CASE REPORT

Rare presentation of an old bug

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SUMMARY

We highlight a rare presentation of *Legionella* infection in a 77-year-old woman with a clinical diagnosis of giant cell arteritis 2 months prior to presentation. She was started on 60 mg prednisone that was tapered to 10 mg after 4 weeks following her diagnosis. She presented with a 1-month progressive dyspnoea in the absence of any other symptoms. Her exposure history was significant only for a recent trip to Florida where she stayed at a hotel. Initial laboratory workup was significant for hyponatraemia (127 mmol/L). Workup including bronchoalveolar lavage (BAL) and induced sputum for gram stain, acid fast stain and bacterial culture were negative for *Pneumocystis jirovecii* pneumonia and other opportunistic infectious agents. However, BAL was positive for *Legionella pneumophila* via PCR that was confirmed by a positive urinary *Legionella* antigen. The patient received treatment with levofloxacin that led to full resolution of her symptoms.

BACKGROUND

Pulmonary infections with *Legionella pneumophila* typically present acutely in immunosuppressed patients. We find this case unique due to the subacute presentation and the long duration of symptoms in an immunosuppressed host, considering that immunosuppressed patients tend to deteriorate quickly. Moreover, the patient only presented with isolated dyspnoea in the absence of any of the other typical features of pneumonia and Legionnaires' disease. We speculate that this may be due to blunting of inflammatory response by prednisone. This case should alert physicians to the fact that community-acquired pneumonia, and Legionnaires' disease in particular, may have atypical presentations in immunosuppressed patients. Therefore, Legionnaires' disease should be considered in the differential diagnosis in patients presenting purely with shortness of breath even with a long duration of symptoms and in the absence of the classic features of pneumonia.

CASE PRESENTATION

A 77-year-old woman with medical history significant for hypertension, non-insulin-dependent diabetes and Graves' disease presented with a 1-month history of progressively worsening dyspnoea. Two months prior to presentation, she suffered from monocular left lower hemianopia. Further workup revealed elevated erythrocyte sedimentation rate of 64 mm/hour. As a result, she was diagnosed clinically with giant cell arteritis (GCA). She was started on clopidogrel and prednisone

60 mg daily, with the dose tapered to 10 mg daily over the course of 4 weeks. Due to a documented sulfa allergy, the patient was never started on *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis.

On presentation, in addition to her month-long progressively worsening dyspnoea, she reported being unable to walk more than 10 steps without resting. The patient denied fevers, chills, cough, sputum production or chest pain. She denied lower limb pain, swelling or redness. She also denied having any diarrhoea, headache, myalgias, arthralgias and nausea or vomiting. Exposure history was significant for recent trip to Florida where she stayed at a hotel.

On admission, the patient was afebrile and in mild respiratory distress with respiratory rate of 30 rpm. Her resting heart rate of 93 bpm increased to 124 bpm on minimal exertion. She was hypoxic on room air (SpO₂ of 83%) and required 3 L of oxygen via nasal cannula. Auscultation of the lungs revealed good air entry bilaterally with no crackles. No jugular venous distension and no lower limb swelling were appreciated.

INVESTIGATIONS

Laboratory tests revealed white cell count of $8.7 \times 10^9/L$, with neutrophil predominance, haemoglobin concentration of 12.6 g/dL, sodium of 127 mmol/L, alkaline phosphatase of 66 U/L and aspartate aminotransferase of 22 U/L.

Chest X-ray on admission showed scattered infiltrates bilaterally (figure 1). CT angiogram of the chest excluded pulmonary embolism but revealed patchy bilateral ground glass opacities most prominent in the upper lobes (figure 2). Viral studies were negative for influenza A and B, respiratory syncytial virus and adenovirus by PCR. Viral cultures were negative as well. Possibility of atypical infection in an immunosuppressed patient was raised and levofloxacin at 750 mg was started empirically. Induced sputum was negative for PJP with negative gram stain, acid fast stains and bacterial culture.

Figure 1 Admission chest X-ray showing diffuse infiltrates.

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Figure 2 CT angiogram of the chest showing diffuse ground glass opacities and mosaicism.

Flexible bronchoscopy with bronchoalveolar lavage (BAL) was performed and showed normal appearing mucosa with minimal thin mucoid secretions throughout the bronchial tree. BAL was negative for PJP but positive for *L. pneumophila* via PCR. *Legionella* urinary antigen came back positive on the same day as the PCR from the BAL.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis considered in this case were:

1. opportunistic pulmonary infection
2. community-acquired pneumonia
3. pulmonary embolism
4. pulmonary complications of GCA, although rare.

TREATMENT

Given the possibility of atypical infection in this immunosuppressed host, she was started on levofloxacin 750 mg empirically. The treatment was continued after the diagnosis was confirmed. The patient had full resolution of symptoms with treatment.

OUTCOME AND FOLLOW-UP

Our patient had full resolution of symptoms following levofloxacin treatment and was discharged home on room air 3 days after admission. The positive urinary antigen and BAL PCR result for *L. pneumophila* and the response to levofloxacin treatment confirmed *Legionella* infection.

DISCUSSION

Legionnaires' disease was first described in 1976 following an outbreak of pneumonia among the participants of the American Legion Convention in Philadelphia.¹ The family Legionellaceae is made up of more than 50 species^{2,3} and includes more than 70 serogroups.⁴ *L. pneumophila* is the most common species accounting for at least 80% of human infections. Serogroups 1, 4 and 6 are the serogroups that most commonly cause infection in humans.⁵ Legionnaires' disease is responsible for 2%–9% of cases of community-acquired pneumonia.^{6–10}

Legionella is capable of causing two distinct syndromes: Legionnaires' disease being the most common and presenting as pneumonia; and Pontiac fever, a milder form presenting with influenza-like symptoms of fever, headache and muscle aches without pneumonia. Classically, patients with Legionnaires' disease present with high fever, chills, dry cough, pleuritic

chest pain, lung consolidation and diarrhoea.¹¹ Other symptoms include muscle aches, headache, tiredness, anorexia and vomiting.¹² On physical examination, relative bradycardia has been associated with *Legionella* infection.¹³

Legionella spp are aerobic, Gram-negative bacilli that require a special culture media—buffered charcoal yeast extract—to grow.¹⁴ Classically, no person-to-person transmission occurs with *Legionella*; however, a single possible episode has been reported.¹⁵ It is transmitted by the aspiration of contaminated water; once in the respiratory tract, the bacteria attach to the respiratory epithelial cells and macrophages through flagella and pili.¹⁶ Previous studies have shown that phagocytosis of *Legionella* is mediated by human monocyte complement receptors, namely CR1 and CR3.¹⁷ However, a newer study showed that *L. pneumophila* entry to cells is not or only marginally mediated by complement receptors.¹⁸ On the other hand, macrophage infectivity potentiator protein (MIPP) on the surface of *L. pneumophila* plays an important role in pathogenesis.¹⁹ The MIPP gene is necessary for optimal multiplication of the bacteria within human alveolar macrophages.²⁰

Following phagocytosis, *L. pneumophila* has the ability to inhibit phagolysosome fusion via the defective organelle trafficking and intracellular multiplication genes. It is also capable of producing exotoxins including haemolysin, cytotoxin, deoxyribonuclease and ribonuclease.²¹

Laboratory abnormalities are common but non-specific including renal and hepatic dysfunction, leucocytosis and thrombocytopenia. However, hyponatraemia (serum Na<130 mEq/L) are significantly more associated with Legionnaires' disease than pneumonia due to other organisms.²² Other non-specific laboratory abnormalities include hypophosphataemia and haematuria.²²

On chest roentgenograms, pneumonia caused by *Legionella* show rapidly developing peripheral consolidation, often bilateral, which resolves slowly. Pleural effusions and empyema are common. Additionally, the most common chest CT scan findings are multilobar or multisegmental consolidation and ground glass opacities.²³

Infection with *L. pneumophila* can be confirmed using a variety of tests. Urine *Legionella* antigen testing is a rapid test capable of detecting serogroup 1 only, with specificity of 99.1% and sensitivity of 74%.²⁴ Infection can also be confirmed using sputum culture, with sensitivities ranging from 10% to 80%.¹² Serologic diagnosis of *Legionella* is a valuable epidemiologic tool but has little impact on clinical decision-making due to delay before final results are available.¹² PCR is a valuable tool that can aid in diagnosing *Legionella* infections. The 16S rRNA-based PCR has sensitivity and specificity of 86% and 95%, respectively. The *mip* gene-based PCR has sensitivity and specificity of 92% and 98%, respectively.²⁵

In immunocompromised hosts, pulmonary bacterial infections often involve the same pathogens seen in immunocompetent hosts with community-acquired pneumonias.²⁶ Patients who are taking corticosteroids are at an increased risk to develop pulmonary infections²⁷ and to have an impaired host response to infections, especially to pathogens that are known to cause community-acquired pneumonia.^{28,29} Furthermore, with the advent and increase use of biological agents for inflammatory diseases, there has been an increase in intracellular infections such as *Legionella*,³⁰ and increase in the risk of hospitalisation due to pneumonia in patients using prednisone for rheumatoid arthritis.³¹

L. pneumophila has a wide spectrum of clinical presentations in immunocompromised patients. One study performed at the

University of Texas MD Anderson Cancer Center analysed the clinical features of 33 consecutive *Legionella* cases. All except one patient—who was found to be an asymptomatic carrier—had clinical signs and symptoms and radiographic imaging consistent with pneumonia.³² Asymptomatic *L. pneumophila* infection is very rare. One study reported that only 4 out of 5502 (0.073%) patients with culture positive for *L. pneumophila* were asymptomatic.³³ In immunocompromised patients, *L. pneumophila* tends to progress to abscess formation which is not common otherwise. One study analysed 62 of the 79 case reports on *Legionella* abscess found in the literature at the time of the study. It demonstrated that corticosteroids were administered in 69.4% of patients who developed lung abscess in the setting of *L. pneumophila* infection.³⁴ We could not find any studies that reported dyspnoea only as a presentation for *Legionella* pneumonia.

Learning points

- *Legionella pneumophila* should be considered in patients presenting with isolated dyspnoea even if duration of symptoms is long.
- Immunocompromised patients with Legionnaires' disease may not present with the classic signs and symptoms of the disease.
- Confirmation of pulmonary infections in immunosuppressed hosts may be delayed as immunosuppressive drugs alter the usual signs and symptoms of infection.
- Recent travel and exposure history are important clues to reach the appropriate diagnosis in patients with respiratory symptoms.

Contributors HAHA, AGM and KGL participated in planning the report of this case, data collection and manuscript preparation. AGM was involved in obtaining patient consent.

Competing interests None declared.

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REFERENCES

- 1 Fraser DW, Tsai TR, Orenstein W, *et al.* Legionnaires' disease: description of an epidemic of pneumonia. *N Engl J Med* 1977;297:1189–97.
- 2 Svarrer CW, Lück C, Elverdal PL, *et al.* Immunochromatographic kits Xpect Legionella and BinaxNOW Legionella for detection of Legionella pneumophila urinary antigen have low sensitivities for the diagnosis of Legionnaires' disease. *J Med Microbiol* 2012;61:213–7.
- 3 Svarrer CW, Uldum SA. The occurrence of Legionella species other than Legionella pneumophila in clinical and environmental samples in Denmark identified by mip gene sequencing and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. *Clin Microbiol Infect* 2012;18:1004–9.
- 4 Fields BS, Benson RF, Besser RE. Legionella and Legionnaires' disease: 25 years of investigation. *Clin Microbiol Rev* 2002;15:506–26.
- 5 Ricketts KD, Joseph CA. European Working Group for Legionella Infections. Legionnaires disease in Europe: 2005–2006. *Euro Surveill* 2007;12:E7–8.
- 6 Bartlett JG, Mundy LM. Community-acquired pneumonia. *N Engl J Med* 1995;333:1618–24.
- 7 Fang GD, Fine M, Orloff J, *et al.* New and emerging etiologies for community-acquired pneumonia with implications for therapy. A prospective multicenter study of 359 cases. *Medicine* 1990;69:307–16.
- 8 Marston BJ, Plouffe JF, File TM, *et al.* Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance study in Ohio. The community-based pneumonia incidence study group. *Arch Intern Med* 1997;157:1709–18.
- 9 Von Baum H, Ewig S, Marre R, *et al.* Community-acquired Legionella pneumonia: new insights from the German competence network for community acquired pneumonia. *Clin Infect Dis* 2008;46:1356–64.
- 10 Cunha BA, Burillo A, Bouza E. Legionnaires' disease. *Lancet* 2016;387:376–85.
- 11 Kirby BD, Snyder KM, Meyer RD, *et al.* Legionnaires' disease: report of sixty-five nosocomially acquired cases of review of the literature. *Medicine* 1980;59:188–205.
- 12 Murdoch DR. Diagnosis of legionella infection. *Clin Infect Dis* 2003;36:64–9.
- 13 Ostergaard L, Huniche B, Andersen PL. Relative bradycardia in infectious diseases. *J Infect* 1996;33:185–91.
- 14 Chatfield CH, Cianciotto NP. Culturing, media, and handling of legionella. *Methods Mol Biol* 2013;954:151–62.
- 15 Correia AM, Ferreira JS, Borges V, *et al.* Probable person-to-person transmission of Legionnaires' disease. *N Engl J Med* 2016;374:497–8.
- 16 Stone BJ, Abu Kwaik Y. Expression of multiple pili by Legionella pneumophila: identification and characterization of a type IV pilin gene and its role in adherence to mammalian and protozoan cells. *Infect Immun* 1998;66:1768–75.
- 17 Payne NR, Horwitz MA. Phagocytosis of Legionella pneumophila is mediated by human monocyte complement receptors. *J Exp Med* 1987;166:1377–89.
- 18 Weissgerber P, Faigle M, Northoff H, *et al.* Investigation of mechanisms involved in phagocytosis of Legionella pneumophila by human cells. *FEMS Microbiol Lett* 2003;219:173–9.
- 19 Cianciotto NP, Fields BS. Legionella pneumophila mip gene potentiates intracellular infection of protozoa and human macrophages. *Proc Natl Acad Sci U S A* 1992;89:5188–91.
- 20 Vijayan R, Subbarao N, Manoharan N. In silico analysis of conformational changes induced by normal and mutation of macrophage infectivity potentiator catalytic residues and its interactions with rapamycin. *Interdiscip Sci* 2015;7:326–33.
- 21 Friedman RL, Iglewski BH, Miller RD. Identification of a cytotoxin produced by Legionella pneumophila. *Infect Immun* 1980;29:271–4.
- 22 Yu VL, Kroboth FJ, Shonnard J, *et al.* Legionnaires' disease: new clinical perspective from a prospective pneumonia study. *Am J Med* 1982;73:357–61.
- 23 Kim KW, Goo JM, Lee HJ, *et al.* Chest computed tomographic findings and clinical features of legionella pneumonia. *J Comput Assist Tomogr* 2007;31:950–5.
- 24 Shimada T, Noguchi Y, Jackson JL, *et al.* Systematic review and metaanalysis: urinary antigen tests for Legionellosis. *Chest* 2009;136:1576–85.
- 25 Diederer BM, Kluytmans JA, Vandenbroucke-Grauls CM, *et al.* Utility of real-time PCR for diagnosis of Legionnaires' disease in routine clinical practice. *J Clin Microbiol* 2008;46:671–7.
- 26 Camps Serra M, Cervera C, Pumarola T, *et al.* Virological diagnosis in community-acquired pneumonia in immunocompromised patients. *Eur Respir J* 2008;31:618–24.
- 27 White DA. Drug-induced pulmonary infection. *Clin Chest Med* 2004;25:179–87.
- 28 Rimmelts HH, Meijvis SC, Biesma DH, *et al.* Dexamethasone downregulates the systemic cytokine response in patients with community-acquired pneumonia. *Clin Vaccine Immunol* 2012;19:1532–8.
- 29 Rimmelts HH, Meijvis SC, Kovaleva A, *et al.* Changes in serum cortisol levels during community-acquired pneumonia: the influence of dexamethasone. *Respir Med* 2012;106:905–8.
- 30 Bodro M, Carratalà J, Paterson DL. Legionellosis and biologic therapies. *Respir Med* 2014;108:1223–8.
- 31 Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006;54:628–34.
- 32 Han XY, Ihegword A, Evans SE, *et al.* Microbiological and clinical studies of Legionellosis in 33 patients with cancer. *J Clin Microbiol* 2015;53:2180–7.
- 33 Fukunaga H, Akagi K, Yabuuchi E. [Asymptomatic infection of Legionella pneumophila in four cases with pulmonary diseases]. *Nihon Saikingu Zasshi* 1990;45:833–40.
- 34 Yu H, Higa F, Koide M, *et al.* Lung abscess caused by Legionella species: implication of the immune status of hosts. *Intern Med* 2009;48:1997–2002.

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