Netherlands
The Journal of Medicine

CASE REPORT

Severe non-type-1 *Legionella pneumophila* infection without pneumonia

A. de Weerd*, M. van Rijn, R. Baggen, A. Dees

Department of Internal Medicine, Ikazia Hospital, Rotterdam, the Netherlands, *corresponding author: tel. +31 (0)10-297 56 96, e-mail: a.deweerd@erasmusmc.nl

ABSTRACT

We present a patient with myalgia and ongoing fever without respiratory symptoms caused by a *Legionella pneumophilia* infection. We conclude that in patients with fever of unknown origin legionellosis should be considered, even in the absence of pulmonary symptoms. When considering legionellosis, diagnostic tests should include the urinary antigen test.

KEYWORDS

Extrapulmonary legionellosis, fever of unknown origin, *Legionella pneumophila* non-type-1, *Legionella* urinary antigen test

INTRODUCTION

Legionella is considered a relatively common cause of pneumonia. The clinical picture ranges from an influenza-like syndrome known as Pontiac fever, to a severe pneumonia requiring mechanical ventilation.[1] In legionnellosis, extrapulmonary manifestation in the absence of pneumonia is not common. To our knowledge, there are no reports in the literature of *Legionella* as the explanation for fever of unknown origin. We present a patient referred because of myalgia and ongoing fever without respiratory symptoms. Since the *Legionella* urinary antigen test can be falsely negative in 10% of infections, serotyping should be performed and repeated.

CASE REPORT

A 56-year old man was admitted for evaluation of fever, myalgia, fatigue and 10 kg weight loss in four weeks. Initially he had experienced headaches and transient coughing. Fever began ten days before admission. In the week preceding admission his general practitioner had prescribed amoxicillin/clavulanate and clarithromycin. His medical history was unremarkable. The patient had travelled as an IT professional to Egypt and Jordan 14 weeks before referral. On physical examination the only remarkable finding was a rectal temperature of 38.5° Celsius. Laboratory results showed an elevated erythrocyte sedimentation rate, mild leucocytosis, elevated C-reactive protein and abnormal liver function tests (*table 1*). Both chest X-ray and computed tomography (CT) scan were normal and did not reveal pulmonary infiltrates. Abdominal ultrasound and CT scan showed neither lymphomas nor a liver abscess. The differential diagnosis was infection, lymphoreticular disease and autoimmune disorders. Extensive diagnostic tests did not reveal a cause: tests were performed to detect viral hepatitis, cytomegalovirus, Epstein-Barr virus, respiratory syncytial virus, parainfluenza, human immunodeficiency virus, dengue, rickettsioses, *Mycoplasma pneumoniae*, *Chlamydia psittaci*, *Coxiella burnetii*, *Brucella*, malaria, lues, leishmaniasis, schistosomiasis and leptospirosis. Biopsy of the temporal artery showed no signs of vasculitis. Bone marrow aspiration revealed normal trilinear haematopoiesis, whereas cultures remained negative, as did staining and culture for mycobacteria. Serology for *Legionella*, a specimen taken one day after admission, revealed no positive ELISA titres. The urinary *Legionella* antigen test was not performed on admission. Despite empirical treatment with intravenous amoxicillin/clavulanate and nonsteroid-anti-inflammatory drugs, his fever and myalgia persisted. Two weeks after admission, seroconversion for *Legionella* IgM from 6 E/ml to 254 E/ml was demonstrated. Serotyping revealed *L. pneumophila* non-type-1 infection (possibly type 5 with an elevated titre of 1:256, *table 2*). Intravenous ciprofloxacin and rifampicin were administered (400 mg and 600 mg twice

Table 1. *Laboratory values*

	Unit	Admission	Reference range
Erythrocyte sedimentation rate	mm/u	99	0-15
Haemoglobin	mmol/l	8.9	8.5-11.0
Leucocytes	10.9/l	12.3	4.3-10.0
Thrombocytes	10.9/l	676	150-400
Bilirubin, total	µmol/l	20	0-17
Aspartate	U/l	118	0-37
Alanine	U/l	187	0-41
Lactate dehydrogenase	U/l	423	0-450
Alkaline phosphatase	U/l	731	25-120
Gamma-glutamyltransferase	U/l	244	0-50
Creatine kinase	U/l	<20	0-200
C-reactive protein	mg/l	152	0-10

Table 2. *Legionella pneumophila subroup titres*

	Serum titre
L. pneumophila 1	Negative
L. pneumophila 2	1:128
L. pneumophila 3	1:64
L. pneumophila 4	1:64
L. pneumophila 5	1:256
L. pneumophila 6	1:64
L. pneumophila polyvalent	Negative

daily respectively). The patient recovered well. On inquiry, he had installed a steam shower at home eight weeks before admission. Afterwards the cultures from this shower for *Legionella* spp. remained negative.

DISCUSSION

In adults with legionellosis, systemic manifestations besides pneumonia are often reported. The absence of pulmonary symptoms though is rare. Therefore in our patient, an important clue to the clinical diagnosis was missing: his chest X-ray was normal. In a prospective study, Tan *et al*. describe chest X-ray findings in 43 patients with a diagnosis of community-acquired pneumonia due to legionellosis.[2] In 40 of the 43 patients, admission radiographs were compatible with pneumonia, and in three patients admission radiographs were normal. Atypical presentation of legionellosis is described in a Japanese study from 2002.[3] Clinical features and CT-scan findings are described in an outbreak of *Legionella* pneumonia in eight patients. All patients were febrile; however respiratory symptoms were observed in only four. Chest CT scan, though, showed abnormalities in all eight patients (ground glass opacity, consolidation, pleural effusion). Although rare, extrapulmonary symptoms may be the presenting features of legionellosis: endocarditis, arthritis and liver function disturbances have all been described in the absence of pneumonia.[4,5] Lowry *et al*. reported 22 patients with extrapulmonary legionellosis, five (23%) of whom died.[6] Transient nonproductive coughing was one of patient's initial complaints (the other was headache). Protracted upper respiratory tract infection can be the explanation of his symptoms. Lieberman *et al*. found the same pathogens in upper and lower respiratory tract infection (RTI).[7] This serological study challenges the distinction between upper and lower RTI. Patients with upper RTI are usually not admitted and general practitioners do not perform serology for self-limiting diseases such as upper RTI: the true prevalence of *L. pneumophila* upper RTI is not known. The patient did not recover until combination therapy for *Legionella* was prescribed. Dutch Working Party on Antibiotic Policy (SWAB) guidelines advise treatment with macrolides or fluorochinolones for proven *Legionella* infection.[8] The general practitioner had already prescribed clarithromycin. After seroconversion the patient was treated with ciprofloxacillin, but fever did not resolve completely. De Vries *et al*. suggest combination therapy, for example rifampicin, in case of failing monotherapy.[9] We added rifampicin, which has a good sensitivity for *Legionella*. Both the patient's travelling and his installing a steam shower are well-known causes of legionellosis. Since the incubation period of *Legionella* is usually less than three weeks, his visit to the subtropics 14 weeks before admission seems a less likely cause given the time frame. *Legionella* is an intracellular Gram-negative bacterium, of which *Legionella (L.) pneumophila* type 1 is responsible for approximately 90% of *Legionella* infections in the Netherlands.[10] The urinary antigen test only detects type 1. Therefore, when legionellosis is suspected, serology should be performed and repeated in case of a negative urinary antigen test. We found no evidence in literature for a predilection for extrapulmonary sites for non-type 1 infections.

CONCLUSION

Legionella pneumophila type 1 is responsible for the majority of cases of legionellosis in the Netherlands. Pulmonary symptoms are key findings in this diagnosis. We report a case of severe non-type-1 *Legionella pneumophila* infection manifesting itself as ongoing fever, but without pneumonia. We conclude that in patients with fever of unknown origin legionellosis should be considered, even without pulmonary symptoms. Furthermore, when considering legionellosis, diagnostic tests should include the urinary antigen test. In approximately 10% of legionellosis though, this test is false-negative, due to one of the more seldom reported non-type-1 subgroups. Serology should be performed and repeated.

REFERENCES

1. Van Riemsdijk-Van Overbeeke IC, van den Berg B. Severe Legionnaire's disease requiring intensive care treatment. Neth J Med. 1996;49(5);196-201.
2. Tan MJ, Tan JS, Hamor RH, File TM Jr, Breiman RF. The radiologic manifestations of Legionnaire's disease. The Ohio community-based pneumonia incidence study group. Chest. 2000;117(2):398-403.
3. Yaghu H, Nakamura H, Tsuchida F, et al. Chest CT findings and clinical features in mild Legionella pneumonia. Intern Med. 2003;42(6):477-482.
4. Bemer P, Leautez S, Nini E, Jarraud S, Raffi F, Drugeon H. Legionella pneumophilia arthritis : use of medium specific for Mycobacteria for isolation of L. pneumophilia in culture of articular fluisd specimens. Clin Infect Dis. 2002;35(1): E6-7.
5. Nelson DP, Rensimer ER, Raffin TA. Legionella pneumophilia pericarditis without pneumonia. Arch Intern Med. 1985;145(5):926.
6. Lowry PW, Tompkins LS. Nosocomial legionellosis: a review of pulmonary and extrapulmonary syndromes. Am J Infect Control. 1993;21(1):21-7.
7. Lieberman D, Lieberman D, Korsonsky I, et al. A comparative study of the etiology of adult upper and lower respiratory tract infections in the community. Diagn Microbiol Infect Dis. 2002;42(1):21-8.
8. Schouten JA, Prins JM, Bonten M, et al. Optimaliseren van het antibioticabeleid in Nederland. VIII. Herziene SWAB-richtlijnen voor anti-microbiële therapie bij thuis opgelopen pneumonie. Ned Tijdschr Geneesk. 2005;149:2495-500.
9. Vries PAM de, Zijlstra JG, Manson WL, van der Werf TS. Antibioticakeuze bij een Legionella-infectie. Ned Tijdschr Geneeskd. 2005;149:452-7.
10. Bencini MA, Ijzerman EP, Bruin JP, den Boer JW. Drie patiënten met Legionella-pneumonie in verband gebracht met een sauna, een koeltoren en een caravan in Nederland. Ned Tijdschr Geneeskd. 2005;149(36):1973-7.