Case report

Legionnaires' disease presenting with exanthem; Case and review of previously published cases

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Abstract

Infection with Legionella spp. (legionellosis) causes two distinct clinical presentations: Legionnaires' Disease and Pontiac Fever. Legionnaire's Disease primarily involves the lungs, often with accompanying gastrointestinal symptoms, and can also affect the liver, central nervous system, and kidneys, and cause metabolic derangements. Manifestations in the integumentary system are rare; to date, there have been eleven cases reported in the literature of Legionellosis with associated rash, with varied presentation. The relationship between Legionella pneumophila and the skin has not yet been clearly defined; immunological and/or toxic pathogenesis are possible. We report a case of Legionnaires’ Disease in a young immunocompromised man with a largely benign clinical course consisting of predominantly gastrointestinal symptoms and an extensive maculopapular rash. Chest radiography showed lobar infiltrate in the absence of clinical symptoms of pneumonia. The importance of this case is for clinicians to maintain high clinical suspicion for Legionella when extra-pulmonary symptoms predominate, specifically in immunocompromised hosts who may have atypical presentations and have higher mortality rates when treatment is delayed.

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Case

A 29-year-old man with Crohn’s Disease well-controlled on infliximab (TNF-α inhibitor) presented with five days of fevers, malaise, myalgias, nausea, and vomiting. On day three of illness, he developed a non-pruritic, non-painful rash. The rash was maculopapular with areas of confluence mainly in the right axilla with eventual involvement of the bilateral flanks, axillae and upper thighs (Fig. 1). Non-bloody, watery diarrhea started on the day five of illness. Vital signs were notable for a temperature of 38.7 °C and tachycardia with heart rates in the 100–110 beats/min range. Otherwise, the patient was hemodynamically stable and his oxygen saturations were normal while breathing ambient air. He denied shortness of breath, chest pain, cough, and all upper respiratory symptoms. Laboratory abnormalities included sodium 128 mmol/L, chloride 92 mmol/L, AST 67 units/L, ALT 68 units/L, total bilirubin 1.3 mg/dL, C-reactive protein 19.1 mg/dL and erythrocyte sedimentation rate 67 mm/hour. Chest x-ray revealed a left base infiltrate and CT chest showed a left lower lobe consolidation with prominent hilar and axillary lymph nodes (Fig. 2). The patient was initially treated with broad spectrum antibiotics including vancomycin, pseudomonal dosing of piperacillin-tazobactam, and azithromycin.

An extensive evaluation for gastrointestinal pathogens common in immunocompromised hosts was negative. However, urine Legionella pneumophila serogroup 1 urine antigen was positive. His
antibiotic regimen was switched to oral azithromycin 500 mg daily for twenty-one days. Punch biopsy of skin of left flank showed spongiosis, mild lymphocytic exocytosis with focal intraepidermal spongiotic micro-vesiculation, mild to focally moderate superficial perivascular lymphocytic infiltrate, and occasional eosinophils. These findings are synonymous with swelling and erythema seen in

Fig. 2. Chest Radiography. A. Opacity in lower left lung field on chest X-ray. B. Consolidation in left lower lobe on chest computed tomography.

Fig. 3. Histopathology showing spongiosis, mild lymphocytic exocytosis with focal intraepidermal spongiotic micro-vesiculation, mild to focally moderate superficial perivascular lymphocytic infiltrate, and occasional eosinophils. A. 40x. B. 100x. C. 400x.
| Case Year & Location | Age (years) | Gender | Rash, cough, fever, malaise, myalgia, diarrhea, anorexia | Chest Imaging | Immunosuppression | Rash Description & Histopathology |
|----------------------|------------|--------|---------------------------------------------------------|--------------|-------------------|-----------------------------------|
| 1980 South Africa | 38 | M | Rash, cough, emesis, myalgia, headache, encephalopathy | CXR: no pneumonia | None reported | Description: Diffuse erythematous maculopapular rash over trunk & extremities; moderate to marked edema & recent hemorrhage with associated widespread petechial rash on the chest, back, upper abdomen, head & neck, with initial sparing of the limbs. Subsequent desquamation & mild chronic inflammatory infiltrate with minimal eosinophils noted in skin biopsy. |
| 1980 Los Angeles, USA | 62 | M | Rash, cough, fever | CXR: B/L infiltrates | Prednisone | Description: Pruritic rash |
| 1981 Iowa, USA | 46 | M | Rash, cough, fever, malaise | CXR: N/A | Methotrexate | Description: Diffuse petechial rash starting at time of encephalopathy |
| 1984 Vermont, USA | 43 | M | Rash, fever | CT: B/L consolidation | None reported | Description: Papular rash |
| 1985 Kansas | 69 | M | Rash, fever, fall | CT: B/L infiltration | None reported | Description: Diffuse erythematous maculopapular rash over trunk & extremities; moderate to marked edema & recent hemorrhage with associated widespread petechial rash on the chest, back, upper abdomen, head & neck, with initial sparing of the limbs. Subsequent desquamation & mild chronic inflammatory infiltrate with minimal eosinophils noted in skin biopsy. |
| 2005 Italy | 43 | M | Rash, cough, fever, chills, diarrhea, anorexia | CT: B/L infiltrates, moderate right pleural effusion | None reported | Description: Diffuse erythematous maculopapular rash over trunk & extremities; moderate to marked edema & recent hemorrhage with associated widespread petechial rash on the chest, back, upper abdomen, head & neck, with initial sparing of the limbs. Subsequent desquamation & mild chronic inflammatory infiltrate with minimal eosinophils noted in skin biopsy. |
| 2006 Germany | 64 | M | Rash, cough, fever, chills, abdominal pain | CT: IL infiltration, moderate right pleural effusion | None reported | Description: Diffuse erythematous maculopapular rash over trunk & extremities; moderate to marked edema & recent hemorrhage with associated widespread petechial rash on the chest, back, upper abdomen, head & neck, with initial sparing of the limbs. Subsequent desquamation & mild chronic inflammatory infiltrate with minimal eosinophils noted in skin biopsy. |
| 2010 Maryland, USA | 29 | M | Rash, fever, malaise, myalgia | CT: CTR, RML & RLL pneumonia | None reported | Description: Papular rash |

**Key:** M, male; N/A, not applicable; CXR, chest X-ray; B-CLL, B-cell chronic lymphocytic leukemia; RML, right middle lobe; RLL, right lower lobe; B-CLL, B-cell chronic lymphocytic leukemia; RML, right middle lobe.
a non-specific inflammatory reaction, and the differential noted by the dermato-pathologist included spongiotic dermatitis versus drug eruption (Fig. 3).

Discussion and review of published cases

This case is unique because the patient was immunosuppressed but had a benign inpatient course with predominantly gastrointestinal symptoms and an extensive rash. Known risk factors for moderate to severe disease course with Legionella infections include compromised cellular immunity and solid organ transplant. Mortality rates for patients with these risk factors are as high as 14% and up to 51% or higher in cases of coinfection [5–7]. The spectrum of disease typically falls from mild to severe respiratory symptoms with possible multi-organ system involvement [5]. Our patient was at elevated risk for severe disease. However, his extra-pulmonary symptoms were predominant and clinical course was mild. Therefore, awareness of unusual presentations of legionellosis, is paramount as delayed treatment leads to higher rates of mortality [9].

Exanthems are not commonly associated with legionellosis. A systematic review of the PubMed database was performed using the following search terms: “Legionella,” “Legionnaires,” or “Legionnaire’s Disease,” in combination with “cutaneous,” ”rash,” “extrapulmonary,” “exanthem,” or “skin manifestations.” All adult case reports and case series published in English through from 1985 to 2021 were included. Pediatric cases, primary legionella skin and soft tissue infections, and cases with skin findings solely attributable to associated coagulopathy. Skin infections attributable to Legionella spp. Are not included in this review of exanthems but do occur and are worth considering clinically also; reports of primary abscesses [11], cellulitis[12,13], panniculitis [14], ulcer [15], and several other soft tissue infections due to Legionella spp [16] were noted in the literature review.

Cases are reported from South Africa, Italy, Germany, Norway, and the United States, with patients ranging in age from 32 to 69 years old. Cases include both Pontiac Fever and Legionnaires’ Disease associated with rash; four cases occurred in immunocompromised individuals. Rash presentations were broad, including painless and painful, non-pruritic and pruritic, and maculopapular, indurated plaques, erythematous, petechial, and hemorrhagic lesions. Histopathology was also variable, including edema with hemorrhage, slightly spongiotic with focal parakeratosis, fibrin thrombi, fibrinoid degeneration of the vascular wall, spongiform micro-vesiculations, and perivascular lymphocytic infiltrate, for example [10,17–24]. In most cases, rash occurred before presentation but after other symptoms (current, [10,17]), accompanying worsening symptoms [17], or during hospitalization and antimicrobial treatment [20–23,25]. In one case rash was present at presentation but it is not noted whether it was co-incident with other symptom onset [10]; this patient also developed a rash consistent with DIC [10] and it’s not clear if these two rashes were part of the same pathologic process or not. To date, there is no consistent etiology for skin findings reported in the literature.

Previous cases propose that pathogenesis may be related to a legionella toxin [20,21], host immune response [22], or drug reaction [18]. Systemic inflammatory responses, whether secondary to bacterial toxins or host immune response to Legionella spp. or antimicrobial treatment, all seem plausible. However, there is no known toxin associated with legionellosis and legionella staining has been negative in two of the reported cases [20]. Our patient’s histopathology was consistent with a systemic inflammatory response versus drug reaction. His only medication prior to hospitalization was infliximab, which is associated with adverse dermatologic reactions including an undescribed rash, and erythematous or urticarial rashes in 10% or < 1% of patients, respectively, though he had been taking this medication for several years, according to the patient, without issue [26].(Table 1).

Conclusion

To our knowledge, we report the first case of mild Legionnaire’s Disease in an immunocompromised host with the predominate extrapulmonary symptom of rash. Our case adds to the limited existing literature of similar patients with legionellosis associated exanthems. The etiology of rash in Legionnaires’ Disease has been yet to be determined. The diagnosis of Legionnaire’s Disease can be difficult, particularly when presenting without obvious pneumonia. A high index of suspicion for legionellosis is warranted in cases with atypical presentations, particularly in immunocompromised patients.

CRedit authorship contribution statement

Christine Carter: Writing – original draft. Elizabeth M. Corley: Writing – original draft. Hannah Canepa: Writing – review & editing. Sarah Schmalzle: Writing – review & editing.

Declaration of Interests

None.

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Informed consent

Written informed consent was obtained from the patient for publication of this case report, and is available upon request.

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