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Chapter

Legionnaires Disease in Immunocompromised Host

Venkat Rajasurya and Salim Surani

Abstract

Legionella bacteria are aerobic, pleomorphic, gram negative bacilli found in fresh water environments and are usually transmitted through inhalation aerosols from contaminated water or soil. Legionnaire's disease is a severe form of pneumonia caused by legionella species and can be community acquired or hospital acquired. The reported incidence of Legionnaires' disease is approximately 1.4–1.8 cases per 100,000 persons and immunocompromised state is a very important risk factor. Some of the other important risk factors include old age, impaired cellular immunity, hematologic malignancies, solid organ transplantation, splenectomy, tumor necrosis factor-alpha inhibitors, chronic respiratory disease, diabetes and end stage renal disease. *Legionella pneumophila* serotype 1 is the most commonly reported cause of human Legionella infections. The pathogenesis of legionnaire's disease involves invasion of alveolar macrophages and cell mediated immunity is the primary means of immune control. The prevalence of Legionnaires disease has risen possibly from increased awareness and reporting. The symptoms of the disease are nonspecific requiring a high index of suspicion in vulnerable hosts, as effective treatment could be life-saving. Sensitivity of urinary antigen testing is lower in immunocompromised patients because of higher likelihood of infections caused non L. pneumophila species. Extrapulmonary manifestations and higher mortality are particularly more common in immunocompromised patients than in immunocompetent hosts.

Keywords: transplant, legionnaires' disease, immunocompromised patients, immunocompromised hosts

1. Introduction

Legionnaire's disease is a severe form of atypical pneumonia caused by gram-negative bacteria Legionella [1]. Although Legionnaire's disease is commonly reported in immunocompetent patients, immunocompromised state, particularly impaired cellular immunity is an independent risk factor for legionella infection. Diabetes, hematologic malignancies, chronic corticosteroid use, solid organ transplantation, TNF-alpha inhibitors are all risk factors for development of legionella infection [2]. *Legionella micdadei*, *Legionella longbeachae*, *Legionella bozemanae*, *Legionella dumoffii* and *Legionella feeleii* are some of the non-pneumophila species that predominantly cause infections in individuals with impaired immunity [3]. In immunosuppressed patients legionella can disseminate outside the lungs causing extrapulmonary manifestations like skin abscess, cellulitis, septic arthritis, myocarditis, endocarditis, peritonitis etc. [4]. Secondary to the increased incidence

Legionella testing should be routinely done in immunosuppressed patients presenting with symptoms suggestive of Community acquired pneumonia.

2. Anti-Legionella immunity

Legionella pneumophila is an intracellular pathogen that replicates within alveolar macrophages. There are more than 60 species of legionella and out of which, serogroup 1 causes majority of legionella disease. Humans become infected after inhaling contaminated aerosols. *L. pneumophila* then enters and replicates within the lung alveolar macrophages. Bacteria are initially engulfed by phagocytes from a vacuole that blocks phagolysosome fusion by delivering bacterial proteins into host cell cytosol [5]. These proteins subsequently modulate endoplasmic reticulum and prevent lysosomal mediated killing of the bacteria. Another defense mediator of the body involves toll like receptors (TLR) on host cells, which senses various signaling proteins produced by *L. pneumophila*. This is in turn induces transcription factor, nuclear factor kappa B and produces inflammatory cytokines that sets up a potent immune response against *L. pneumophila*. A common genetic variation of the stop codon in the ligand binding domain of TLR increases the risk of acquiring legionella infection [6].

Tumor necrosis factor alpha is vital in protecting the body from *L. pneumophila* infection and the incidence of Legionnaires disease is reported to be higher in patients receiving TNF-alpha antagonists when compared to controls [7]. Defective monocytic-macrophagic system seen in hematological conditions can lead to the development of Legionnaire's disease. T lymphocytes are essential for effective anti-legionella control but the exact role of B lymphocytes is unclear. Though some studies have highlighted the role of immunoglobulins during legionella infection an increased incidence of Legionnaire's disease has not been found in patients with humoral immune deficiency [8].

3. Splenectomized patients

Legionella infection has not been frequently reported in splenectomized patients as these patients primarily have impairment in humoral immune response and B-lymphocyte function. A case report in 2004 reported two cases of Legionnaire's disease in splenectomized patient. The first patient developed multiorgan failure and laboratory testing was positive for *Legionella hackeliae* and *Legionella longbeachae*. The second patient was positive for *Legionella micdadei* [9]. Another patient with hairy cell leukemia and splenectomy died from multiorgan failure from *L. longbeachae* infection [10]. In 2012, *Legionella pneumophila* pneumonia was been reported in a patient with Myelodysplastic syndrome and splenectomy [11].

4. Primary immunodeficiencies

Primary immunodeficiency disorder is the result of defective immune system development and the absence of functional immune system leads to severe infections. There has been only one case of legionella pneumonia reported in a patient with primary immunodeficiency disorder. It was a 35-year-old male with hyper IgE disease who presented with hemoptysis and was later diagnosed to have cavitary pneumonia due to legionella which was isolated from the BAL cultures and the patient also had a positive urinary legionella antigen [12].

5. Organ transplant patients

Although there are many species of Legionella, *L. pneumophila* is the most common one to cause pneumonia in recipients of organ transplant. Among the non-pneumophila species, *L. micdadei*, followed by *L. longbeachae*, *L. bozemanii*, *L. parisiensis* and *L. cincinnatiensis* commonly caused pneumonia in transplant recipients [3].

A Spanish group of physicians retrospectively reviewed 287 cases of Legionnaires' disease in solid organ transplant patients. They reported that 3% of the transplant recipients had contracted Legionnaires' disease. Incidence of legionnaire's disease was variable but higher in kidney, lung and heart transplant patients [13].

Extrapulmonary manifestations of *Legionella* infection were described in four solid organ transplant patients. The extrapulmonary sites were aorta, pericardium, liver and soft tissue.

A group in Seattle, Washington reviewed 15 year longitudinal data in a hospital that cares for transplant patients and reported 32 cases of Legionnaires disease over a period of 15 years and 10 of them were in solid organ transplant patients [14].

6. Biologic agents

Biologic drugs are very commonly used for treatment of number of diseases and are associated with an increased risk of serious infections by lowering the immunity. A study done in France in 2006 over a period of 1 year revealed a case series of 10 patients treated with anti-TNF alpha therapy who were diagnosed with *Legionella pneumophila* infection [15]. Another French study that looked into risk factors for legionella infection from 2004 to 2007 concluded that anti TNF alpha therapy was associated with 13-fold increased risk of developing legionella infection. There was a 15-fold higher risk associated with infliximab, 38-fold higher risk associated with adalimumab and 3-fold increase with etanercept. Patients had different degrees of presentation. 28% presented with bilateral pneumonia, 24% had ARDS, 33% were hospitalized in ICU and 1 patient died [7]. A recent review from 2004 to 2011 reported 105 cases of Legionnaire's disease in patients treated with biologic treatment [16].

7. Malignancies

Patients with hematological and solid tumors are at higher risk for developing legionnaire's disease. A study found that Legionella caused 29% of pneumonia in patients with head and neck malignancies [17]. A retrospective study over 4 years conducted in a oncology center in 1986 found 36 cases of Legionnaire's disease. 42% had hematological malignancy and 22% had lung cancer. Neutropenic patients and patients on chronic steroids had higher risk of getting legionnaire's disease [18].

Two retrospective studies were done at MD Anderson cancer hospital in Texas. First study reported 49 cases of Legionnaire's disease in cancer patients over a period of 13 years from 1991 to 2003. The majority of patients had an underlying hematologic malignancy. 37% were bone marrow transplant recipients. Lymphopenia, use of corticosteroids and chemotherapy were the most common risk factors in these patients [19]. Second retrospective study reviewed 33 consecutive cases of Legionnaire's disease between 2002 and 2014. Out of this 27 had hematologic malignancies, 23 had neutropenia, 6 had allogeneic hematopoietic stem cell transplant and all patients except 1 had lung infection [20].

Clinical presentation of LD in immunocompromised patients:

Legionnaires disease in immunocompromised patients presents with fever, cough, chills, shortness of breath. GI symptoms can also occur. The incubation period for Legionnaires' disease is usually around 2–10 days from the time of exposure to symptom onset. In immunocompromised patients in addition to consolidation legionnaire's disease can present with cavitations, diffuse bilateral infiltrates and pleural effusions. In transplant patients nodular opacities that eventually cavitate have been reported [21]. Pleural effusions have been reported in 15–50% of cases.

Pneumonia with cavitation has been reported in L pneumophila serotypes 1, 3, 4, 5, 6, and 8 as well as other Legionella species including *L. micdadei*, *L. bozemanae*, *L. dumoffii*, and *L. longbeachae* [22]. Legionella species can also cause lung abscesses and the most important risk factor for it is prolonged use of glucocorticoid therapy. Abscesses generally arise after 4 weeks of starting high dose glucocorticoid therapy. Complicated pleural effusions, empyema and lung abscesses caused by legionella are more commonly seen in patients with solid organ transplant [23].

Extrapulmonary manifestations are usually seen in immunocompromised hosts [4]. The incidence of Neurologic manifestations including meningoencephalitis, meningitis and transverse myelitis are similar to as in immunocompetent hosts. Cutaneous legionella has been reported in patients on chronic corticosteroids, solid organ transplants, stem cell transplants and hematological malignancies. They present with erythema, nodules, induration, ulcer or abscess. Most of them have concomitant lung infection [24].

Legionella can also affect the heart. *L. pneumophila* causing aortitis has been reported in heart transplant patients. Twelve cases of pericarditis were reported and most of them were in immunocompromised patients including transplant recipients, dialysis patients and cancer patients [25].

8. Conclusion

In conclusion while Legionella infection can occur in both immunocompetent and immunocompromised patients, certain risk factors in the immunocompromised are associated with an increased incidence. T cell and cell mediated immunity play a key role in body's defense against the bacteria. TNF Alpha inhibitors are associated with an increased risk of Legionnaire's disease. Extrapulmonary manifestations involving the skin, pericardium and aorta were seen more in immunocompromised, predominantly in patients on chronic corticosteroids, solid organ and stem cell transplant patients. The incidence of neurological manifestations remained the same. The signs and symptoms of Legionnaire's disease are non-specific and patients with the above high risk features, especially on TNF alpha inhibitors should be screened for Legionella infection.

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