, FL 32608, USA; e-mails: spanophiliac@yahoo.com, biplab.saha@medicine.ufl.edu

https://doi.org/10.14712/23362936.2024.8

Introduction

Tularemia is an uncommon and potentially fatal zoonotic disease caused by *Francisella tularensis*. Less than 200 cases are reported in the United States (US) each year (Centers for Disease Control and Prevention, 2009). Tularemia is endemic in the northern hemisphere affecting North America, Europe, Asia, and northern Africa. *F. tularensis* is a facultative gram negative aerobic intracellular coccobacillus that can be transmitted incidentally to humans from direct contact with the infected animals or via an invertebrate vector, such as tick or deer fly (most prevalent mode of transmission). The common animal reservoirs are small mammals such as rabbits, hares, and rodents, but natural infection has been reported in more than 250 wild species (Golovliov et al., 2021). As *F. tularensis* can survive in soil, water, and vegetation for up to 3 to 4 months, contact with contaminated environment or ingestion of contaminated food could also cause disease (Matyas et al., 2007; Golovliov et al., 2021).

Depending on the mode of transmission, there are several distinct ways tularemia can present in clinical practice. Although pneumonic tularemia is considered an uncommon presentation, it could be due to the lack of consideration of tularemia as a potential etiology for pneumonia. The incidence of pneumonic tularemia has varied between 25 to 64% in the United States (Centers for Disease Control and Prevention, 2009; Thomas and Schaffner, 2010). In contrast, the incidence of pneumonic tularemia appears to be less in Europe (Väyrynen et al., 2017). This could be because the *F. tularensis* subspecies *tularensis*, the most virulent strain, is the most common infecting agent in the USA. In contrast, nearly all cases in Europe are caused by *F. tularensis* subspecies *holarctica,* a less virulent organism. Pulmonary involvement can occur in two ways: 1) inhalation of the pathogen, or 2) hematogenous spread from a non-pulmonary source, generally from ulceroglandular or typhoidal forms of tularemia (Tärnvik and Berglund, 2003).

In addition to pulmonary parenchymal involvement, pneumonic tularemia is often associated with hilar and mediastinal lymphadenitis (Väyrynen et al., 2017; Martinet et al., 2021). The pulmonary parenchymal involvement may radiologically manifest as consolidation, pulmonary nodule, or masses. The combination of parenchymal lesions and intrathoracic lymphadenopathy often raises concerns for lung cancer (Kravdal et al., 2020). Patients also report constitutional symptoms, including high fever, fatigue, and significant weight loss raising the suspicion of malignancy even higher. During the acute and subacute phases of the disease, the pulmonary infiltrate and thoracic lymph nodes have been reported to have intense positron emission tomography (PET) positivity, making the distinction nearly impossible (Martinet et al., 2021). However, isolated fluorodeoxyglucose (FDG) avid mediastinal and hilar lymph nodes in patients with a remote history of tularemic pneumonia have never been reported.

Case report

A middle-aged man in his 50s was seen in the pulmonary office for lung cancer evaluation. The patient was an active smoker and had more than a 45-pack-year history of smoking. He underwent a low-dose computed tomography (LDCT) scan for lung cancer screening by his primary care provider and was found to have an 8 mm endobronchial lesion in the right main stem bronchus (Figure 1). No significant intrathoracic lymphadenopathy was noted. He was referred to the oncology team. A PET-CT was obtained at the oncologist's request, which revealed no endobronchial lesion, but incidentally, FDG avidity was present in the right hilar (SUV 13.2) and right paratracheal lymph nodes (Figure 2). The patient was then referred to the pulmonary service.

In the office, the patient complained of mild chronic cough with sputum production throughout the year, occasional episodes of wheezing, and exertional shortness of breath while walking uphill, needing to rest. He denied any fever, night sweats, chills, or loss of appetite. He reported nearly 6.8 kg weight loss over the past two months. He did not have any personal history of tuberculosis, exposure to patients with tuberculosis, or other sick contacts. The patient had worked as a car mechanic his whole life and regularly participated in hunting activities. He lived in a mid-western state and did not travel outside the US or to the south-western US. The patient suffered from pneumonic tularemia 13 months ago. Computed tomography (CT) of the chest at that time revealed dense bronchocentric consolidation in the right upper lobe with hilar and mediastinal lymphadenopathy (Figure 3). The diagnosis was made from bronchoscopy and bronchoalveolar lavage.

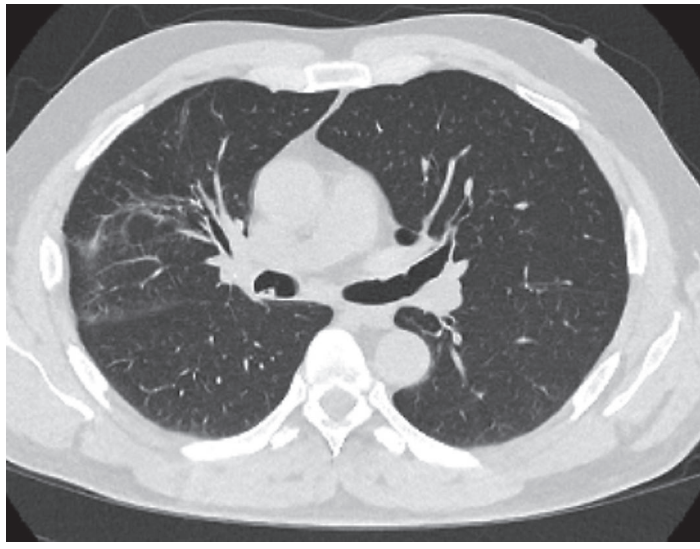

Figure 1 – Axial computed tomography (CT) of the chest demonstrated an 8 mm endobronchial lesion in the right main stem bronchus.

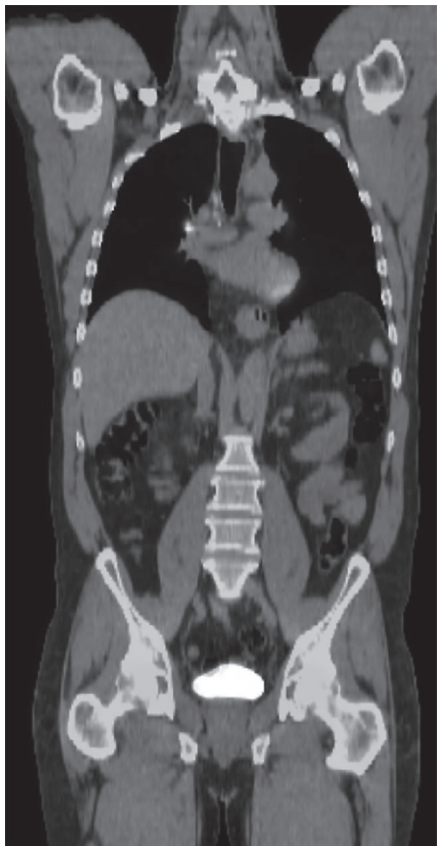

Figure 2 – Coronal view of the positron emission tomography (PET) scan revealed fluorodeoxyglucose (FDG) avid right hilar and paratracheal lymph nodes. The endobronchial lesion was not present on the PET-CT scan.

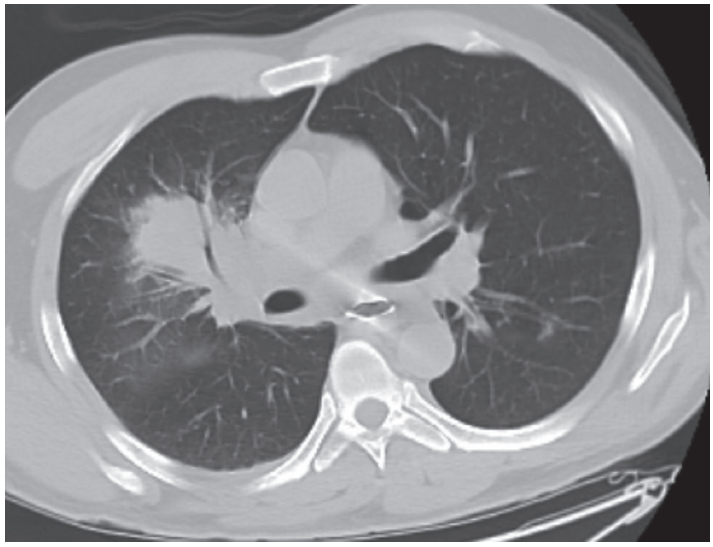

Figure 3 – Axial computed tomography (CT) of the chest 13 months ago showed dense bronchocentric right upper lobe consolidation and right hilar lymphadenopathy.

On physical examination, the patient appeared to be tired and without any distress. Chest examination was unremarkable other than bilateral reduced breath sound. There was no skin rash, joint pain, or swelling.

Given his extensive history of smoking and high FDG avidity in the intrathoracic lymph nodes, the patient underwent bronchoscopy and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of station 7 and 10 R lymph nodes. The fine needle aspiration (FNA) revealed necrotizing epithelioid granuloma without any evidence of malignancy from both lymph node biopsies (Figure 4). The acid-fast bacilli (AFB) and Grocott methenamine silver (GMS) stains were negative for mycobacteria and fungi, respectively. As the patient was a heavy smoker for years, the primary concern was for metastatic lung malignancy. Small cell carcinoma (SCC) of the lung can present with hilar and mediastinal involvement without a parenchymal lesion. The other concern was lymphoma. However, it was very unusual that the patient had FDG avid intrathoracic lymph nodes but without lymphadenopathy. The list of etiologies for FDG avid intrathoracic lymph nodes is extensive; however, his clinical presentation was not suggestive of any particular etiology. As intrathoracic lymphadenitis in the setting of acute pneumonic tularemia has been previously reported to have FDG avidity, given his past history, we also considered that to be a potential etiology. The immunohistochemical staining (IHC) for *F. tularensis* on FNA samples at the Center for Disease Control and Prevention (CDC) was negative, suggesting the absence of active infection.

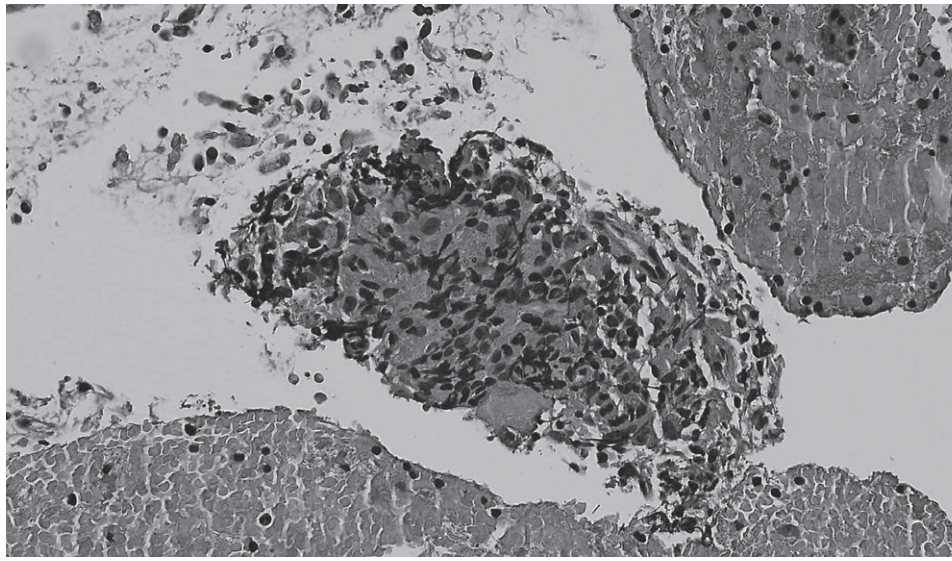

Figure 4 – Histopathologic analysis of fine needle aspiration from the right hilar lymph node revealed necrotizing epithelioid granuloma.

The intense PET avidity in the intrathoracic lymph nodes was determined to be secondary to prior tularemic intrathoracic lymphadenitis. Since the IHC for *F. tularensis* was negative, the patient was not treated with antibiotics. The patient did not require any further imaging or diagnostic study. He was asked to continue with yearly LDCT for lung cancer screening. He was advised to quit smoking.

Discussion

We have reported the case of an active smoker with PET-positive right hilar and paratracheal lymph nodes without lymphadenopathy. The patient had suffered from pneumonic tularemia about 13 months ago, and the FDG avidity was determined to be secondary to the prior intrathoracic lymphadenitis from tularemia. To the best of our knowledge, PET-positive intrathoracic lymph node beyond one year without evidence of active tularemia has not been previously reported.

F. tularensis is one of the most virulent bacteria known to man, with an infective dose of 10 cells (Dennis et al., 2001). As a result, it has been considered a potential bioterrorism agent. Once the bacteria gain access to the human body either by inoculation or inhalation, it proliferates locally and infects the macrophages and neutrophils (Pechous et al., 2009). *F. tularensis* is capable of evading the host defence mechanisms by escaping in the cytosol from the phagosome and causing death of the immune cells and release of pro-inflammatory cytokines and chemokines and thus propagating more tissue damage (Kinkead and Allen, 2016). *F. tularensis* can also infect the erythrocytes and survive there despite adequate antibiotic therapy causing recurrence of the disease (Horzempa et al., 2011). After the initial episode of nonspecific systemic illness, patients generally seek medical attention with symptoms consistent with one of the six distinct phenotypes, depending on the mode of transmission (Evans et al., 1985). These are: a) ulceroglandular disease (most common presentation, up to 80%), b) oculoglandular disease, c) glandular disease (refers to lymph node involvement), d) pharyngeal or oropharyngeal disease, e) typhoidal disease, and f) pneumonic disease.

Primary pneumonic tularemia due to inhalation of the bacteria is a rare occurrence. Most cases of pulmonary involvement are due to hematolymphogenous dissemination in the setting of typhoidal tularemia (Thomas and Schaffner, 2010). In case of primary pneumonic type, patients often present with high-grade fever, headache, cough, mild sputum production (which can progress over time), and occasionally retrosternal or pleuritic chest pain. However, a subacute presentation is also common. A history of potential exposure to an infected animal or tick bite may or may not be present. The differentiation from community-acquired pneumonia (CAP) may not be possible clinically. Acute respiratory distress syndrome occurs infrequently (Sunderrajan et al., 1985). Patients with pneumonic tularemia are more likely to be hospitalized and have a higher risk of death (Väyrynen et al., 2017).

The physical examination findings are nonspecific. Signs of consolidation, crackles, and pleural friction rub can be audible. Initial imaging with a chest X-ray could be unrevealing (Väyrynen et al., 2017). Unilobar or multilobar infiltrates are common. Hilar lymphadenopathy has been reported in approximately 30 to 45% of patients (Miller and Bates, 1969; Rubin, 1978). About one-third of patients suffer from pleural effusion (Thomas and Schaffner, 2010). In most cases, pneumonia and intrathoracic lymphadenopathy resolve with time. One study showed a median time of 14 weeks (range 6–28 weeks) for the resolution of radiographic abnormalities following treatment (Väyrynen et al., 2017). Although PET positivity has been consistently reported during the active phase of the disease, how long the FDG avidity persists is unknown. Perhaps, no study has ever evaluated this, as it would be a moot point to repeat a PET-CT in a patient with a known infection and no malignancy. In one case series where four patients with suspected lung cancer and positive PET-CT were followed longitudinally (all patients had tularemia), 3/4 patients had a complete resolution of the CT within three months. Only one patient did not have regression of the lesion (Fachinger et al., 2015). Other retrospective studies have also reported regression of lesions or complete resolution with short-term (3 months) follow-up (Martinet et al., 2021). PET positivity more than one year after the initial infection has never been reported in the literature. More interestingly, the FDG avidity could be present without any lymphadenopathy. The histopathologic analysis of the pulmonary lesions or lymph nodes may show necrotizing epithelioid granuloma mimicking tuberculosis and other fungal infections. Sometimes nonspecific lymphadenitis can be seen in EBUS-TBNA samples.

A definitive diagnosis of pulmonary tularemia can be made by isolating the bacteria in a culture medium from appropriate samples. Otherwise, a fourfold rise of the antibody titter in 2–3 weeks following initial presentation is diagnostic. Although rarely commercially available, a positive *F. tularensis* PCR or IHC from a clinical sample is also diagnostic. The first line of therapy for severe disease includes an aminoglycoside. Patients are generally treated for 7–10 days. Second-line medications are doxycycline and ciprofloxacin. The risk of relapse is higher with doxycycline (Meric et al., 2008).

Conclusion

Fluorodeoxyglucose avidity is common during active intrathoracic tularemia, which can persist beyond one year, raising suspicion of malignancy. Necrotizing epithelioid granulomas can be seen in patients with tularemia and may mimic tuberculosis and endemic fungal infections. Considering tularemia as a diagnostic possibility in the appropriate setting may assist in the accurate diagnosis and prevent more invasive lung interventions, such as lung resection.

References

Centers for Disease Control and Prevention (2009) Tularemia – Missouri, 2000–2007. *MMWR Morb. Mortal. Wkly. Rep*. **58(27)**, 744–748.

Dennis, D. T., Inglesby, T. V., Henderson, D. A., Bartlett, J. G., Ascher, M. S., Eitzen, E., Fine, A. D., Friedlander, A. M., Hauer, J., Layton, M., Lillibridge, S. R., McDade, J. E., Osterholm, M. T., O'Toole, T., Parker, G., Perl, T. M., Russell, P. K., Tonat, K.; Working Group on Civilian Biodefense (2001) Tularemia as a biological weapon: Medical and public health management. *JAMA* **285(21)**, 2763–2773.

Evans, M. E., Gregory, D. W., Schaffner, W., McGee, Z. A. (1985) Tularemia: A 30-year experience with 88 cases. *Medicine* **64(4)**, 251–269.

Fachinger, P., Tini, G. M., Grobholz, R., Gambazzi, F., Fankhauser, H., Irani, S. (2015) Pulmonary tularaemia: All that looks like cancer is not necessarily cancer – Case report of four consecutive cases. *BMC Pulm. Med*. **15**, 27.

Golovliov, I., Bäckman, S., Granberg, M., Salomonsson, E., Lundmark, E., Näslund, J., Busch, J. D., Birdsell, D., Sahl, J. W., Wagner, D. M., Johansson, A., Forsman, M., Thelaus, J. (2021) Long-term survival of virulent tularemia pathogens outside a host in conditions that mimic natural aquatic environments. *Appl. Environ. Microbiol*. **87(6)**, e02713–20.

Horzempa, J., O'Dee, D. M., Stolz, D. B., Franks, J. M., Clay, D., Nau, G. J. (2011) Invasion of erythrocytes by *Francisella tularensis*. *J. Infect. Dis*. **204(1)**, 51–59.

Kinkead, L. C., Allen, L.-A. H. (2016) Multifaceted effects of *Francisella tularensis* on human neutrophil function and lifespan. *Immunol. Rev*. **273(1)**, 266–281.

Kravdal, A., Stubhaug, Ø. O., Wågø, A. G., Steien Sætereng, M., Amundsen, D., Piekuviene, R., Kristiansen, A. (2020) Pulmonary tularaemia: A differential diagnosis to lung cancer. *ERJ Open Res*. **6(2)**, 00093-2019.

Martinet, P., Khatchatourian, L., Saidani, N., Fangous, M.-S., Goulon, D., Lesecq, L., Le Gall, F., Guerpillon, B., Corre, R., Bizien, N., Talarmin, J.-P. (2021) Hypermetabolic pulmonary lesions on FDG-PET/CT: Tularemia or neoplasia? *Infect. Dis. Now* **51(7)**, 607–613.

Matyas, B. T., Nieder, H. S., Telford, S. R. 3rd (2007) Pneumonic tularemia on Martha's Vineyard: Clinical, epidemiologic, and ecological characteristics. *Ann. N. Y. Acad. Sci*. **1105(1)**, 351–377.

Meric, M., Willke, A., Finke, E.-J., Grunow, R., Sayan, M., Erdogan, S., Gedikoglu, S. (2008) Evaluation of clinical, laboratory, and therapeutic features of 145 tularemia cases: The role of quinolones in oropharyngeal tularemia. *APMIS* **116(1)**, 66–73.

Miller, R. P., Bates, J. H. (1969) Pleuropulmonary tularemia. *Am. Rev. Respir. Dis*. **99(1)**, 31–41.

Pechous, R. D., McCarthy, T. R., Zahrt, T. C. (2009) Working toward the future: Insights into *Francisella tularensis* pathogenesis and vaccine development. *Microbiol. Mol. Biol. Rev*. **73(4)**, 684–711.

Rubin, S. (1978) Radiographic spectrum of pleuropulmonary tularemia. *AJR Am. J. Roentgenol*. **131(2)**, 277–281.

Sunderrajan, E. V., Hutton, J., Marienfeld, R. D. (1985) Adult respiratory distress syndrome secondary to tularemia pneumonia. *Arch. Intern. Med*. **145(8)**, 1435–1437.

Tärnvik, A., Berglund, L. (2003) Tularaemia. *Eur. Respir. J*. **21(2)**, 361–373.

Thomas, L. D., Schaffner, W. (2010) Tularemia pneumonia. *Infect. Dis. Clin. North Am*. **24(1)**, 43–55.

Väyrynen, S. A., Saarela, E., Henry, J., Lahti, S., Harju, T., Kauma, H. (2017) Pneumonic tularaemia: Experience of 58 cases from 2000 to 2012 in Northern Finland. *Infect. Dis. (Lond.)* **49(10)**, 758–764.