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Clinical Presentation of *Legionella pneumophila* Serogroup 1-Associated Pneumonia and Diffuse Alveolar Hemorrhage: A Case Report and Literature Review

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 44-year-old
Final Diagnosis: *Legionella pneumophila* serogroup 1-associated pneumonia and diffuse alveolar hemorrhage
Symptoms: Dyspnea
Medication: —
Clinical Procedure: Bronchoalveolar lavage
Specialty: Infectious Diseases

Objective: Rare disease

Background: We report a case of diffuse alveolar hemorrhage (DAH) caused by *Legionella pneumophila* serogroup (SG) 1 and review the existing literature to identify risk factors and determine the prognosis of patients with *Legionella* pneumonia-associated DAH.

Case Report: A 44-year-old woman was admitted to our hospital following the presentation of dyspnea for a few days. Chest computed tomography (CT) findings revealed "crazy-paving" pattern in the right upper lobe implicating DAH and consolidation in the lower lobe. Analysis of the bronchoalveolar lavage (BAL) fluid revealed DAH, with further analyses identifying *L. pneumophila* SG 1 as the causative agent. The patient was successfully treated with levofloxacin and a red blood cell transfusion and discharged on the 32nd day of hospitalization. A literature review of 6 reported cases (including our case) of *Legionella* pneumonia-associated DAH revealed that the median age of patients with DAH was 59 years (range, 44-75 years), involving female patients in 4 cases (67%) and the use of immunosuppressive drugs in 2 cases (33%). Three cases were BAL *Legionella* polymerase chain reaction (PCR)-positive and 4 cases were diagnosed using a urinary *Legionella* antigen test (one case was simultaneously PCR-positive). These infections were caused by *L. pneumophila* SG 1 in three cases and SG 3 in one case. Mechanical ventilation was used in 5 cases (83%) and one patient had an unfavorable prognosis. Steroids for DAH were used in 5 cases (83%), and 2 cases responded to this treatment.

Conclusions: Our case highlights that clinicians should be aware of *Legionella* spp. as a cause of DAH in an immunocompetent host with "crazy-paving" pattern on chest CT, and perform a urinary antigen test and BAL PCR for diagnosis.

Keywords: *Legionella pneumophila* • Bronchoalveolar Lavage • Hemorrhage • Dyspnea • Serogroup • Pneumonia

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/936309

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Background

Legionella spp. are aerobic gram-negative rods that grow at temperatures of 25-43°C, with the highest growth observed at approximately 36°C. *Legionella* pneumonia occurs following the inhalation of aerosols or oral ingestion of contaminated water from a water supply source, hot water facilities, cooling towers, circulating bathtubs, and fountains, including both humidifiers and sprinklers, containing *Legionella* spp. [1]. It accounts for 2-9% of community-acquired pneumonia cases [2], and the risk groups for *Legionella* infections include immunocompromised patients such as transplant recipients, dialysis patients, elderly, those with chronic liver disease or obstructive pulmonary disease, those who consume alcohol, and smokers [3]. *Legionella pneumophila* is further classified into 15 serogroups (SGs), with SGs 1, 2, 3, and 5 being the most common in Japan [4] and serogroup 1 accounting for >80% of all *Legionella* pneumonia cases [5].

Diffuse alveolar hemorrhage (DAH) represents a syndrome that can complicate many clinical conditions and may be life-threatening, requiring prompt treatment. The typical presentations of DAH are anemia, hemoptysis, and pulmonary infiltrates on chest X-ray. A variety of diseases are associated with the development of DAH. Most cases of DAH are caused by the disruption of pulmonary capillarity and closely associated with systemic vasculitis and findings such as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, anti-glomerular basement membrane (GBM) disease, systemic lupus erythematosus (SLE), and connective tissue diseases [6]. DAH also co-occurs with several other conditions, including the use of certain drugs, infection, and transplantation. Here, we report our experience with a case of DAH caused by *L. pneumophila* SG 1 and describe the findings of our literature review examining the risk factors and prognoses of patients with *Legionella* pneumonia-associated DAH.

Case Report

A 44-year-old woman with a history of SLE and Sjögren's syndrome, who had been prescribed valganciclovir and methylprednisolone for retinitis and optic neuritis caused by Epstein–Barr virus for 3 months, presented with dyspnea, which had been occurring for a couple of days prior to admission. She prescribed regular drug and did not started new drug these days. The patient visited our outpatient clinic and denied the experience of any bloody sputum or orthopnea. She stated that she replaces the water in her bathtub once every 3 days and has been using a humidifier at her workplace. She also had an allergy to sulfamethoxazole/trimethoprim that was identified as a skin rash in a previous round of treatment. She had no history of smoking or alcohol consumption and was conscious with an oxygen saturation of 86% on room air upon admission. Her respiratory rate was 22 breaths/min, blood pressure was 124/54 mmHg, and pulse rate was 92 beats/min. Physical examination revealed respiratory effort while breathing and bilateral coarse crackles, but there was no swelling in the lower legs or jugular vein distention. Laboratory data revealed the following: white blood cell count, 13,400 cells/μL (neutrophils 97.5%); hemoglobin, 6.0 g/dL; platelet count, 15.1×10^3/μL; blood urea nitrogen, 85.8 mg/dL; creatinine, 2.09 mg/dL; lactate dehydrogenase, 1,164 U/L; aspartate aminotransferase, 40 U/L; alanine aminotransferase, 70 U/L; creatine kinase, 325 U/L; sodium, 144 mEq/L; C-reactive protein, 23.1 mg/dL; β-d-glucan, 47.0 pg/mL; C3 protein, 124 mg/dL; and C4 protein, 34 mg/dL. The anti-GBM antibody, PR3-ANCA, and MPO-ANCA evaluations were all negative. The anti-DNA antibody was <2 IU/mL, anti-IgG antibody was 745 mg/dL, and natriuretic test-pro-B-type natriuretic peptide was 2,056 pg/mL. Urine antigen tests for *Streptococcus pneumoniae* and *L. pneumophila* were both negative. Chest radiography revealed an infiltrative shadow in the right middle and lower lung fields (**Figure 1**) and chest computed tomography (CT) showed consolidation shadows with a crazy-paving pattern with right lung and lower lobe predominance (**Figure 2A-2D**). Echocardiogram indicated no valvular disease or myocardial dysfunction. Piperacillin/tazobactam and minocycline treatments were initiated. Because the patient had severe cellular immunodeficiency due to her steroid treatment and elevated lactate dehydrogenase, we administered clindamycin and primaquine in combination with prednisolone (80 mg/day) for treatment of possible pneumocystis pneumonia. We also performed a bronchoscopy on the first day of hospitalization, which revealed DAH (**Figure 3**). The cell

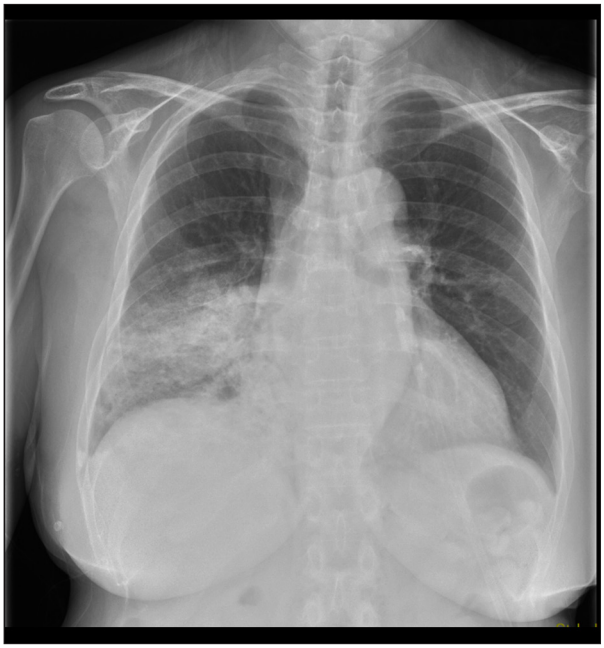

Figure 1. Chest radiograph at admission showed ill-defined, patchy consolidation and ground-glass opacity in the right lower lung zone.

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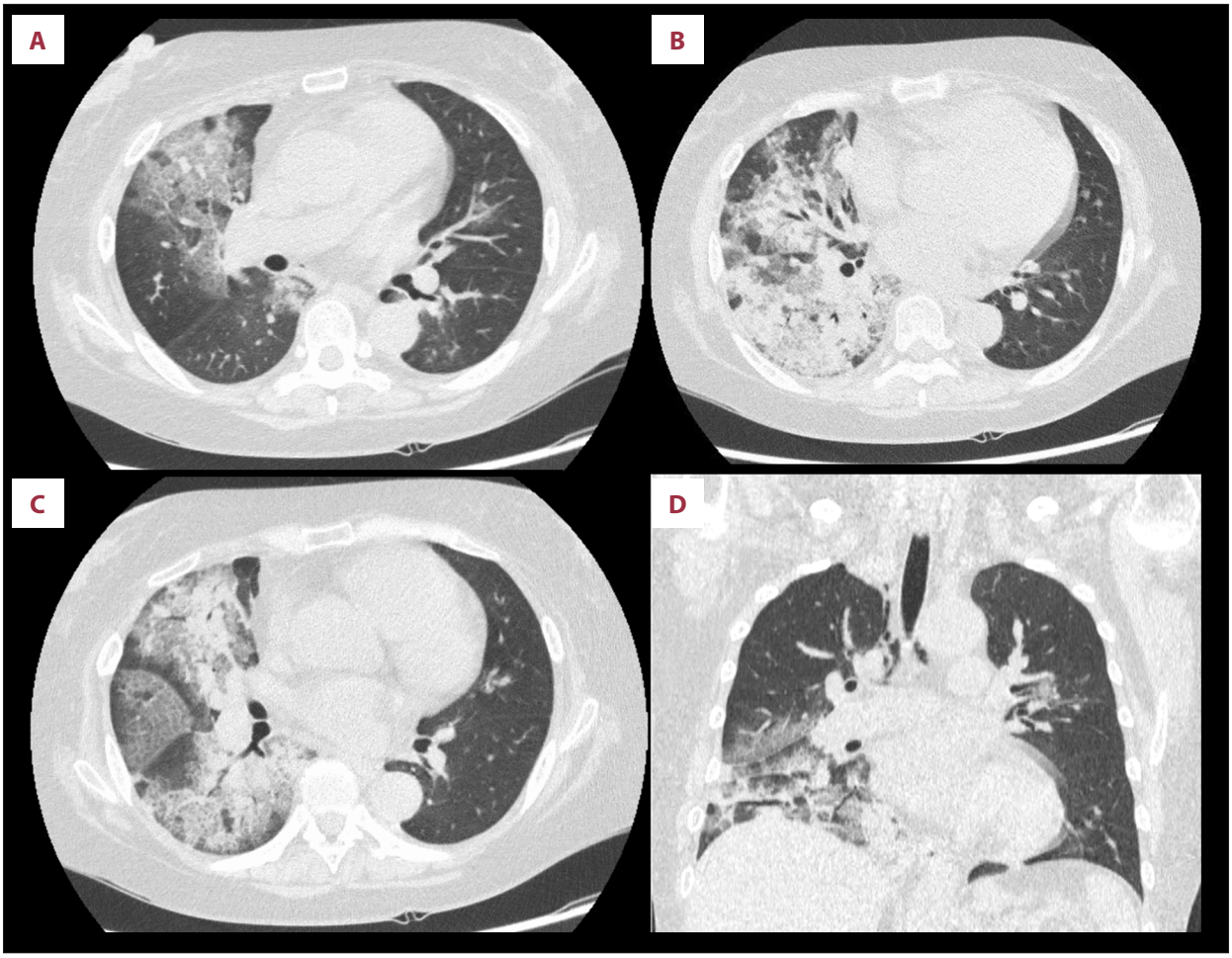

Figure 2. CT on admission. The axial plane of chest CT showed pulmonary consolidations with a confluent appearance and signs of air-bronchogram in the right middle (**B**) and inferior lobes (**C**). Consolidations associate with interspersed areas of ground-glass opacities with superimposed intralobular septal thickening, defining a "crazy-paving" pattern in the right upper (**A**) and middle robe (**B**) and sparing some secondary lobules. The coronal plane on chest CT showed the distribution of parenchymal findings (mostly right lung area in **D**) and pneumomediastinum (arrow, **D**).

count in the bronchoalveolar lavage (BAL) fluid was approximately 3,280/μL (96.5% neutrophils), and the red blood cell count was determined to be 3+. On the fourth day of admission, her oxygen demand increased and she required oxygen support; oxygen was supplied through a reservoir mask at a rate of 9 L/min. We escalated her regimen to intravenous meropenem and added voriconazole for the treatment of possible invasive aspergillosis. Cytomegalovirus polymerase chain reaction (PCR) test results for serum and BAL samples were negative. The serum and BAL *Aspergillus* galactomannan antigen were 0.1 and 0.1, respectively. Grocott's staining of the BAL fluid did not reveal *Pneumocystis jerovecii*. We then performed a Respiratory 2.1 plus Panel (BioFire Diagnostics, Salt Lake City, UT, USA) analysis, including severe acute respiratory syndrome coronavirus 2, influenza, and *Mycoplasma pneumoniae* targets; the test results for all targets were negative. Cytological analysis of the BAL fluid revealed only inflammatory cells. Therefore, clindamycin and primaquine were discontinued. Culture of the BAL fluid revealed only *Candida* sp.; therefore, the voriconazole treatment was stopped. Minocycline was replaced by levofloxacin after a positive BAL PCR test for *Legionella* sp. Finally, meropenem and levofloxacin were administered for 14 days. We confirmed the diagnosis of DAH caused by *L. pneumophila* through a partial 16S rRNA gene sequencing analysis of the BAL specimen, performed by experts at Toho University. The BAL specimen was then cultured on Wadowsky-Yee-Okuda-α-ketoglutarate agar (Eiken Chemical, Tokyo, Japan), a selective culture medium for *Legionella* isolation. Further analysis using matrix-assisted laser desorption/ionization-time of flight using the colony on the agar and *Legionella* species-specific monovalent antisera (Denka Seiken, Tokyo, Japan) confirmed the identity of the causative agent as *L. pneumophila* SG 1. The patient received a red blood cell transfusion on days 1 and 3 to treat the DAH-associated

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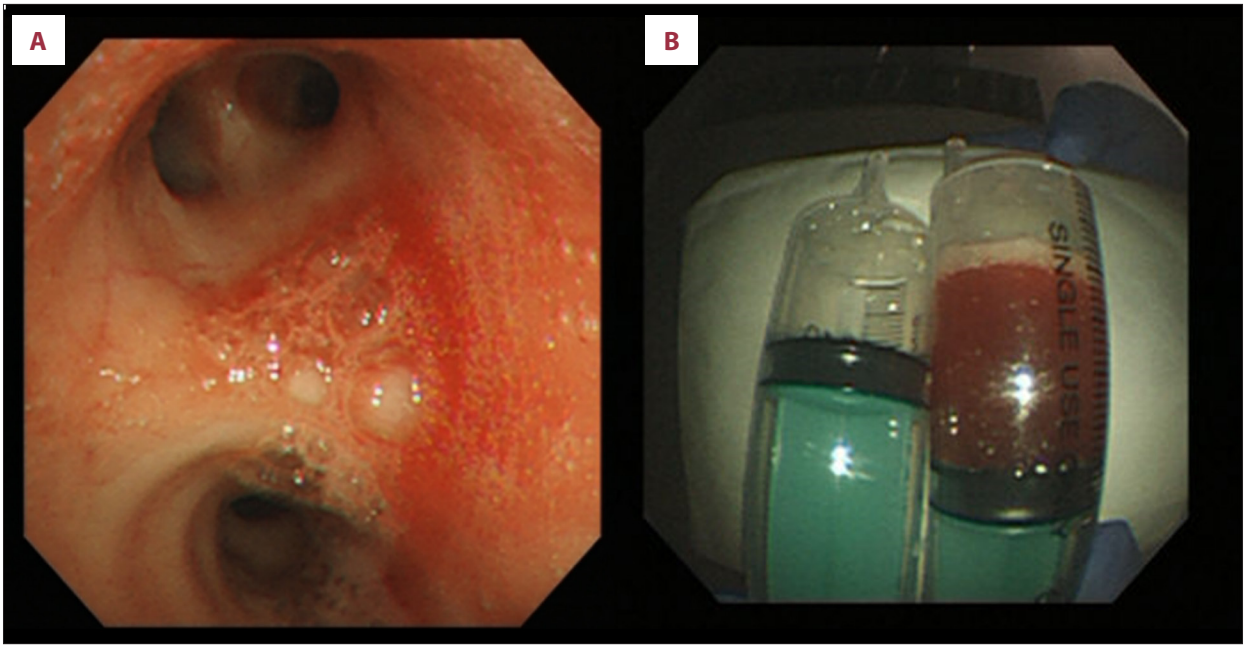

Figure 3. Image of bronchoscopy/syringe filled with bronchoalveolar fluid. (**A**) Bronchoscopy showing hemorrhagic fluid in the membrane of the bifurcation of the right upper lobe bronchi and truncus intermedius. (**B**) Bronchoalveolar lavage fluid presenting as "bloody."

anemia; thereafter, her hemoglobin did not decrease any further. The patient's symptoms improved clinically, and she was discharged on the 32nd day of hospitalization (**Figure 4**).

Discussion

We first identified our target papers with a literature search of the relevant databases including PubMed, Embase, and Ichushi (up to June 2021) (process described in **Supplementary Table 1**). We then reviewed the titles and abstracts of the database records and retrieved the full text for studies deemed appropriate for this evaluation before extracting the relevant case data. These evaluations returned 5 articles describing 5 cases of DAH due to *Legionella* [7-11]. The clinical characteristics of all 6 cases, including our case, are presented in **Supplementary Table 2**.

Evaluation of the case data revealed that the median age of patients with DAH was 59 years (range, 44-75 years) and was reported in 4 females (67%) and 2 males, with 3 from the United States, 2 from Europe, and one from Japan. The use of immunosuppressive drugs such as steroids and azathioprine was found in only 2 cases. Non-immunosuppressed patients also had DAH due to *Legionella*. In all cases, the patients were examined in an outpatient clinic within a few days of the onset of their respiratory symptoms. BAL was used in all cases to diagnose DAH, and *Legionella* as the cause was diagnosed based on a BAL *Legionella* PCR-positive result in 3 cases and using a urinary *Legionella* antigen test in 4 cases (one case was simultaneously PCR-positive). These infections were shown to be caused by *L. pneumophila* SG 1 in three cases and by *L. pneumophila* SG 3 in one case. Azithromycin was used in 3 cases (in one case it was replaced with minocycline due to the experience of side effects), levofloxacin in 2 cases (which was combined with azithromycin in one case), moxifloxacin in one case, and clarithromycin with rifampicin in one case. Mechanical ventilation was used in 5 cases (83%), and one patient had an unfavorable prognosis. Steroids for DAH were used in 5 cases (83%); among these, 2 cases responded to this treatment.

DAH is used to describe a condition in which the alveolar space is filled with blood, which is usually caused by hemorrhages within the pulmonary microcirculation resulting from collagen diseases such as SLE, ANCA-related vasculitis syndrome, Goodpasture syndrome, and conditions caused by certain drugs, infections, cardiac diseases, and allergies [12,13]. DAH is a life-threatening condition that requires prompt diagnosis and treatment as it progresses rapidly, presenting as dyspnea, bloody sputum, and cough [12]. The mortality rate is reportedly 25-50% [14]. For the evaluation of the causative agent of DAH in our patient, we first considered connective tissue diseases such as SLE, ANCA-associated vasculitis, and Goodpasture syndrome, and examined the echocardiogram for valvular disease or congestive heart failure. The patient tested negative for all these diseases/conditions, which left the possibility of DAH caused by infection. The most common DAH-causing infections are influenza A, dengue hemorrhagic fever, leptospirosis, malaria, and *Staphylococcus aureus* [15,16]. However, this patient was negative for all these pathogens when evaluated

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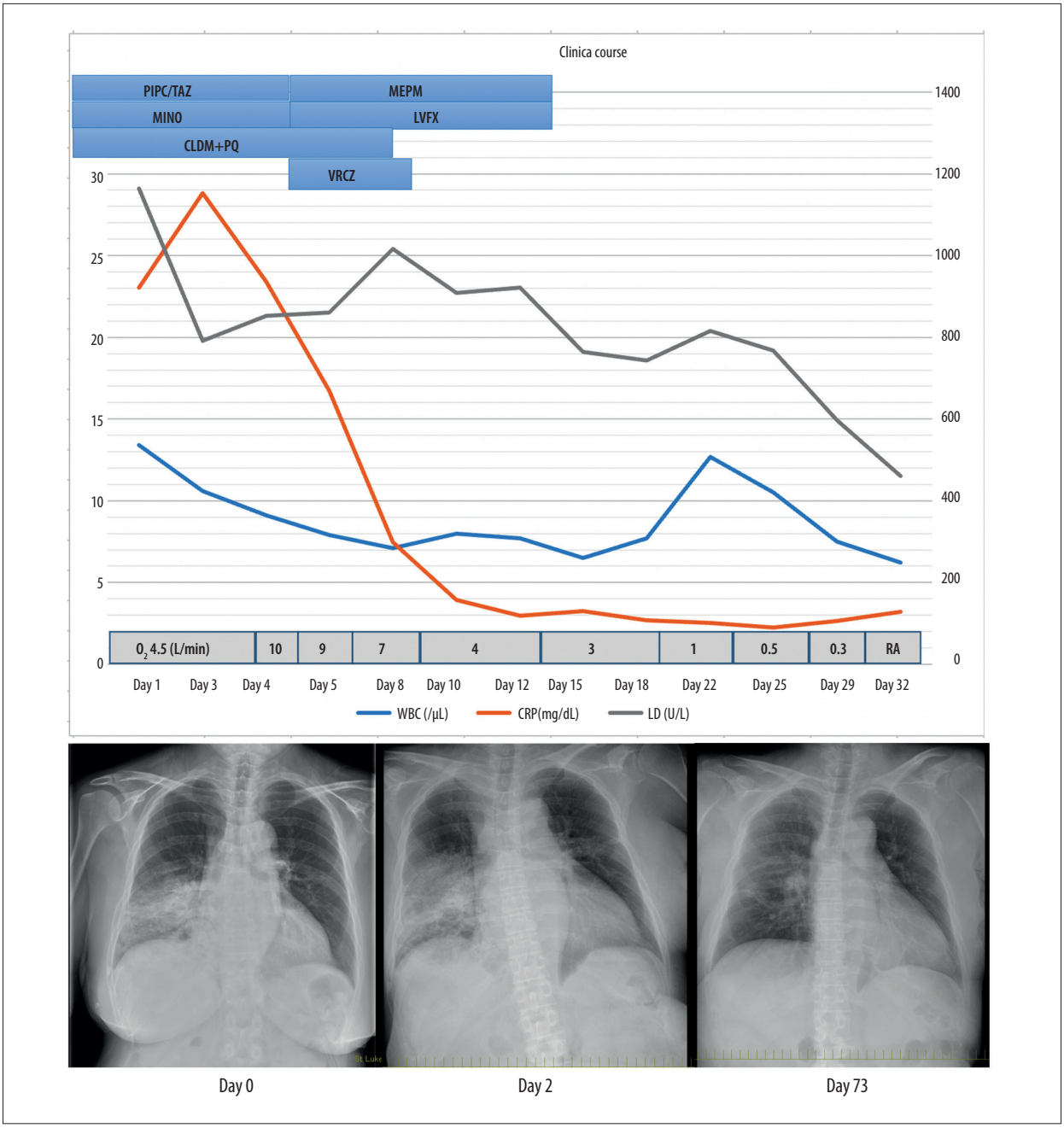

Figure 4. Clinical course during admission (above). Chest radiography revealed gradual improvement of consolidation in the right lung field over time (below). O2 unit: L/min. PIPC/TAZ – piperacillin/tazobactam; MEPM – meropenem; MINO – minocycline; LVFX – levofloxacin; CLDM – clindamycin; PQ – Plaquenil; VRCZ – voriconazole; WBC – white blood cell; CRP – C-reactive protein; LD – lactate dehydrogenase; RA – room air. Chest X-ray time course (below). The consolidation in the right lung gradually improved.

using both FilmArray and BAL culture. *Legionella*-mediated DAH was first reported in Italy in 2003 [10], and our literature review suggests that *L. pneumophila* SGs 1 and 3 have been the most common causative agents, with our patient being infected with an SG 1 strain via the aerosol exposure route. Our literature review revealed that only some patients who developed *Legionella*-mediated DAH were immunosuppressed due to treatment with azathioprine or steroids. This may be similar to the previously reported risk factors for Legionella pneumonia [3]. For our case, the *Legionella* urinary antigen test result was negative and the PCR result was positive. The sensitivity of the *Legionella* urinary antigen test is 71-84% [17]; however, the sensitivity varies

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based on the number of days since onset as follows: 88% for 1-3 days, 80% for 4-7 days, 89% for 8-14 days, and 100% after 14 days. PCR has been reported to be useful for the identification of *Legionella* in sputum, with a sensitivity of 96.8% and specificity of 99.4%, and in BAL samples, with a sensitivity of 97.7% and specificity of 98.6% [18]. Unfortunately, this means that neither test is optimal for the clinical diagnosis of *Legionella*-associated DAH, meaning that suspected cases should be evaluated using a combination of urinary antigen and PCR tests.

In general, CT finding of DAH is the "crazy-paving" pattern consisting of scattered or diffuse ground-glass attenuation with superimposed interlobular septal thickening and intralobular lines [21]. In contrast, CT findings of *Legionella* pneumoniae include bilateral and unilateral single and multifocal consolidation and ground opacity [22]. In our case, CT findings revealed a "crazy-paving" pattern in the right upper lobe implicating DAH. In contrast, the lower lobe showed consolidation. We can't distinguish pure *Legionella* pneumonia or pneumonia mixed with DAH in the lower lobe.

In total, 4 patients were treated with macrolides (replaced with tetracyclines during treatment due to side effects), and 2 with fluoroquinolones. Of these, 5 patients were intubated, and one patient, who had a particularly poor prognosis, was treated with moxifloxacin. A previous study showed that the efficacy of azithromycin and fluoroquinolone for the treatment of *Legionella* pneumonia is equivalent in terms of in-hospital mortality [19]. Further research to determine the optimal therapy for *Legionella* pneumonia-associated DAH is warranted.

In animal models, the administration of *L. pneumophila* tissue-destructive proteases has been shown to cause hemorrhagic pneumonia [20]. However, the cause of pneumonia-associated DAH remains unknown. Our literature review revealed that all 6 cases of DAH were treated with steroids and that only 2 cases seemed to respond to these treatments [7, 8]. However, the treatment of non-immune-mediated DAH focuses on the targeted management of the underlying disease, meaning that in some cases immunosuppressive treatment could be deleterious [13]. The use of immunosuppressive therapy in patients with infection-related DAH should be individualized and used primarily in patients receiving appropriate antibiotic intervention and experiencing a critical deterioration, as was the case with our patient. Further studies on the usefulness of steroids are warranted.

Despite these observations, there are some limitations to our study. DAH is generally diagnosed using BAL samples (50 mL×3 times), and the color of the BAL fluid becomes more intense between washes due to increased bleeding. In our case, BAL evaluation was performed only once due to concerns about the possibility of BAL worsening the respiratory condition of the patient. However, a chest CT revealed a pattern of DAH. The patient initially needed blood transfusions, but after treatment for *Legionella* pneumonia-associated DAH and pneumonia, the transfusion was no longer necessary. These data were combined and allowed for a clinical diagnosis of pneumonia-associated DAH due to *L. pneumophila* in this case.

Conclusions

Our case study suggests that immunosuppressed patients presenting with DAH, who are known to be exposed to contaminated aerosols, should be evaluated for infectious DAH from pathogens such as *Legionella.* This case and the literature review further highlight that these patients should be evaluated using both urinary antigen tests and *Legionella* PCR prior to a final diagnosis.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Supplementary Tables

Supplementary Table 1. Keywords to search the case report of diffuse alveolar hemorrhage resulting from *Legionella* spp. Infection.

PubMed database	("Legionella"[MeSH Terms] OR "Legionella pneumophila"[MeSH Terms] OR "legionella*" [Text Word]) AND ("Pulmonary Alveoli"[MeSH Terms] OR "alveolar"[Text Word] OR "bronchoalveolar"[Title/Abstract]) AND ("Hemorrhage"[MeSH Terms] OR "hemorrhage*" [Title/Abstract] OR "haemorrhage*"[Title/Abstract] OR "bleeding*"[Title/Abstract]);
Embase database	('legionella'/exp OR legionella OR legionnaire*) AND (('lung alveolus'/exp OR 'lung alveolus') OR ('lung alveolitis'/exp OR 'lung alveolitis') OR alveolar OR bronchoalveolar) AND (('bleeding'/exp OR 'bleeding') OR (hemorrhage* OR haemorrhage*)) AND [humans]/lim
Ichushi database	(((Legionella/TH OR Legionellosis (Japanese)/TH OR pneumonia-Legionella (Japanese)/TH OR "Legionella pneumophila"/TH OR Legionella infection (Japanese)/TH) OR (Legionella (Japanese)/AL or legionella/AL)) AND (alveolar (Japanese)/AL)) AND (hemorrhage (Japanese)/AL)

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Supplementary Table 2. Clinical characteristics of previously reported cases of diffuse alveolar hemorrhage resulting from *Legionella* spp. infection.

	Reference	Age	Sex	Publication year/ Country	Underlying condition	Aerosol exposure	Diagnosis for AH/pathogen
1	Chowdhur et al [7]	67	F	2020/ USA	Crohn's disease on azathioprine	N/A	BAL/BAL PCR, culture
2	Pataka et al [11]	75	M	2018/ Greece	HTN	N/A	BAL/urinary antigen
3	Kashif et al [8]	61	M	2017/ USA	HTN, DL, type 2 DM, obesity	N/A	BAL/urinary antigen
4	Sundar and Pearce [9]	57	F	2004/ USA	PCT, HCV, GERD, heavy smoking for 30 years	N/A	BAL/BAL PCR, culture, urinary antigen
5	Marruchella and Franco [10]	47	F	2003/ Italy	MS	N/A	BAL/urinary antigen
6	Present case	44	F	2021/ Japan	SLE, SS, EBV retinitis and optic nephritis, on steroid	Yes	BAL/BAL PCR, sputum culture

	Reference	Chief complaint	SG	ABX for Legionella	Steroid use	Mechanical intubation	Prognosis
1	Chowdhur et al [7]	Fever, appetite loss, fatigue, dizziness, cough	3	AZM, DOXY (AZM discontinued due to persistently prolonged QTc)	Yes	Yes	Cured
2	Pataka et al [11]	Fever, myalgia, dyspnea	1	MFLX	Yes/PR3-ANCA (+)	Yes	Unresponsive to the treatment
3	Kashif et al [8]	Progressive dyspnea, acute cough, production of yellowish sputum, fever	N/A	AZM+LVFX for 21 days	Yes	Yes	Cured
4	Sundar and Pearce [9]	Progressive dyspnea, fever, bloody sputum	N/A	AZM	Yes	Yes	Cured
5	Marruchella and Franco [10]	Fever, worsening dyspnea, pleuritic chest pain	1	CAM+RFP	N/A	Yes	Cured
6	Present case	Dyspnea	1	LVFX for 14 days	Yes	No	Cured

M – male; F – female; HTN – hypertension; type 2 DM – type 2 diabetes mellitus; SLE – systemic erythematous; SS – Sjögren's syndrome; PCR – polymerase chain reaction; BAL – bronchoalveolar lavage; LVFX – levofloxacin; DOXY – doxycycline; AZM – azithromycin; SG – serogroup; PCT – porphyria cutanea tarda; HCV – hepatitis C; N/A – not applicable; MS – mitral valve stenosis; CAZ – ceftazidime; HTN – hypertension; MFLX – moxifloxacin; AH – alveolar hemorrhage; DL – dyslipidemia; PR3-ANCA – proteinase 3-antineutrophil cytoplasmic antibody.

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