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LEGIONELLA PNEUMOPHILA PRESENTING AS A RARE CAUSE OF ACUTE THROMBOCYTOPENIA: A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT

Introduction: Legionella pneumophila can cause a wide spectrum of clinical manifestations, ranging from a mild flu-like illness to fulminant multi-organ involvement, characterised by severe pneumonia, diarrhoea, encephalopathy, shock, hepatic dysfunction and renal failure. Very rarely, it can be associated with haematologic conditions such as thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS) and immune thrombocytopenic purpura (ITP). We report a rare case of *L. pneumophila* causing ITP and review previously published cases of thrombocytopenia associated with Legionellosis in the literature.

Case description: A 53-year-old male presented with fevers, chills, a productive cough and severe haemoptysis. Blood work was remarkable for leukocytosis, severe thrombocytopenia and hyponatraemia. Computed tomography (CT) imaging showed left lower lobe lung consolidation, and a peripheral blood smear showed giant platelets consistent with ITP. Legionella urine antigen testing returned positive. He was treated with intravenous immunoglobin, steroid taper and a ten-day course of azithromycin, which led to normalisation of his platelet count and resolution of the pneumonia.

Discussion: L. pneumophila can lead to complement-mediated destruction of platelets resulting in ITP. Antibodies against *L. pneumophila* can also cross-react with the enzyme ADAMTS13, inhibiting its function and resulting in TTP and HUS. Additionally, *L. pneumophila* can infect vascular endothelial cells causing their death and stimulating release of von Willebrand factor (vWF) multimers into the bloodstream, promoting thrombosis and platelet consumption.

Conclusion: It is important for internists to consider *L. pneumophila* in the differential for any patient presenting with pneumonia and severe thrombocytopenia. Earlier detection and intervention can lead to prevention of critical bleeding and better outcomes.

KEYWORDS

Legionella pneumophila thrombocytopenia, immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome

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LEARNING POINTS

- *Legionella pneumophila* is rarely associated with different haematologic disorders resulting in severe bleeding diathesis as well as thrombosis.
- It is important for internists to consider *Legionella pneumophila* in the differential diagnosis for any patient presenting with pneumonia and severe thrombocytopenia.
- Earlier detection and intervention can lead to prevention of critical bleeding and better outcomes.

INTRODUCTION

Legionella pneumophila, a Gram-negative intracellular aerobic bacillus, can cause a wide spectrum of clinical manifestations, ranging from a mild flu-like illness (Pontiac fever) to fulminant multi-organ involvement (Legionnaires disease), characterised by severe pneumonia, diarrhoea, encephalopathy, shock, hepatic dysfunction and renal failure[1,2].

It was first described in 1977 and is known to cause both community-acquired and nosocomial infections[3]. It has been estimated that between 2 and 15% of community-acquired Legionella infections result in hospitalisation[4]. Immunosuppression and exposure to contaminated water storage and distribution systems are major risk factors for developing Legionellosis[3].

Very rarely, it has been associated with different haematologic conditions, resulting in thrombocytopenia and severe bleeding diathesis, including thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS) and immune thrombocytopenic purpura (ITP).

We report a rare case of *L. pneumophila* causing ITP, which resolved with treatment of the underlying infection and systemic steroids. We also review previously published cases of thrombocytopenia associated with *L. pneumophila* in the literature.

CASE DESCRIPTION

A 53-year-old male had a history of active tobacco and marijuana smoking as well as remote exposure to tuberculosis several decades ago, for which he completed six months of isoniazid. He presented to an outside hospital with three days of fevers, chills and productive cough associated with nausea and vomiting. His vitals revealed a temperature of 38°C, heart rate 107/min, blood pressure 121/82 mmHg, respiratory rate 24/min and oxygen saturation 96% on room air. A computed tomography (CT) angiogram showed no pulmonary embolism but demonstrated a left lower lobe consolidation consistent with pneumonia *(Fig. 1)*. A complete blood count showed a white blood cell count of 15,000/ µl, neutrophilia 88%, bandemia 6%, haemoglobin 13.7 g/dl and a platelet count of 21,000/µl. Chemistry showed hyponatraemia with serum sodium 129 mEq/l, blood urea nitrogen 14 mg/dl, serum creatinine 0.8 mg/dl and total bilirubin of 0.8 mg /dl. Liver function tests, lactate dehydrogenase (LDH) and haptoglobin were noted to be within normal limits. Virology work-up was negative for influenza A/B, respiratory syncytial virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) based on polymerase chain reaction testing. Blood, sputum and urine cultures were negative. Urine antigen testing detected *L. pneumophila* serotype 1 antigen; broad spectrum antibiotics were switched to azithromycin. The patient was discharged home to complete a course of oral azithromycin.

The following day, he presented again to the same outside hospital reporting six episodes of large-volume haemoptysis, which led to readmission. A repeat complete blood count showed a white blood cell count of 7,800/µl, haemoglobin 13 g/dl and a worsened platelet count of 9,000/µl. Due to severe thrombocytopenia in combination with life-threatening haemoptysis, he was transferred to our hospital for haematology consultation. A peripheral blood smear showed severe thrombocytopenia with giant platelets consistent with ITP *(Fig. 2)*. Human immunodeficiency virus (HIV) 1/2, hepatitis B and C serology were negative. Serum vitamin B12 and folate were within normal limits. He was started on intravenous immunoglobin 1 g/kg and prednisone 60 mg daily for symptomatic ITP. His platelet

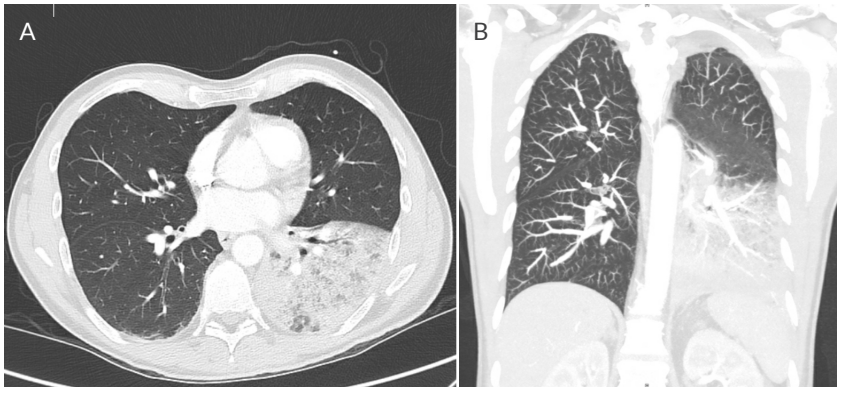

Figure 1. Computerised tomography (CT) scan of the chest obtained upon admission showing left lower lobe lung consolidation consistent with pneumonia in A) cross-sectional and B) coronal view.

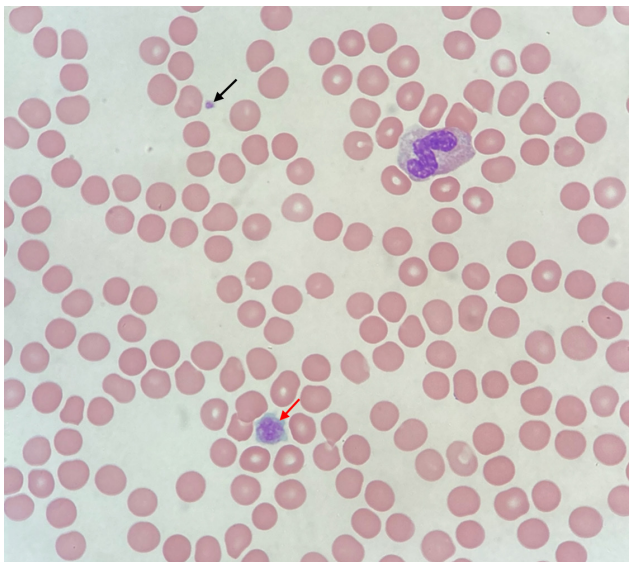

Figure 2. Peripheral blood smear obtained upon admission showing severe thrombocytopenia and giant platelet (red arrow) consistent with immune thrombocytopenic purpura (ITP). Normal platelet also seen for size comparison (black arrow).

count normalised to 204,000/µl on day four of therapy, with resolution of haemoptysis. After discharge, he completed a full ten-day course of azithromycin and continued to follow up with haematology for tapering of prednisone. He had a repeat CT chest four weeks after discharge, which showed resolution of left lobe pneumonia *(Fig. 3)*.

DISCUSSION

We performed a comprehensive literature search on PubMed with keywords '*Legionella pneumophila*' and 'thrombocytopenia'. We screened the results by reviewing the abstract and the full manuscript to identify relevant articles which met our criteria. We retrieved seven articles and extracted data on eight patients. We cross-checked the references of the selected articles to identify any additional articles which met our criteria. We have summarised the clinical details of all patients with *L. pneumophila* and thrombocytopenia, including our own patient, in *Table 1*.

Of all the patients included in our literature review, one other patient had ITP, two had TTP, one had HUS, three had thrombocytopenia with acute renal failure and one had thrombocytopenia of unclear aetiology. Six patients had identifiable risk factors for contracting *L. pneumophila*, which included significant smoking, solid organ transplant, exposure to contaminated water or travel to an area with known outbreaks of *L. pneumophila*. Diagnostic work-up for *L. pneumophila* included urine antigen testing and direct/indirect immunofluorescent assay for antibodies or culture. One patient had a negative urine antigen but a positive immunofluorescent assay for antibodies against *L. pneumophila*. This could be because the urine antigen test is specific for *L. pneumophila* serotype 1 only, while most outbreaks of Legionnaires disease in the community are attributed to other serotypes[5]. All patients received treatment with either fluoroquinolone or macrolide. Treatment for thrombocytopenia varied based on the associated haematologic disease; two patients had a negative outcome despite treatment.

ITP is characterised by immune-mediated destruction of platelets. It is a diagnosis of exclusion but certain infections, medications, pregnancy and immune disorders have been associated with this condition[1]. Among infections, HIV, cytomegalovirus, streptococcus, mycoplasma, brucella, varicella zoster virus and *Helicobacter pylori* are the usual triggers[1,5]. Corticosteroids and intravenous immunoglobin are the standard initial therapy for patients with ITP who experience severe bleeding. *L. pneumophila* can activate the complement cascade by binding to the C1q component independently[6]. Platelets express C1q receptor on their surface; interaction between immune complexes containing C1q and the receptor result in platelet activation, aggregation and consumption, leading to thrombocytopenia[6].

TTP and HUS are thought to be a continuum of the same disease process. It occurs due to a deficiency of the von Willebrand factor (vWF)-cleaving protease ADAMTS13, which leads to formation of large vWF multimers[5]. These multimers are not easily degraded: they bind to platelets and damage endothelial cells, forming extensive microthrombi throughout the circulation, resulting in consumption of platelets and destruction of red cells[5]. TTP can either be hereditary due to genetic mutations in the *ADAMTS13* gene or acquired in the setting of a trigger, which over-activates the immune system[5]. Riggs et al. demonstrated the presence of *L. pneumophila* in the lung tissue autopsy specimen of a patient diagnosed with TTP[7]. Chiaraviglio et al. showed that *L. pneumophila* can directly infect endothelial cells causing their death, and stimulate the release of vWF multimers

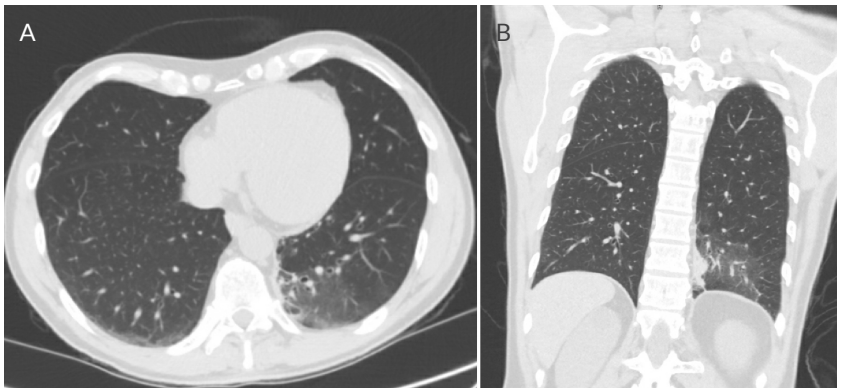

Figure 3. Repeat CT scan of the chest obtained four weeks after discharge showing improvement in left lower lobe lung consolidation in A) cross-sectional and B) coronal view.

Study	Age (years)	Gender	Comorbidities	Risk factor for *L. pneumophila*	Initial presentation	Haematologic diagnosis	Platelet count (×10⁹/l)	White count (×10⁹/l)	Haemoglobin (g/dl)	Serum creatinine (mg/dl)	Coagulation profile	Peripheral smear	Bone marrow examination	*L. pneumophila* testing	Treatment	Follow-up platelet count (×10⁹/l)	Outcome
Current study	53	M	-	Extensive smoking; works as a fuel attendant for refrigerated trailer trucks	Chills, productive cough, haemoptysis, nausea/vomiting	ITP	9	7.8	13.0	0.8	Normal	Giant platelets, severe thrombocytopenia	-	Positive *L. pneumophila* serotype 1 urine antigen	Azithromycin, IVIG, prednisone	204	PC normalised 4 days after treatment; patient discharged home with haematology follow-up
Javed et al., 2022[1]	61	F	Asthma	Underlying lung disease	Epistaxis, fever, non-productive cough, SOB, haematochezia	ITP	2	20.69	10.2	-	Normal except elevated fibrinogen >700 mg/dl, D-dimer 947 ng/mlL	Giant platelets, anisocytosis, microcytosis	-	Positive for *L. pneumophila* urine antigen	Levofloxacin, cefepime, IVIG, prednisone	293	PC normalised; patient discharged home one week later
Talebi et al., 2011[5]	65	M	HTN	Recent travel to the Bahamas	Epistaxis, fever, cough, headache, AMS	TTP	8	17.0	5.9	1.6	Normal	Multiple schistocytes, reticulocytes, severe thrombocytopenia	-	Positive IFA for *L. pneumophila* at 1:256 Negative for *L. pneumophila* urine antigen	Levofloxacin, methylprednisolone, plasma exchange	-	PC normalised; patient discharged home with haematology follow-up
Larsson et al., 1999[6]	73	M	Sinus thrombosis	-	Fever, cough, dyspnoea, renal insufficiency	Thrombocytopenia with acute renal failure	-	3.3	-	-	Elevated serum fibrinogen 730 mg/dl	-	-	Positive tracheal mucus culture Positive *L. pneumophila* urine antigen	Intubation, NO, CVVH, LMWH, antibiotics	-	Passed away one week later from respiratory failure
Larsson et al., 1999[6]	49	M	Arteriosclerosis	-	Pneumonia, septic shock	Thrombocytopenia with acute renal failure	-	22.0	-	-	Elevated serum fibrinogen 890 mg/dl	-	-	Positive IFA for *L. pneumophila* in tracheal mucus Positive tracheal mucus culture for *L. pneumophila* serogroup 8	Intubation, NO, CVVH, heparin, antibiotics	-	Patient survived and was transferred to a regular ward
Canaud et al., 1989[2]	35	M	HTN	Swimming pool maintenance worker	Headache, productive cough, asthenia, myalgia, oliguria	HUS with malignant HTN	40	9	7.6	5	FDP > 40 mg/l	Schistocytes	-	Positive IFA for *L. pneumophila* serotype 1–6 antibody at 1:512	Erythromycin, prostacyclin, epoprostenol	487	PC normalised six days after treatment
Barendregt et al., 1988[3]	53	F	Polycystic kidney disease, liver cysts, cadaveric renal transplant	Immunosuppression	Fever, pleuritic CP, bloody sputum	Thrombocytopenia with acute renal failure	5	-	-	8.5	Normal	-	-	Positive culture on a buffered charcoal yeast extract Positive indirect IFA for *L. pneumophila* serotype 4 antibody at 1: >2048	Erythromycin, rifampicin, prednisone, RATG, haemodialysis	-	-
Riggs et al., 1982[7]	45	M	-	Recent travel to Los Angeles; a cluster of other cases reported in the area	Fever, chills, productive cough, arthralgia, watery diarrhoea	TTP	25	8.6	7.6	2.1	Elevated PT 16s, FDP 80–160 mg/l	Schistocytes, few spherocytes, several nucleated RBCs	Erythroid hyperplasia with adequate megakaryocytes	Positive Dieterle stain for GNRs on transbronchial biopsy Positive indirect IFA for *L. pneumophila* antibody at 1:32	Erythromycin gluceptate, methylprednisolone sodium succinate, dipyridamole, cyproheptadine, haemodialysis, plasma exchange	55	Patient suffered a cardio-respiratory arrest on day 13 of hospitalisation despite haematologic improvement
Gasper et al., 1978[8]	22	M	Right calf DVT	-	Bronchospasm, epistaxis, diaphoresis malaise, pleuritic CP, slurred speech, unsteady gait	Thrombocytopenia	40	8.7	15.8	-	Normal except elevated FDP 40–80 mg/l	Toxic granulations, left shift, thrombocytopenia	Normal	Positive *L. pneumophila* antibody titre at 1:>1020	Erythromycin, flucloxacillin	180	PC normalised five days after treatment

Abbreviations: AMS, altered mental status; CP, chest pain; CVVH, continuous veno-venous haemofiltration; F, female; FDP, fibrin degradation products; GNRs, Gram negative rods; HTN, hypertension; HUS, haemolytic uraemic syndrome; IFA, immunofluorescent assay; ITP, immune thrombocytopenic purpura; IVIG, intravenous immunoglobulin; LMWH, low molecular weight heparin; M, male; NO, nitrous oxide; PKD, polycystic kidney disease; PT, prothrombin time; RATG, rabbit anti-thymocyte globulin; RBCs, red blood cells; SOB, shortness of breath; TTP, thrombotic thrombocytopenic purpura.

Table 1. Patient's hypercoagulable test results.

into the bloodstream[4]. It is hypothesised that antibodies against *L. pneumophila* cross-react and target *ADAMTS13*, inhibiting its function, resulting in an acquired form of TTP[5]. Regardless of the aetiology, TTP is treated with steroids and plasmapheresis, which removes auto-antibodies as well as large vWF multimers from the circulation.

CONCLUSION

L. pneumophila is a rare cause of acute thrombocytopenia. It has been associated with life-threatening haematologic diseases such as ITP, TTP and HUS, which can result in major bleeding as well as thrombosis. It is important for internists to consider *L. pneumophila* in the differential for any patient presenting with pneumonia and severe thrombocytopenia. History of significant smoking, immunosuppression, exposure to contaminated water or travel to an area with known outbreaks of *L. pneumophila* are major risk factors for developing Legionellosis. Earlier detection and intervention can lead to prevention of critical bleeding and better outcomes.

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