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Peer reviewed
Cutaneous *Legionella* infections in allogeneic hematopoietic cell transplantation recipients

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**Abstract**

To date, only twenty cases of cutaneous legionellosis have been reported. Cutaneous legionellosis has heterogeneous manifestations including abscesses, nodules, and cellulitis. The detection of most cutaneous *Legionella* species requires specific diagnostic cultures and assays. Herein, we report a case of cutaneous legionella in a hematopoietic cell transplantation recipient with culture-negative nodules unresponsive to empiric antibiotics. We also discuss the varied morphology of cutaneous legionellosis and important diagnostic considerations.

**Keywords:** cutaneous legionellosis, hematopoietic cell transplantation recipients

**Case Synopsis**

A 50-year-old woman with acute myeloid leukemia developed fever, dry cough, and painful erythematous nodules with turbid drainage and surrounding erythema on bilateral lower extremities on day +78 following peripheral blood stem cell transplantation (PBSC). *Figure 1.* Sputum culture identified pharyngeal flora and empiric levofloxacin for one week was initiated. Incision and drainage of nodules was performed. Bacterial, fungal, and mycobacterial wound cultures were negative, though Gram stain revealed 1+ Gram-negative rods (GNR). While awaiting wound culture results, trimethoprim/sulfamethoxazole for 10 days and topical mupirocin was initiated for pustular skin/soft tissue infection. Pulmonary symptoms resolved and skin nodules size, drainage, and pain decreased. Following treatment, cutaneous nodules recurred on day +112. Skin 4mm punch biopsies of a left shin nodule revealed a dense acute inflammatory infiltrate with necrotic debris and forms suspicious for bacterial rods on Brown-Hopps stain, some of which appeared intracellular (*Figure 2*). Periodic acid Schiff diastase and acid-fast bacillists were negative. Biopsy tissue bacterial Gram stain again revealed 1+ GNR, and culture demonstrated 3+ coagulase-negative staphylococci, consistent with skin flora. Fungal and mycobacterial cultures were negative. A 28-day levofloxacin course was initiated.

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**Introduction**

*Legionella* species are opportunistic pathogens in humans. Cutaneous legionellosis is an uncommon but important differential diagnosis to consider in immunocompromised patients. Herein, we report a hematopoietic cell transplantation recipient with cutaneous legionella, the varied morphology of cutaneous legionellosis and important diagnostic considerations.
given GNRs on Gram stain and prior improvement on levofloxacin. Broad-range 16S rRNA gene amplification and sequencing of biopsy tissue confirmed *Legionella*. Because antimicrobials previously used had activity against *Legionella*, no additional treatment was initiated. Skin lesions resolved following treatment completion.

**Case Discussion**

To the best of our knowledge, to date there are twenty confirmed cases of cutaneous legionellosis (*Table 1*). Seventy percent (N=14) cases occurred in females and 30% (N=6) occurred in males. Patient age of onset ranged from three to 73 years old (average 51.2±21.4 years). Skin manifestations are varied, though abscesses (N=5) and nodules (N=5) were the most common presentations, followed by cellulitis (N=4), ulcers (N=2), bullae (N=1), pustules (N=1), panniculitis (N=1), and diffuse erythema (N=1). Approximately 50% of cutaneous cases were associated with pulmonary legionellosis and spread hematogenously [1]. In non-pulmonary cases, direct inoculation with contaminated water may be the infectious source; the patient in this case bathed in well water.

Eighty percent of cases (N=16) were associated with immunosuppression, a risk factor for legionellosis [2]. The majority of these patients (N=9) had a history of hematologic or solid organic malignancy. Systemic antibiotics were initiated in all cases (*Table 1*). The majority of cases resulted in resolved infection (N=12) or improved cutaneous lesions (N=3). Three of these patients died following presentation. Of these, one death was related to infection (necrotizing soft tissue chest infection) and two were not related to infection (multi-organ failure following worsening respiratory distress, and severe adenoviral hepatitis).

*Legionella* pneumonias are commonly caused by *L. pneumophila* serogroup-1 [3], which can be detected by urine antigen testing. However, most cutaneous cases are non-serogroup-1 *L. pneumophila* or non-*L. pneumophila* species and therefore require specific diagnostic cultures and assays. Buffered charcoal yeast extract agar is the gold standard and may be used as a “test of cure” for treatment efficacy monitoring. PCR assays targeting 16S rRNA and *mip* genes are more sensitive for species detection than culture [4]. Though environmental *Legionella* species could have caused contamination, repeated treatment response with recurrence after treatment discontinuation and visualization of forms

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**Figure 1.** Clinical presentation of cutaneous legionellosis in a 50-year-old female with painful erythematous, compressible nodules.

**Figure 2.** A) Diffuse predominantly neutrophilic inflammatory infiltrate is present in dermis. H&E, 30×. B) Higher magnification showing neutrophils, fibrinoid debris, and possible bacterial forms (arrow). H&E, 600×. C) Brown-Hopps stain highlights a cluster of gram-negative rods (inset), 600×.
suggestive of bacterial rods within tissue biopsy including possibly phagocytosed forms in this case are supportive of true infection.

**Conclusion**

Cutaneous legionellosis is an uncommon but important infection in the differential diagnosis to consider in immunocompromised patients with culture-negative cutaneous lesions with histologic rods, particularly when the infection is unresponsive to empiric antibiotics. Careful history and early initiation of macrolides or fluoroquinolones may reduce associated morbidity.

**Potential conflicts of interest**

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Table 1. Clinical characteristics of 20 confirmed cases of cutaneous legionellosis.

| Case | Age | Gender | Skin manifestation | Pulmonary infection | Microbiology | Treatment | Immuno-compromised | Infection outcome | Ref |
|------|-----|--------|-------------------|--------------------|--------------|-----------|------------------|-------------------|-----|
| 1    | 46  | F      | Abscess           | Yes                | L. pneumophila serogroup 3 | Erythromycin | Yes (treated with high dose corticosteroid therapy for idiopathic diffuse proliferative glomerulonephritis) | Resolved | [5] |
| 2    | 71  | M      | Ulcer             | No                 | L. pneumophila serogroup 4 | Erythromycin | No               | Resolved | [6] |
| 3    | 62  | F      | Abscess           | No                 | L. micdadei    | Erythromycin | Yes (treated with prednisone and cyclophosphamide for rapidly progressive glomerulonephritis secondary to necrotizing vasculitis) | Resolved | [7] |
| 4    | 39  | F      | Cellulitis        | No                 | L. micdadei    | Erythromycin | Yes (renal transplantation) | Resolved | [8] |
| 5    | 66  | M      | Cellulitis        | Yes                | L. pneumophila | Erythromycin | Yes (follicular lymphoma) | Resolved | [9] |
| 6    | 73  | F      | Abscess           | No                 | L. cincinnatiensis | Clarithromycin | Yes (immunoglobulin A gammopathy, lymphoma) | Resolved | [10] |
| 7    | 9   | F      | Abscess           | No                 | L. micdadei    | Clarithromycin | No               | Resolved | [11] |
| 8    | 63  | F      | Bullae            | Yes                | L. pneumophila | Cefazolin, imipenem/cilastatin, tobramycin | No               | Death | [12] |
| 9    | 68  | F      | Nodule            | No                 | L. maceachernii | Levofloxacin | Lesions persisted | No                | [13] |
| 10   | 65  | F      | Cellulitis        | Yes                | L. pneumophila serogroup 1 | Vancomycin, cefepime, erythromycin | Yes (treated with high-dose corticosteroids for interstitial lung disease and idiopathic thrombocytopenic purpura) | Relapsing disease, death | [14] |
| 11   | 48  | M      | Ulcer             | Yes                | L. pneumophila serogroup 5 | Tigecycline, moxifloxacin | Yes (liver transplantation) | Improved | [15] |
| 12   | 66  | F      | Cellulitis        | No                 | L. feelei      | Amoxicillin-clavulanate/levofloxacin | Yes (chronic lymphocytic leukemia) | Unclear | [16] |
| 13   | 27  | F      | Nodule            | Yes                | L. pneumophila serogroup 8 | Azithromycin | Yes (pre-B cell acute lymphoblastic leukemia) | Relapsing disease, death | [3] |
| 14   | 72  | M      | Abscess           | Yes                | L. pneumophila serogroup 1 | Levofloxacin | Yes (rectal adenocarcinoma with lung metastasis) | Resolved | [17] |
| 15   | 70  | F      | Nodules           | No                 | L. longbeachae | Ciprofloxacin, azithromycin, rifampin | Yes (long-term corticosteroids for immune thrombocytopenia) | Resolved | [18] |
|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 16 | 44 | M | Diffuse erythema | Yes | *L. pneumophila* serogroup 1 | Ceftriaxone, doxycycline, moxifloxacin | No | Resolved | [19] |
| 17 | 23 | F | Pustules | No | *L. feeleii* | Moxifloxacin | Yes (cardiac transplantation) | Resolved | [1] |
| 18 | 3  | M | Nodule | No | *L. anisa* | Levofloxacin | Yes (familial hemophagocytic lymphohistiocytosis) | Resolved | [20] |
| 19 | 38 | F | Panniculitis | No | *L. pneumophila* | Azithromycin, ciprofloxacin | Yes (treated with prednisolone and azathioprine for systemic lupus erythematosus and myasthenia gravis) | Improved | [21] |
| 20 | 50 | F | Nodule | Yes | *Legionella* subtype indeterminate | Trimethoprim-sulfamethoxazole, levofloxacin | Yes (acute myeloid leukemia) | Improved | - |