Upper Gastrointestinal Bleeding Following Legionnaires' Disease Case Report

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Abstract

Background:

Legionnaires' disease can involve multiple systems of the human body. However, in the majority of cases, it presents as a pneumonic illness responsible for 2–15% of community-acquired pneumonia cases that necessitate hospitalization. Herein described is a case of a 51-year-old male presenting with productive cough and headache who was later diagnosed with legionella pneumonia. He suffered from several episodes of gastrointestinal bleeding subsequently. To the best of our knowledge, prior to this case, only sixteen cases of gastrointestinal bleeding following Legionnaires' disease have been reported.

Methods:

Approval was obtained from the Institutional Review Board of Kern Medical. A retrospective review of the patient's record was performed. The literature search was conducted on PubMed and Google Scholar. These search terms were applied: Legionnaires' disease, Legionnaires' disease complication, gastrointestinal bleeding following Legionnaires' disease, legionella pneumonia.

Results:

GI bleeding is rare in LD and the relationship between this association is uncertain. *Legionella pneumophila* is equipped with Dot/Icm Type IV Secretion System (T4SS), which is a cable to deliver up to 300 effector proteins into the cytoplasm of the host cells. These proteins function as virulence factors. It is worth mentioning that *Helicobacter pylori* (*H. pylori*) a known GI pathogen is also armed with a T4SS like *Legionella pneumophila* called *H. pylori* Cag T4SS.

Conclusion:

Further studies are needed to prove the relationship, but clinicians should search for the presence of this pathogen in other organs to understand the pathophysiology of extrapulmonary diseases. We must learn to cast a finer net when fishing for the cause of the symptoms. The etiology may be passing right through our screening methods

Introduction

Legionnaires' disease (LD) is recognized as a multi-system illness that can negatively affect the pulmonary, renal, gastrointestinal tract, and central nervous system. LD can be severe, and early administration of appropriate antimicrobial therapy is associated with improved outcomes. Even though gastrointestinal (GI) symptoms following Legionella pneumonia are common, associated GI bleed is rarely reported. Only sixteen cases of GI bleeding related to Legionella pneumonia have been previously reported. [1–8]

Methods

Approval was obtained from the Institutional Review Board of Kern Medical. A retrospective review of the patient's record was performed. Literature search was conducted on PubMed and Google Scholar. These search terms were applied: Legionnaires' disease, Legionnaires' disease complication, gastrointestinal bleeding following Legionnaires' disease, legionella pneumonia.

Case Presentation

Herein presented is a 51-year-old Latinix homeless man with a past medical history of diastolic heart failure (HF) with preserved ejection fraction, uncontrolled hypertension, chronic kidney disease (CKD) stage IV, and polysubstance abuse who presented to the emergency room (ER) with one week-history of headache and productive cough associated with blood tinged, yellowish sputum.

Upon presentation, he was hypertensive with blood pressure (BP) of 212/130 mmHg due to medication non-adherence. Physical exam revealed diffuse expiratory wheezing in all lung fields bilaterally and bilateral +1 pitting lower extremity edema.

Laboratory studies were remarkable for leukocytosis, anemia, prolonged coagulation markers, and acute kidney injury. [Table 1] Chest x-ray on admission revealed right upper lung airspace consolidation. [Figure 1] The patient was initiated empirically on intravenous (IV) ceftriaxone and azithromycin for presumed community acquired pneumonia. Repeat Chest x-ray on hospital day three demonstrated an increase in the size of the infiltrate of the right upper lobe. [Figure 2] A follow-up chest computed tomography (CT) demonstrated a moderate to large-sized infiltrate in the right upper lobe with mild mediastinal lymphadenopathy. [Figure 3] Fluconazole and linezolid were then added for coverage of possible methicillin-resistant *Staphylococcus aureus* (MRSA) and coccidioidomycosis endemic to the area of his living. Blood and sputum cultures did not reveal any pathogens. Coccidioidomycosis serology, Quantiferon-TB gold and three sputum acid-fast bacillus (AFB) smears came back negative.

Table 1
Laboratory findings during the patient hospitalization.

		First Admission	Second Admission
Complete Metabolic Panel	Sodium (mmol/L)	138	142
	Potassium (mmol/L)	3.3	6.7
	BUN (mg/dL)	38	110
	Creatinine (mg/dL)	2.98	4.87
	eGFR (mL/min/ 1.73 m2)	27	15
Inflammatory Markers	C-Reactive Protein (mg/dL)	24.5	2.37
	ESR (mm/hr)	79	83
Urine Chemistry	Urine Albumin/Creatinine Ratio (mcg/mg Cr)	338.5	106.3
CBC/Differential	WBC (x10 ³ /mcL)	17.8	19.8
	Neutrophils (%)	90.8	84
	Hemoglobin (g/dL)	12.9	6.9
	Platelets (x10 ³ /mcL)	252	276
Coagulation Studies	PT (seconds)	17.6	19.1
	PTT (seconds)	41.3	36.7
Immunology/Serology	Coccidioidomycosis IgM	Non-Reactive	
	Coccidioidomycosis IgG	Non-Reactive	
	Coccidioidomycosis Comp Fixation	<1:2	
	TB Quantiferon Gold	Negative	
	Urine Legionella antigen	Detected	
	Stool Lactoferrin	Positive	
Microbiology	Bronchial wash culture	No growth	
	Blood culture	No growth	
	Sputum culture with Gram Stain	Moderate Usual throat flora	
	Urine Culture	No growth	

	First Admission	Second Admission
Stool Culture		No Salmonella, Shigella, or Campylobacter
BAL culture	No growth	
Bronchial wash KOH-Prep	No Fungus or Yeast observed	
BAL KOH-Prep	No Fungus or Yeast observed	
Sputum AFB culture	Negative	
Bronchial wash AFB culture	Negative	
BAL AFB culture	Negative	
Legionella DNA real time PCR	Detected	

As the patient's symptoms progressed, urine legionella antigen test was ordered. Additionally, he underwent bronchoscopy on hospital day five which revealed moderate bronchitis in addition to thick tenacious mucoid secretions in the anterior subsegment of the right upper lobe. Bronchoalveolar lavage (BAL) and bronchial wash did not grow any bacteria. AFB smears from BAL also came back negative. Legionella deoxyribonucleic acid (DNA), real time polymerase chain reaction (PCR) for the BAL was ordered. Cytology report showed respiratory epithelial cells and macrophages with scattered hemosiderin-laden macrophages. The patient's symptoms improved gradually during his hospital stay and he was discharged home on day seven.

The urine legionella antigen test came back positive after the patient's discharge and Legionella pneumophila was detected in his BAL by the PCR test one week later. Two days after the hospital discharge, the patient returned to the emergency room (ER) with complaints of few episodes of bright red blood per rectum with lightheadedness. On arrival, He appeared pale, and was found to be hypotensive. He was admitted to the intensive care unit (ICU) for concerns of hemorrhagic shock secondary to severe upper GI bleed. He was stabilized by transfusion of 4 units of packed red blood cells (PRBC) along with IV pantoprazole and octreotide drip.

During his second admission the previously ordered urine legionella antigen came back positive, in addition legionella pneumophila was positive in the BAL by PCR test performed a week post his initial discharge. As a result, IV azithromycin was added to his treatment regimen. Esophagogastroduodenoscopy (EGD) was performed emergently and revealed erosive gastritis of the antrum in addition to multiple ulcers in the duodenal bulb with one of them actively bleeding requiring placement of four endoclips. [Figure 4] Giemsa stain of the gastric antrum biopsy was negative for *Helicobacter pylori*. Given the acute nature of the patient's presentation biopsy of the duodenal ulcers was

not performed. The patient continued to have hematochezia that required another EGD demonstrating a new actively bleeding ulcer on the superior aspect of the duodenal bulb. The bleeding eventually needed fluoroscopic guided coil embolization of the gastroduodenal artery to control. [Figure 5] The patient was then discharged home on hospital day seven after the successful management of his GI bleed.

Discussion

Legionellosis is a bacterial disease caused by *Legionella pneumophila* and divided into two main clinical conditions LD and Pontiac fever. LD is a pneumonic illness and can cause multisystem infection whereas Pontiac fever is limited to a flu-like illness without pneumonia.^[9]

The first case of LD was reported in 1976 after an outbreak among attendees of the American Legion convention in Philadelphia. The suspected source of infection was the contaminated water in the air conditioning system of the hotel.^[9, 10] The most common risk factors for LD are smoking, chronic pulmonary diseases, immunosuppression, transplant recipients, AIDS, malignancy, diabetes, and CKD.^[9, 10] Our patient was a smoker and had CKD.

Legionella pneumophila is the most common causative agent of the legionellaceae family and causes 90% of legionella infections.^[9] There are more than 70 serogroups in the legionellaceae family. Most of the legionella infections are caused by serotypes 1-6 of *Legionella pneumophila*.^[11] The main natural source for *Legionella* is water, and the bacterium can be found in several aquatic environments like air conditioning and water systems of buildings, including hospitals.^[12]

There are several methods to diagnose LD, with urine antigen test being the most common. It is a rapid, highly specific (99-100%) test that can be used to detect the infection for days after initiation of the treatment due to the persistence of antigen excretion in urine for several days and sometimes up to ten months.^[9, 10, 13] However, it has some limitations. It can only detect serogroup 1 of *Legionella pneumophila* in addition to variation in sensitivity which ranges between 69-100% depending on disease severity.^[9, 13, 14] About 8% of patients do not excrete the urine antigen.^[13] Culture and isolation are considered the “gold standard” for diagnosis of LD along with buffered charcoal yeast extract (BCYE) agar being the most successfully used medium and sputum the most used specimen.^[10] Culture has a very high specificity of approximately 99%, and all legionella serotypes can be detected using this method.^[9, 13] A few disadvantages of this test include the highly variable sensitivity ranging from <10–80% and the significant number of patients who produce little or no sputum.^[10, 14] Serological studies have high specificity; however, seroconversion can take 4-12 weeks causing a delay in the diagnosis.^[9] Less than 50% of patients show seroconversion during the first two weeks after the onset of LD.^[11] Polymerase chain reaction (PCR) currently remains the most sensitive and rapid tool for diagnosis of this disease with a 30%-100% sensitivity and 95%-100% specificity.^[10, 13, 14] Its sensitivity approaches 100% and it has a similar characteristic of being able to detect all types and serogroups of legionella, but with lesser time than with culture.^[14]

Antibiotics are the mainstay of therapy with fluoroquinolones and macrolides being the most common. They have shown to be highly efficacious in successfully treating patients with legionella pneumonia.^[15] Other known effective antibiotics are rifampin and doxycycline.^[15] LD is a pneumonic disease with extrapulmonary manifestations involving the GI, renal, and central nervous systems.^[9] The most common systemic features are confusion, headache, watery diarrhea, relative bradycardia, and hyponatremia.^[11] In our case, the patient presented with productive cough and headache for one week without any associated GI symptoms in addition to normal sodium levels initially. GI manifestations are frequent in LD with common symptoms including watery diarrhea, vomiting and abdominal pain.^[11, 16] Paralytic ileus, intestinal perforation, and jaundice are considered unusual features.^[16]

GI bleeding is rare in LD and the relationship between this association is uncertain.^[7] In 1982, Dournon *et al*/reported a case of LD complicated by the inflammation of the terminal ileum and haemorrhagic peritonitis. *Legionella pneumophila* serogroup (sg) 1 was detected in the peritoneal exudate, the ileal wall, and the mucus of the small bowel.^[1] In the same year, Fogliani *et al*/described a case of inflammatory colitis with perforation of the cecum in context of LD. *L. pneumophila* sg 1 was demonstrated in the diseased colon.^[2] In 1986, Ozoux *et al*/mentioned a case of Legionella pneumonia associated with haemorrhagic necrotizing enteritis of the terminal ileum due to infection with *L. pneumophila* sg 4.^[3] In 1989, Schmidt *et al*/reported a case from Germany regarding legionella presenting as an acute attack of ulcerative colitis in a patient with long-standing history of ulcerative colitis. *L. pneumophila* sg 3 was detected in the submucosal edema of the affected colon in this case by direct immunofluorescence staining.^[4] In 1996, van Riemsdijk-van Overbeeke *et al*/mentioned four additional cases of upper GI bleeding. GI bleeding was considered as a complication of LD and the presumed etiology was stress-induced ulcers.^[5] In 2007, Kay *et al*/described a case of upper GI bleeding in the context of LD with multiple organ failure. No causal relationship was established in this case, however, the bleeding was found to be secondary to underlying peptic ulcer disease and GI malignancy.^[6] There were only six reported cases in Japan till 2011.^[7] In 2020, Mengiste *et al*/reported a case from the United States with GI bleeding associated with LD.^[8] Table 2 demonstrates a summary of the sixteen reported cases in the medical literature of Legionnaires' disease associated with GI bleeding.

Table 2
Literature review of cases of Legionnaires' disease associated with gastrointestinal bleeding

Age	Gender	Bleeding source	Outcome	Cause of death	Reported	Author
70	Male	terminal ileum, peritoneum	death	hemorrhagic shock	1982	Dournon ⁽¹⁾
Unknown	Unknown	cecum	Unknown		1982	Fogliani ⁽²⁾
Unknown	Unknown	terminal ileum	Unknown		1986	Ozoux ⁽³⁾
42	Female	colon	Unknown		1989	Schmidt ⁽⁴⁾
Mean 52 (4 cases)	Unknown	stomach and duodenum	discharged		1996	Overbeeke ⁽⁵⁾
61	Male	stomach, sigmoid colon	death	multiple organ failure	2000	Kasahara ⁽⁷⁾
73	Male	stomach	discharged		2006	Itabashi ⁽⁷⁾
62	Male	stomach, hepatic flexure mass	discharged		2007	Kay ⁽⁶⁾
63	Male	stomach	death	hemorrhagic shock	2007	Kuwabara ⁽⁷⁾
49	Male	duodenum	death	hemorrhagic shock	2007	Inoue ⁽⁷⁾
60	Male	stomach	death	multiple organ failure	2009	Endo ⁽⁷⁾
70	Female	stomach	discharged		2011	Sugimoto ⁽⁷⁾
55	Male	upper and lower GI	death	hypovolemic shock	2020	Mengiste ⁽⁸⁾
51	Male	stomach and duodenum	discharged		This case	Issa

Legionella pneumophila is equipped with Dot/Icm Type IV Secretion System (T4SS), that is cable to deliver up to 300 effector proteins into the cytoplasm of the host cells. These proteins function as virulence factors, highjack multiple cell mechanisms and allows the pathogen to survive and replicate within the cell. Functional redundancy, co-opting host vesicular trafficking, hijacking host lipids and transcriptome, and utilizing autophagy are examples of manipulations because of these substrates.^[17] It is worth mentioning that *Helicobacter pylori* (*H. pylori*) a known GI pathogen is also armed with a T4SS like *Legionella pneumophila* called *H. pylori* Cag T4SS. Both are very large in their class.^[18, 19, 20] As Schmidt *et al* demonstrated in 1989, legionella was identified within the gastrointestinal tissue.^[4] Even

though the direct relationship between presence of pathogen to GI bleed has not been established, further investigation is paramount.

Conclusion

LD is known to be a pneumonic illness but involves other systems such as gastrointestinal tract. There are several reported cases of gastrointestinal bleeding with associated mortality in patients infected with legionella. Further studies are needed to prove the relationship, but clinicians should search for presence of this pathogen in other organs to understand the pathophysiology of extrapulmonary diseases. We must learn to cast a finer net when fishing for the cause of the symptoms. The etiology may be passing right through our screening methods.

Declarations

Funding:

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Conflicts of interest/Competing interests:

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Ethics approval:

Ethical approval to report this case was obtained from the Kern Medical Institutional Review Board, ID#: 20018.

Consent to participate:

Informed consent from the patient was obtained.

Consent for publication:

Informed consent for patient information to be published in this article was obtained.

Availability of data and material:

Not applicable.

Code availability:

Not applicable.

Authors' contributions:

Not applicable.

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Figures

Figure 1

Chest X-ray showing right upper lung airspace consolidation.

Figure 2

Chest X-ray showing an increase in the size of the infiltrate of the right upper lobe

Figure 3

Chest CT showing a large-sized infiltrate in the right upper lobe.

Figure 4

EGD images showing actively bleeding ulcers in the duodenal bulb (A, B, C). Endoclips were placed on the main bleeding ulcer (D, E).

Figure 5

Fluoroscopic guided coil embolization of the gastroduodenal artery. Endoclips are also present.

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