

Legionella-Induced Autoimmune Hemolytic Anemia: A Delayed and Unexpected Complication

Richard Jesse Durrance^{a, c}, Fabiano Das Gracas^a, Shetra Sivamurthy^b,
Bhupinder B. Singh^a

Abstract

Legionella pneumophila is a multi-systemic disease primarily affecting the pulmonary, gastrointestinal, and to a lesser extent, renal systems. We present a case of *Legionella* pneumonia, which after resolution of respiratory compromise, was complicated by the development of autoimmune hemolytic anemia (AIHA) as determined by a positive Coombs test, and negative workup of other causes. Steroid immunosuppression was initiated, and red cell counts subsequently improved. While AIHA has only been anecdotally described in one prior case, the separation in time of the development and resolution of respiratory symptoms with the development of anemia most likely makes this an under-appreciated entity. An *in vitro* mechanism has been suggested; however *in vivo* causation has yet to be proven. Given the prolonged deleterious clinical consequences associated with the development of AIHA and the increase in recognition of *Legionella* outbreaks, greater recognition of this potential complication and research into the pathophysiology is warranted for the future.

Keywords: Legionella; Autoimmune Hemolytic anemia; Hemolytic anemia

Introduction

Legionella pneumophila became well-known after the American Legion outbreak in Philadelphia in 1976 [1, 2]. While pathology is multi-systemic, pulmonary, gastrointestinal, and to a lesser extent, renal symptoms tend to dominate the clinical course [1, 3]. Hemolytic anemia has only anecdotally been associated with Legionellosis. One such case of hemolysis associated with disease was reported in an epidemiologic review

of the initial Philadelphia outbreak [1]; however a Coombs test was never done. In addition, one specific case report from 1981 in which *legionella* was suspected to be the etiologic origin of autoimmune hemolytic anemia (AIHA) given a positive direct Coombs test [4]. While the very limited cases of association has been observed, the mechanism of the same has been proposed *in vitro* [5], but has yet to be elucidated *in vivo* [4]. We present a case of *Legionella* pneumonia with a clinical course marked by severe disease, which, despite overall clinical improvement, was complicated by the development of hemolytic anemia.

Case Report

A 66-year-old female presented with 4 days of progressively worsening generalized weakness, chills, and loss of appetite, complicated by confusion and lethargy in the 24 h prior to presentation. Past medical history was remarkable for bipolar disorder, hypertension, and diabetes.

On evaluation, patient was febrile and tachycardic. Labs were remarkable for bandemia (18%), lactic acidosis, acute kidney injury, and elevated creatine phosphokinase (CPK) (> 6,000 U/L). Physical exam, imaging and initial studies were suggestive of pneumonia, and treatment for sepsis syndrome of suspected pulmonary origin was initiated. Urine antigen testing was positive for *Legionella* spp., and treatment with quinolone therapy was continued. Hospital course was complicated initially by respiratory failure requiring intubation and mechanical ventilation, from which the patient ultimately recovered. While the clinical course of complicated *Legionella* pneumonia was typical of Legionnaires' disease [1, 3], the unexpected occurred when patient developed a persistent drop in her red blood cell (RBC) line, without clinical evidence of bleeding.

Due to religious reasons, the patient refused RBC transfusions (to which she had also never been previously exposed to), and an initial therapy trial with erythropoietin and intravenous iron was unsuccessful in reverting her persistent and worsening anemia. For this reason, workup for hemolysis was pursued, revealing a markedly elevated lactate dehydrogenase (LDH) level (1,439), elevated reticulocyte count (5.9%), unremarkable peripheral smear, and positive direct Coombs test (IgG positive, C3d negative). Family history was unremarkable. Lupus workup was negative. Given the evidence supportive of AIHA, therapy with prednisone 40 mg daily was initi-

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^aDepartment of Medicine, Jamaica Hospital Medical Center, D Building: Ground Floor, 8900 Van Wyck Expressway, Richmond Hill, NY 11418, USA

^bDepartment Hematology, Jamaica Hospital Medical Center, D Building: Ground Floor, 8900 Van Wyck Expressway, Richmond Hill, NY 11418, USA

^cCorresponding Author: Richard Jesse Durrance, Jamaica Hospital Medical Center, 8900 Van Wyck Expressway, Jamaica, NY 11418, USA.
Email: rdurranc@jhmc.org

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ated, and RBC count subsequently stabilized and improved. Without a source of bleeding, a clear explanation for the sudden onset of hemolytic anemia, or confounding medications or conditions, the patient's AIHA was presumed to be induced by her infection to *Legionella*.

Discussion

While *Legionella* is known to incur a multi-systemic effect over the host, autoimmune hemolysis has only been reliably described once. In the previously mentioned case in which AIHA was reliably associated with Legionellosis, Jk (Kidd antigen) antibodies were identified on the patient's erythrocytes [4]. While this mechanism is theoretically plausible, the absence of prior blood transfusions and childbirth more than 30 years ago in our patient makes it less likely. As infectious processes are known to induce the formation of IgG-mediated hemolysis, and accounts for the majority of AIHA [6], the exact mechanism or inciting antibody has not been identified. This case correlates with the slower extra-vascular IgG-mediated warm hemolysis mechanism [7, 8], and falls into this category by systematic investigation.

Given the historical under-diagnosis and increasing awareness of Legionnaire's disease [3], along with recent outbreaks [9], this complication of *Legionella* is most likely under-appreciated and associated with prolonged hospitalization and increased morbidity. Therefore further study is warranted to elucidate the underlying mechanism, prevent the potential deleterious clinical course, and recognized Legionellosis associated with development of AIHA.

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Conflict of Interest

The authors declare no conflicts of interest in the preparation

of this manuscript.

Informed Consent

Written informed consent was obtained from the patient for presentation and publication.

Author Contributions

All authors contributed significantly to the preparation and signed off on the final version of the manuscript.

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