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## 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

### Introduction

*Legionella* species are opportunistic pathogens in humans. Cutaneous legionellosis is an uncommon but important differential diagnosis to consider in immunocompromised patients.

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Herein, we report a hematopoietic cell transplantation recipient with cutaneous legionella, the varied morphology of cutaneous legionellosis and important diagnostic considerations.

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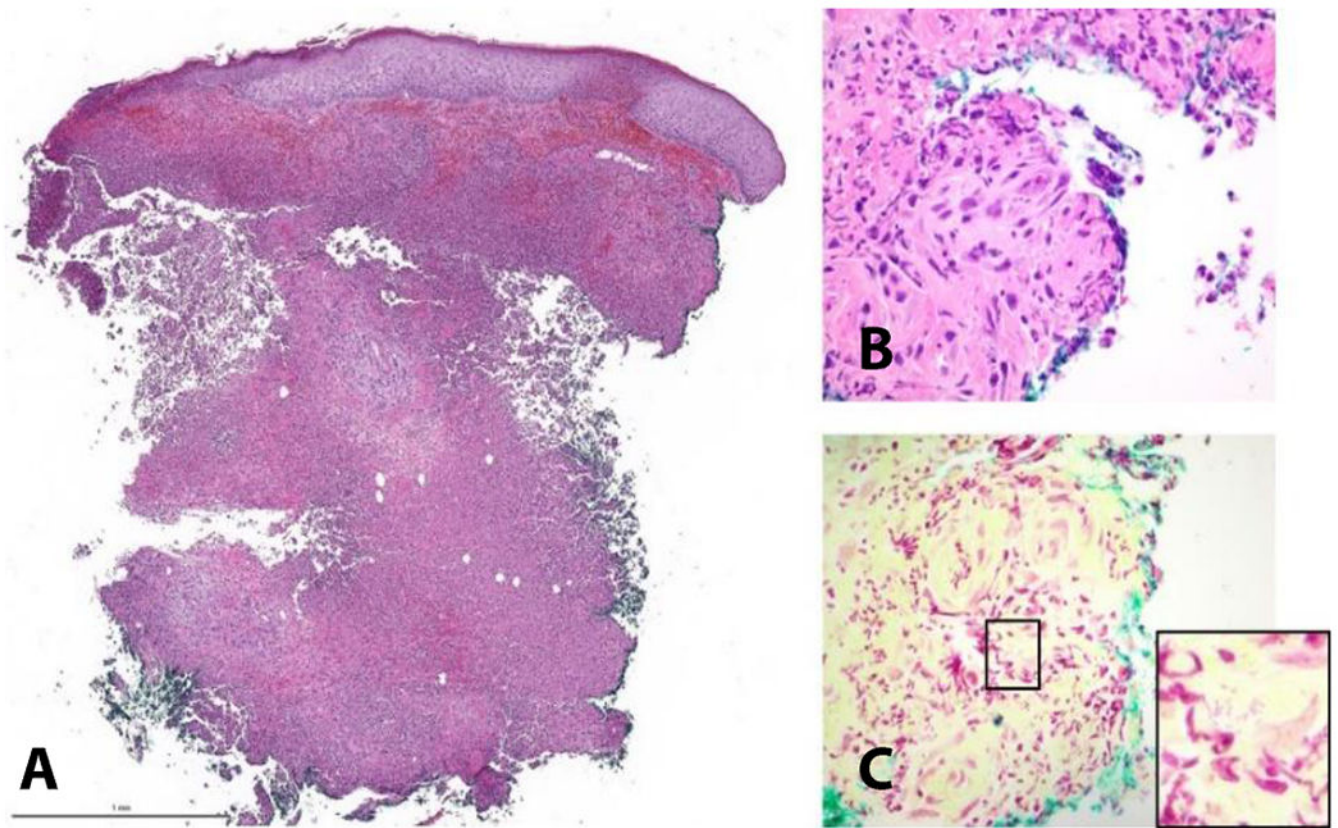
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**Figure 1.** Clinical presentation of cutaneous legionellosis in a 50-year-old female with painful erythematous, compressible nodules.





**Figure 2.**

**A)** Diffuse predominantly neutrophilic inflammatory infiltrate is present in dermis. H&E, 30 $\times$ . **B)** Higher magnification showing neutrophils, fibrinoid debris, and possible bacterial forms (arrow). H&E, 600 $\times$ . **C)** Brown-Hopps stain highlights a cluster of gram-negative rods (inset), 600 $\times$ .

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	<i>L. pneumophila</i> serogroup 3	Erythromycin	Yes (treated with high dose corticosteroid therapy for idiopathic diffuse proliferative glomerulonephritis)	Resolved	[5]
2	71	M	Ulcer	No	<i>L. pneumophila</i> serogroup 4	Erythromycin	No	Resolved	[6]
3	62	F	Abscess	No	<i>L. micdadei</i>	Erythromycin	Yes (treated with prednisone and cyclophosphamide for rapidly progressive glomerulonephritis secondary to necrotizing vasculitis)	Resolved	[7]
4	39	F	Cellulitis	No	<i>L. micdadei</i>	Erythromycin	Yes (renal transplantation)	Resolved	[8]
5	66	M	Cellulitis	Yes	<i>L. pneumophila</i>	Erythromycin	Yes (follicular lymphoma)	Resolved	[9]
6	73	F	Abscess	No	<i>L. cincinnatiensis</i>	Clarithromycin	Yes (immunoglobulin A gammopathy, lymphoma)	Resolved	[10]
7	9	F	Abscess	No	<i>L. micdadei</i>	Clarithromycin	No	Resolved	[11]
8	63	F	Bullae	Yes	<i>L. pneumophila</i>	Cefazolin, imipenem/cilastatin, tobramycin	No	Death	[12]
9	68	F	Nodule	No	<i>L. maceachernii</i>	Levofloxacin	Yes (treated with prednisone and methotrexate for polymyalgia rheumatica)	Lesions persisted	[13]
10	65	F	Cellulitis	Yes	<i>L. pneumophila</i> 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	<i>L. pneumophila</i> serogroup 5	Tigecycline, moxifloxacin	Yes (liver transplantation)	Improved	[15]
12	66	F	Cellulitis	No	<i>L. feeleii</i>	Amoxicillin-clavulanate, levofloxacin	Yes (chronic lymphocytic leukemia)	Unclear	[16]
13	27	F	Nodule	Yes	<i>L. pneumophila</i> serogroup 8	Azithromycin	Yes (pre-B - cell acute lymphoblastic leukemia)	Relapsing disease, death	[3]
14	72	M	Abscess	Yes	<i>L. pneumophila</i> serogroup 1	Levofloxacin	Yes (rectal adenocarcinoma with lung metastasis)	Resolved	[17]
15	70	F	Nodules	No	<i>L. longbeachae</i>	Ciprofloxacin, azithromycin, rifampin	Yes (long-term corticosteroids for immune thrombocytopenia)	Resolved	[18]
16	44	M	Diffuse erythema	Yes	<i>L. pneumophila</i> serogroup 1	Ceftriaxone, doxycycline, moxifloxacin	No	Resolved	[19]

Case	Age	Gender	Skin manifestation	Pulmonary infection	Microbiology	Treatment	Immuno-compromised	Infection outcome	Ref
17	23	F	Pustules	No	<i>L. feeleii</i>	Moxifloxacin	Yes (cardiac transplantation)	Resolved	[1]
18	3	M	Nodule	No	<i>L. anisa</i>	Levofloxacin	Yes (familial hemophagocytic lymphohistiocytosis)	Resolved	[20]
19	38	F	Panniculitis	No	<i>L. pneumophila</i>	Azithromycin, ciprofloxacin	Yes (treated with prednisolone and azathioprine for systemic lupus erythematosus and myasthenia gravis)	Improved	[21]
20	50	F	Nodule	Yes	<i>Legionella</i> subtype indeterminate	Trimethoprim-sulfamethoxazole, levofloxacin	Yes (acute myeloid leukemia)	Improved	-