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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.

Species of the genus *Legionella* are fastidious gram-negative bacilli, which are ubiquitous in aquatic environments and transmitted to humans via inhalation of aerosolized water typically from industrial cooling towers and air-conditioning units. Although there are nearly 50 species of Legionella, *Legionella pneumophila* accounts for approximately 90% of all human infections. eaks [1] Infection with *Legionella pneumophila* can cause two distinct clinical pictures: Legionnaires' Disease and Pontiac fever. The potentially fatal Legionnaires' Disease consists mainly of severe pneumonia associated with extrapulmonary manifestations, often requiring hospitalization. Pontiac fever is typically presents as a self-limited influenza-like illness with milder disease course. Although people of any age can develop legionellosis, middle-aged and elderly patients more often have a moderate to severe disease course. According to the Centers for Disease Control and Prevention's Active Bacterial Core surveillance program, forty-four percent of patients with Legionnaires' Disease require time in intensive care units and nine percent die from complications of their illness [2] In addition to age, patients with dysfunction of their cell-mediated immunity (e.g. HIV, hematologic malignancies, corticosteroid use) are at increased risk of infection and more severe disease. Other conditions resulting in impaired immune systems, such as diabetes mellitus, autoimmune conditions, and malignancies can also place patients at higher risk of infection [3].

Extrapulmonary manifestations of Legionnaires' Disease include gastrointestinal symptoms, elevated serum transaminase, neurological dysfunction (encephalopathy), renal dysfunction (proteinuria, increased serum creatinine), and hyponatremia [4]. Despite multisystem involvement being common, dermatologic manifestations of Legionnaires' Disease remain rare. To date, only eleven cases of legionellosis with associated rash have been reported in the literature. Each case differs in presentation and underlying pathology. Here we report a case of Legionnaires' Disease with associated maculopapular rash in a young immunocompromised man plus a review of published cases of legionellosis associated with rash.

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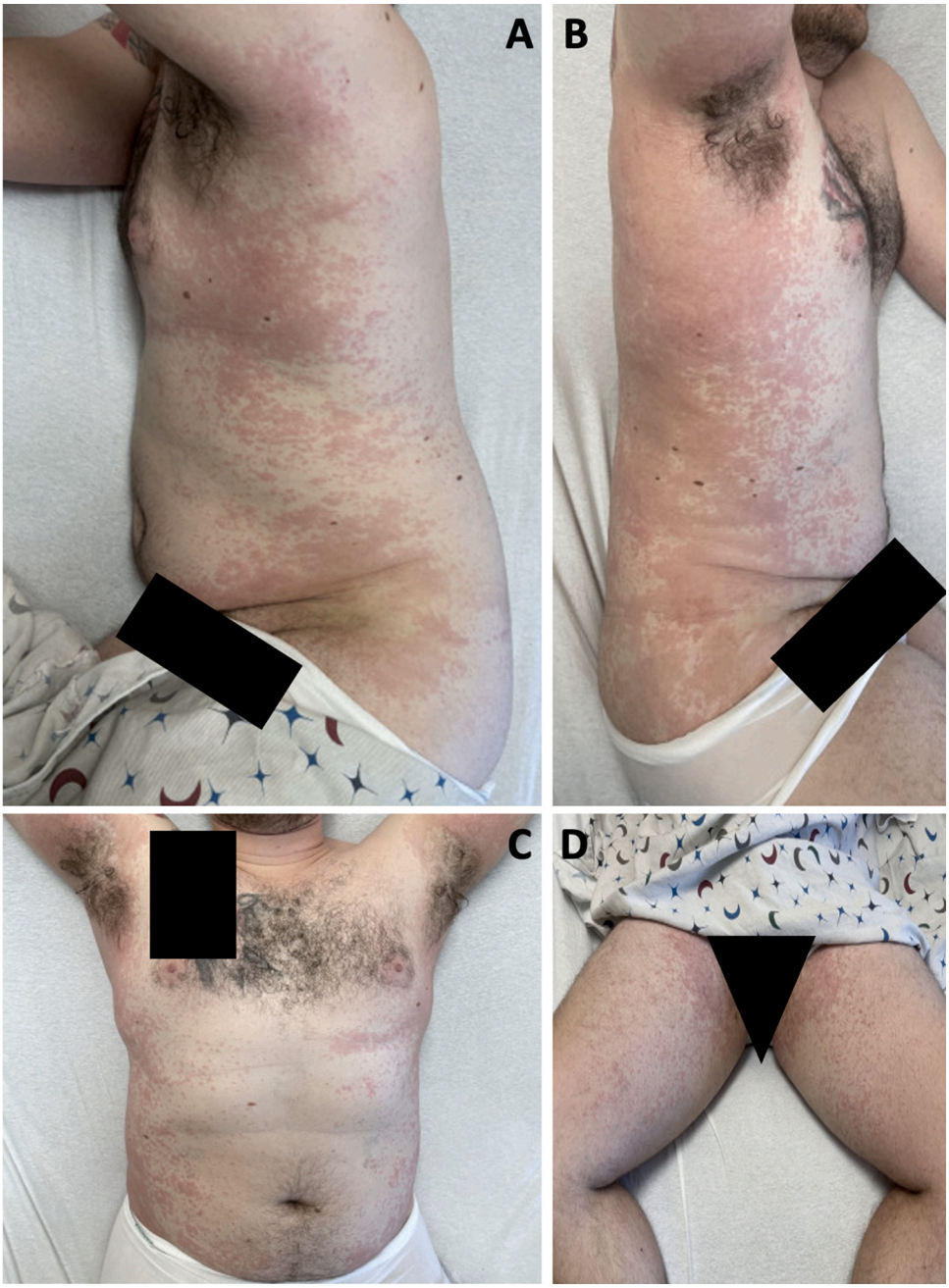

Fig. 1. Maculopapular coalescing rash. A. Left flank. B. Right flank. C. Torso. D. Groin and upper legs.

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 67units/L, ALT 68units/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

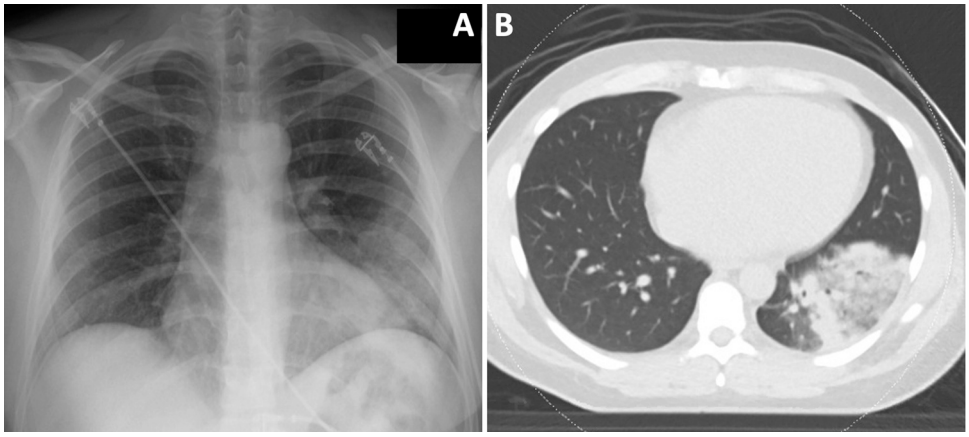

Fig. 2. Chest Radiography. A. Opacity in lower left lung field on chest X-ray. B. Consolidation in left lower lobe on chest computed tomography.

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

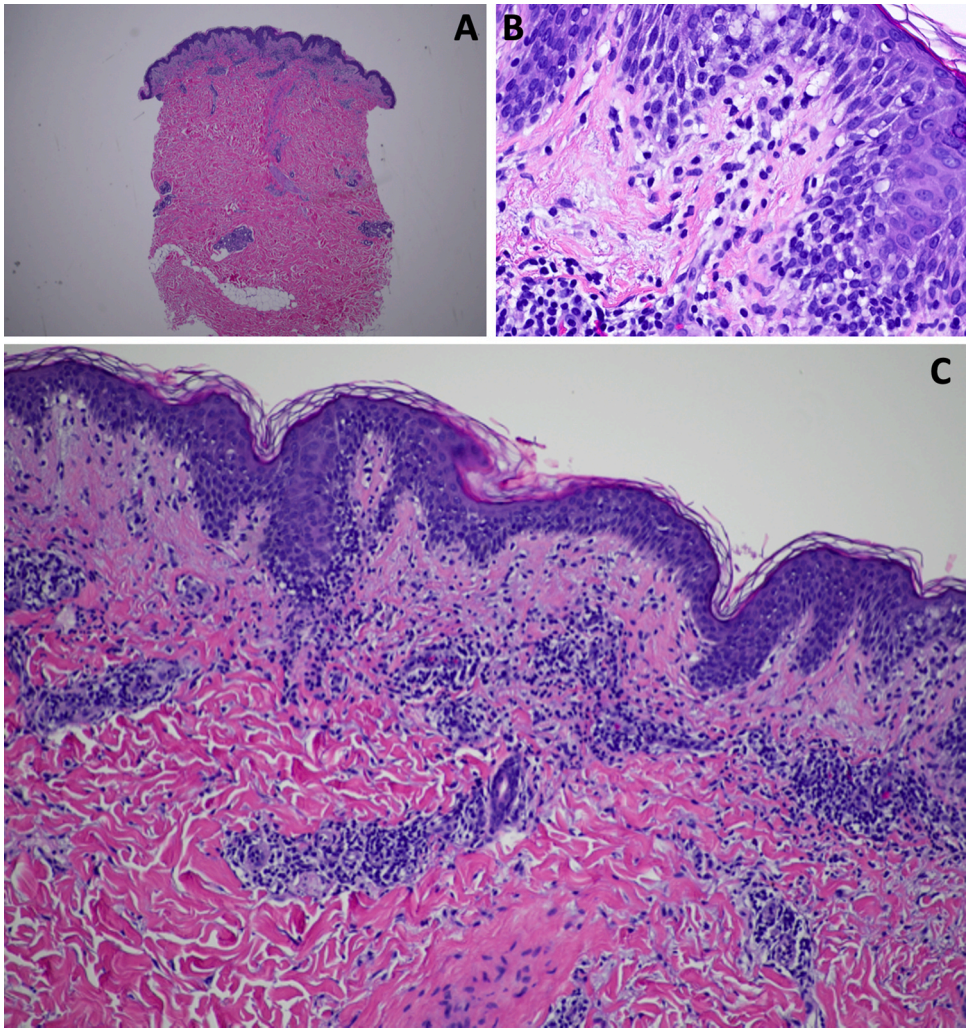

Fig. 3. Histopathology showing spongiosis, mild lymphocytic exocytosis with focal intraepidermal spongiotic micro-vesiculation, mild to focally moderate superficial perivascular lymphocytic infiltrate, and occasional eosinophils. A. 40x. B. 100x. C. 400x.

Table 1
Published cases of legionellosis with rash.

Case year & location	Age, gender symptoms	Chest radiology	Immuno-suppression	Rash description & histopathology
1980[17] South Africa	38, M Rash, cough, emesis, myalgia, headache,encephalopathy	CXR: no pneumonia	None reported	**Description:** Diffuse petechial rash starting at time of encephalopathy **Histopathology:** N/A
1980[18] Los Angeles, USA	62, M Rash, cough, fever	CXR: B/L infiltrates	Hairy Cell Leukemia	**Description:** Pruritic rash **Histopathology:** N/A
1981[23] Iowa, USA	46, M Rash, cough, fever, malaise	CXR: Nodular infiltrates in the LUL & LLL; new RUL infiltrate following day	Prednisone Azathioprine Methylprednisolone DDRT with rejection	**Description:** Painful, non-pruritic, macular, blanchable, erythematous rash limited to B/L pretibial surfaces, onset on fifth day of illness **Histopathology:** N/A
1984[19] Vermont, USA	Two men with Pontiac fever, rash	N/A	None reported	**Description:** Papular rash **Histopathology:** N/A
1985[20] Kansas, USA	69, M Rash, fever, weakness, urinary frequency	CXR: RLL infiltrate	None reported	**Description:** Diffuse erythematous maculopapular rash over trunk & extremities after amoxicillin initiated **Histopathology:** Focal, mild chronic inflammation, edema, & recent hemorrhage. No evidence of eosinophilic infiltrate. Legionella staining negative.
1985[20] Kansas, USA	67, M Rash, fever, fall	CXR: B/L pulmonary infiltrates	None reported	**Description:** Diffuse erythematous maculopapular rash over trunk & extremities within 48 h of presentation **Histopathology:** Moderate to marked edema & recent hemorrhage with increased mast cells, lymphocytes, & histiocytes, with rare eosinophils & polymorphonuclear leukocytes. Legionella staining negative.
1987[24] London, UK	43, M Fever, dry cough, arthralgias, rash	CXR: LLL shadow	None reported	**Description:** Wide spread maculopapular purpuric eruption scattered over legs and buttocks, described as typical of Henoch Schönlein purpura rash **Histopathology:** N/A
2005[21] Italy	32, F Rash, cough fever, chills, diarrhea, asthenia	CXR: B/L diffuse pulmonary infiltrates	None reported	**Description:** Widespread, erythematous, rounding macular lesions 4–6 mm in diameter, non-pruritic, on chest & limb surface, onset 4 days into admission and lasting for 24 h **Histopathology:** N/A
2005[21] Italy	48, F Rash, cough, fever, chills, anorexia, asthenia	CT: B/L diffuse infiltrates, moderate right pleural effusion	None reported	**Description**: Diffuse, rounded, red-colored, macular lesions 3–6 mm in diameter, non-pruriginous, involving chest, abdomen, & limbs, occurring after other symptom onset **Histopathology:** N/A
2009[7] Germany	64, M Rash, fever, chills, abdominal pain	CT: B/L lower lobe pneumonia	B-CLL Chronic alcohol misuse	**Description:** Rapidly extending macular & maculopapular, livid, partially hemorrhagic exanthem with target-like appearance on chest, back, upper abdomen, head & neck, with only initial sparing of the limbs, subsequent focal blisters, onset during hospital course **Histopathology:** Slightly spongiotic but otherwise normal epidermis with focal parakeratosis, papillary dermic with edema leading to subepidermal blister formation, sparse perivascular lymphocytic infiltrate
2015[10] Pennsylvania, USA	44, M Rash, cough, fever, fatigue, myalgia	CXR/CT: RML and RLL pneumonia	None reported	**Description**: Initial maculopapular rash on inner thighs, confluent with dark necrotic appearing areas and spread to arms, legs, trunk, nose tip, and ears 24 h later **Histopathology:** Partial fibrin thrombi in small, superficial vessels & larger mid-dermal vessels, fibrinoid degeneration of the vessel walls
2021 [current report] Maryland, USA	29, M Rash, fever, malaise, myalgia, emesis	CXR: left base infiltrate CT: LLL consolidation, hilar & axillary lymphadenopathy	Infliximab (for Crohn's Disease)	**Description:** non pruritic, non-painful maculopapular with areas of confluence mainly in right axilla with eventual involvement of bilateral flanks, axillae, & upper thighs **Histopathology:** spongiosis, mild lymphocytic exocytosis with focal intraepidermal spongiotic micro-vesiculation, mild to focally moderate superficial perivascular lymphocytic infiltrate, & occasional eosinophils

Key: M, male; N/A, not applicable; CXR, chest X-ray; B/L, bilateral; CT, computed tomography; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RLL, right lower lobe; B-CLL, B-cell chronic lymphocytic leukemia; RML, right middle lobe; RLL, right lower lobe; SLE, systemic lupus erythematosus; MG, myasthenia gravis.

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,” “Legionellosis,” 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, spongiotic 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.

References

[1] Fields BS, Benson RF, Besser RE. Legionella and legionnaires’ disease: 25 Years of investigation. Clin Microbiol Rev 2002:15. https://doi.org/10.1128/CMR.15.3.506-526.2002
[2] Fields BS, Benson RF, Besser RE. Legionella and legionnaires’ disease: 25 Years of investigation. Clin Microbiol Rev 2002:15. https://doi.org/10.1128/CMR.15.3.506-526.2002
[3] Schlossberg D, Bonoan J. Legionella and immunosuppression. Semin Respir Infect 1998;13:13–31.
[4] Cunha BA. Clinical features of legionnaires’ disease. Semin Respir Infect 1998;13:13–27.
[5] El-Ebiary M, Sarmiento X, Torres A, Nogué S, Mesalles E, Bodí M, et al. Prognostic factors of severe Legionella pneumonia requiring admission to ICU. Am J Respir Crit Care Med 1997;156:156–72. https://doi.org/10.1164/ajrccm.156.5.97-04039
[6] Saravolatz LD, Burch KH, Fisher E, Madhavan T, Kiani D, Neblett T, et al. The compromised host and Legionnaires’ disease. Ann Intern Med 1979;90:90–7. https://doi.org/10.7326/0003-4819-90-4-533
[7] Gudiol C, Garcia-Vidal C, Fernández-Sabé N, Verdaguer R, Lladó L, Roca J, et al. Clinical features and outcomes of Legionnaires’ disease in solid organ transplant recipients: Short communication. Transpl Infect Dis 2009:11. https://doi.org/10.1111/j.1399-3062.2008.00337.x
[9] Heath CH, Grove DI, Looke DFM. Delay in appropriate therapy of Legionella pneumonia associated with increased mortality. Eur J Clin Microbiol Infect Dis 1996:15. https://doi.org/10.1007/BF01695659
[10] Thalanayar PM, Holguin F. Rash, disseminated intravascular coagulation and legionella: Episode 10 and a rewind into the past. Respir Med Case Rep 2015:15. https://doi.org/10.1016/j.rmcr.2015.04.001
[11] Barigou M, Cavalie L, Daviller B, Dubois D, Mantion B, Delobel P, et al. Isolation on chocolate agar culture of legionella pneumophila isolates from subcutaneous abscesses in an immunocompromised patient. J Clin Microbiol 2015:53. https://doi.org/10.1128/JCM.01116-15

[12] Han JH, Nguyen JC, Harada S, Baddour LM, Edelstein PH. Relapsing Legionella pneumophila cellulitis: A case report and review of the literature. J Infect Chemother 2010;16:16–42. https://doi.org/10.1007/s10156-010-0072-6
[13] Waldor MK, Wilson B, Swartz M. Cellulitis Caused by Legionella pneumophila. Clin Infect Dis 1993;16. https://doi.org/10.1093/clinids/16.1.51
[14] Chitasombat MN, Ratchatanawin N, Visessiri Y. Disseminated extrapulmonary Legionella pneumophila infection presenting with panniculitis: Case report and literature review. BMC Infect Dis 2018;18:18. https://doi.org/10.1186/s12879-018-3378-0
[15] Valve K, Vaalasti A, Anttila VJ, Vuento R. Disseminated Legionella pneumophila infection in an immunocompromised patient treated with tigecycline. Scand J Infect Dis 2010:42. https://doi.org/10.3109/00365540903359895
[16] Padrnos LJ, Blair JE, Kusne S, Dicaudo DJ, Mikhael JR. Cutaneous legionellosis: Case report and review of the medical literature. 16-14 Transpl Infect Dis 2014;16. https://doi.org/10.1111/tid.12201
[17] Randall TW, Naidoo P, Newton KA, Botha PW, Koornhof HJ, Dubery B. Legionnaires' disease in Port Elizabeth. South Afr Med J 1980:58.
[18] Meyer RD, Edelstein PH, Kirby BD, Louie MH, Mulligan ME, Morgenstein AA, et al. Legionnaires' disease: Unusual clinical and laboratory features. Ann Intern Med 1980:93. https://doi.org/10.7326/0003-4819-93-2-240
[19] Spitalny KC, Vogt RL, Witherell LE. National survey on outbreaks associated with whirlpool spas. Am J Public Health 1984;74:74–6. https://doi.org/10.2105/AJPH.74.7.725
[20] Allen TP, Fried JS, Wiegmann TB, Hodges GR, Dixon AY, Lee SH, et al. Legionnaires' Disease Associated With Rash and Renal Failure. Arch Intern Med 1985;145. https://doi.org/10.1001/archinte.1985.00360040163034
[21] Calza L, Briganti E, Casolari S, Manfredi R, Chiodo F, Zauli T. Legionnaires' disease associated with macular rash: Two cases. 85-4 Acta Derm-Venereol 2005;85. https://doi.org/10.1080/00015550510030050
[22] Ziemer M, Ebert K, Schreiber G, Voigt R, Sayer HG, Marx G. Exanthema in Legionnaires' disease mimicking a severe cutaneous drug reaction. Clin Exp Dermatol 2009;34. https://doi.org/10.1111/j.1365-2230.2008.03176.x
[23] Helms CM, Donaldson MF, Johnson W, Corry RJ. Pretibial Rash in Legionella pneumophila Pneumonia. JAMA: J Am Med Assoc 1981:245. https://doi.org/10.1001/jama.1981.03310420048030
[24] Bull PW, Scott JT, Breathnach SM. Henoch-Schonlein purpura associated with legionnaires' disease. Br Med J (Clin Res Ed) 1987:294. https://doi.org/10.1136/bmj.294.6566.220
[25] Patel H, Shelley P, Hatoum H. Hypertriglyceridemia and massive rhabdomyolysis in a patient with disseminated legionella. Respir Med Case Rep 2021:32. https://doi.org/10.1016/j.rmcr.2020.101321
[26] FDA, 2021, FDADrugs 2021. ⟨https://www-accessdata-fda-gov.proxy-hs.researchport.umd.edu/drugsatfda_docs/label/2020/761072s006lbl.pdf#page=43⟩ (accessed 29 September 2021).