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Atypical presentation of *Legionella* pneumonia among patients with underlying cancer: A fifteen-year review☆

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Summary

Background—Immunocompromised patients, especially those receiving treatment with corticosteroids and cytotoxic chemotherapy are at increased risk for developing *Legionella* pneumonia.

Objective—The aim of this study was to determine clinical and radiographic characteristics of pulmonary infection due to *Legionella* in persons undergoing treatment for cancer and stem cell transplant (SCT) recipients.

Methods—Retrospective review of *Legionella* cases at MSKCC over a fifteen-year study period from January 1999 and December 2013. Cases were identified by review of microbiology records.

Results—During the study period, 40 cases of *Legionella* infection were identified; nine among these were due to non-pneumophila species. Most cases occurred during the summer. The majority [8/9, (89%)] of patients with non-*pneumophila* infection had underlying hematologic malignancy, compared to 18/31 (58%) with *Legionella pneumophila* infections. Radiographic findings were varied-nodular infiltrates mimicking invasive fungal infection were seen only among patients with hematologic malignancy and hematopoietic stem cell transplant (SCT) recipients and were frequently associated with non-*pneumophila* infections (50% vs 16%; $P = 0.0594$). All cases of nodular *Legionella* pneumonia were found incidentally or had an indolent clinical course.

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Conflict of interest

No conflict of interest (for all authors).

Conclusions—*Legionella* should be considered in the differential diagnosis of nodular lung lesions in immunocompromised patients, especially those with hematologic malignancy and SCT recipients. Most cases of nodular disease due to *Legionella* are associated with non-*pneumophila* infections.

Keywords

Legionella; Cancer; Immunocompromised; Stem cell transplant

Introduction

Patients undergoing treatment with cytotoxic chemotherapy are known to be at a higher risk for developing *Legionella* pneumonia.[1,2] Although *Legionella pneumophila*, specifically serogroup 1, is the most commonly recognized species,[3] several non-*pneumophila* *Legionella* types can cause pulmonary infections in severely immunosuppressed patients.[4–6] The clinical and radiographic features of *Legionella* are mostly indistinguishable from other bacterial pneumonias with lobar consolidation described as the most common radiographic finding.[7] Isolated case reports of *Legionella* pulmonary infection with atypical radiographic presentation have previously been described among immunocompromised hosts.[8–11]

Evaluation of atypical pulmonary infiltrates in immunocompromised hosts, especially SCT recipients, is a frequently encountered problem in clinical practice that can pose a diagnostic and management dilemma for clinicians. Invasive diagnostic procedures such as flexible bronchoscopy and lung biopsies are often necessary to make a definitive diagnosis. While this is the favored approach, frequent occurrence of thrombocytopenia, coagulation abnormalities, and frail health status of patients can preclude the performance of these procedures. Recognizing the atypical presentation of common infections in specialized patient populations would be useful when few diagnostic options exist.

The aim of this study was to characterize the clinical and radiographic presentations of *Legionella* pneumonia among patients undergoing treatment for cancer and stem cell transplant recipients.

Methods

Retrospective review of all cases of *Legionella* pneumonia diagnosed at Memorial Sloan Kettering Cancer Center (MSKCC) over a fifteen-year period, from January 1, 1999 to December 31, 2013. MSKCC is a 471 bed tertiary care cancer center in New York City with 19,000 annual admissions and 122,000 patient-days. Cases were identified by review of microbiology records for results of *Legionella* urinary antigen via enzyme immunoassay tests (BinaxNOW® *Legionella*), lower respiratory tract bacterial cultures (sputum, bronchoalveolar lavage, lung tissue, and pleural effusion) and/or serological testing specific for *L. pneumophila* and non-*pneumophila* antibodies. Culture for *Legionella* species was routinely performed on all respiratory samples during the study years using Buffered charcoal yeast extract (BCYE) and BCYE selective (BCYE w/PAV) culture media while the urinary antigen and serology tests were only done on request from the ordering physician. Electronic medical records were reviewed to obtain information on demographic and clinical

characteristics, treatment, and outcomes. All radiographic findings at the time of diagnosis were reviewed and characterized by MSKCC radiologists. Additional review of all cases with nodular infiltrates was performed by MSKCC radiologist (A.P.).

Statistical analysis

Categorical variables were compared using the chi-square or Fisher's exact test. Continuous variables were compared using the Mann–Whitney–Wilcoxon rank-sum tests. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC). All reported *P* values are two-sided. A *P* value ≤0.05 was considered statistically significant.

The MSKCC Institutional Review Board waived the need for informed consent.

Results

During the fifteen-year study period, 40 cases of microbiologically confirmed *Legionella* pneumonia were identified at MSKCC. No *Legionella* outbreaks occurred during the study period, and none of the cases were hospital-acquired. *Legionella* infections showed a seasonal pattern with most cases (53%) diagnosed between July and September (Fig. 1).

Microbiologic characteristics

The causative organism for 31/40 (77.5%) cases was *L. pneumophila*; 9 cases were due to non-*pneumophila* species. The latter group included the following species – *Legionella micdadei* (4 cases); *Legionella jordanis* (2 cases); and one case each of *Legionella maceachernii* and *Legionella bozemanii*. A single case was identified based on serological titers for non-*pneumophila* (1:1024) and compatible clinical illness. Sputum cultures were obtained in this case but did not yield any growth. Majority of cases (8/9) due to *non-pneumophila* species occurred in patients with hematologic malignancy or SCT recipients.

Co-infection was diagnosed in a single case; *Aspergillus ustus* was isolated along with *L. pneumophila* on biopsy of lung nodule in a SCT recipient. In all other cases, *Legionella* species was the only infecting organism identified.

Radiographic features

The radiographic presentation of *Legionella* pneumonia varied among the cohort. Among the 40 cases, eight presented with solitary or multiple nodules; the remaining 32 cases displayed a mix of non-nodular lung abnormalities including lobar consolidation (20/32; 63%), ground glass opacities (5/32; 16%), and patchy infiltrates (4/32; 13%). Para pneumonic pleural effusions were identified in two cases.

When a nodule was present, it was either solid with a ground glass halo or cavitary with the exception of two cases that had solid and well circumscribed nodules without a ground glass halo or cavitation. 6 of 8 cases presented with one or 2 large nodules (Fig. 2). One case presented with numerous bilateral small nodules in a random distribution and the remaining case presented with focal ground glass opacity associated with micro nodules. Amongst all patients who exhibited nodular infiltrates on computed tomography of the chest, only 4 (50%) displayed nodular infiltrates on chest X-ray (Fig. 3).

Due to the atypical radiographic features encountered, we compared the clinical characteristics of the forty patients based on nodular vs non-nodular radiographic presentation of *Legionella* pneumonia.

Clinical characteristics based on radiographic features (nodular vs non-nodular *Legionella* pneumonia)

The comparison between nodular and non-nodular *Legionella* lung infections is summarized in Table 1. The etiologic agent associated with two distinct radiographic presentations varied. Half (4/8) of the patients with nodular infiltrates were infected with a non-pneumophila species, compared to only (5/32; 16%) of the patients in the other group ($P = 0.06$).

All eight patients with lung nodules had underlying hematologic malignancy (37%) or had undergone SCT (63%). The median time from transplant to infection was 163 days (range 63–334 days). FNA (fine needle aspiration) or open lung biopsy was performed in all cases; 5/8 showed abscesses, purulent inflammation or necrotizing pneumonia, granulomatous inflammation was seen in 2 cases; in one case the biopsy material was deemed to be non-diagnostic. Diagnosis was made by bacterial yield on culture from lung tissue in all but one case (positive urine antigen). Only two of the four cases of nodular *L. pneumophila* had a positive urine antigen result, the remaining two were tested and negative.

Among the non-nodular cases of *Legionella*, 44% had underlying solid tumors including lung, esophagus, breast, melanoma and glioblastoma. Seven patients in this group were SCT recipients (median time from transplant to infection: 153 days, range 72–374). A significant difference in neutrophil counts between the two groups was observed. None of the patients with nodular infiltrates were neutropenic at the time of diagnosis, whereas 9 patients (28%) in the other group had an ANC $<1000/mm^3$ ($P = 0.16$).

With regards to clinical presentation, patients with nodular infiltrates had minimal or no respiratory symptoms. Lung nodules were incidentally discovered on routine surveillance imaging in 5 (63%) patients. None of these five patients presented with respiratory or constitutional symptoms, other clinical features for this group is outlined in Table 2.

All 32 patients with non-nodular infiltrates had some degree of symptoms ($P < 0.001$). Overall, the most common symptoms were fever and cough. Other less frequently encountered symptoms included dyspnea, diarrhea, headache, and mental status changes.

The majority of patients in both groups received quinolones, macrolides were used less frequently. Eleven patients (27%) expired within one month of *Legionella* pneumonia diagnosis. No deaths were attributed to *Legionella* infection.

Discussion

It is well recognized that immunocompromised patients are at higher risk of developing infection due to *Legionella* and related complications.[12] Our report highlights the distinct radiographic presentation and associated clinical features of *Legionella* lung infection among a diverse group of immunocompromised patients undergoing treatment for various

types of cancer. Interestingly, the majority of cases with an atypical radiographic presentation of *Legionella* (nodular infiltrates) were associated with the more difficult to diagnose non-*pneumophila* species and had an indolent or asymptomatic clinical presentation. Although clinically milder, this finding is of particular relevance as all cases of nodular infection were encountered in highly immunocompromised patients undergoing treatment for hematologic malignancy or SCT recipients, and were radiographically indistinguishable from invasive fungal infection (IFI) and other opportunistic infections such as *Mycobacterium tuberculosis*, nontuberculous mycobacteria, *Nocardia* species etc (Fig. 2).

Our findings also suggest that infections associated with non-pneumophila *Legionella* affect mostly severely immunocompromised patients. In our study cohort, we found 9 cases of atypical *Legionella* infections, only one case of which occurred in a patient with lung cancer; the remaining patients had underlying hematologic malignancy or had undergone SCT.

Our study has other important findings. Despite consistent testing throughout the study years, we found that the majority of the cases occurred during the summer months (Fig. 1). This might reflect meteorological factors in the northeastern United States, such as increased temperature and humidity that leads to more utilization of cooling systems. [13] Although there are conflicting reports on seasonality of *Legionella* infections,[14] the Centers for Disease Control and Prevention (CDC) and reports from Europe have described seasonal patterns associated with *Legionella* with cases peaking during the summer and early fall.[15,16]

Our study has several limitations given its retrospective nature and small number of cases despite inclusion of all microbiologically confirmed cases over a fifteen-year period. Infection due to *Legionella*, especially non-*pneumophila* types, is likely an underdiagnosed infection in this population due to milder illness and limited clinical suspicion, non-availability of rapid and sensitive testing methods and poor yield on culture based methods. In addition, fluoroquinolones are widely used for neutropenic prophylaxis and empiric treatment of pneumonia, often obviating the need for additional diagnostic testing and decreasing culture yield.

In summary, *Legionella* infections especially due to non-*pneumophila* species present with several atypical characteristics including asymptomatic or mild clinical illness and radiographic features that are indistinguishable from other commonly encountered opportunistic infections. This clinical entity should be promptly recognized and considered in the differential diagnosis when evaluating lung nodules in persons with hematologic malignancies to facilitate early and specific diagnosis.

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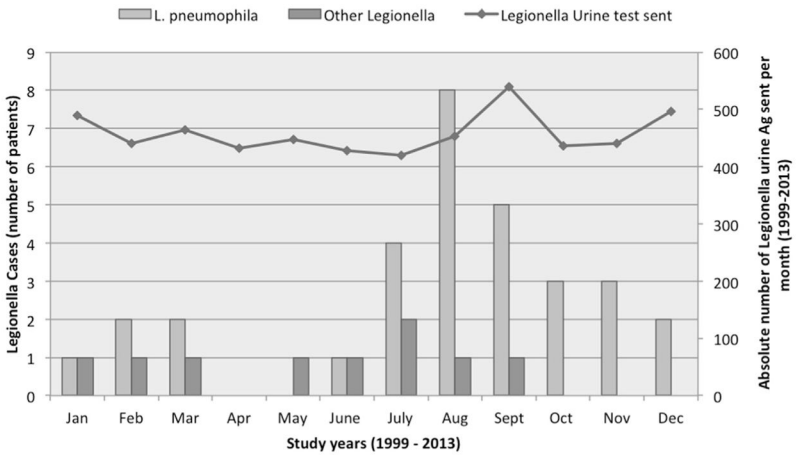

Figure 1.
Seasonal distribution of *Legionella* cases (by date of diagnosis) during the study period.

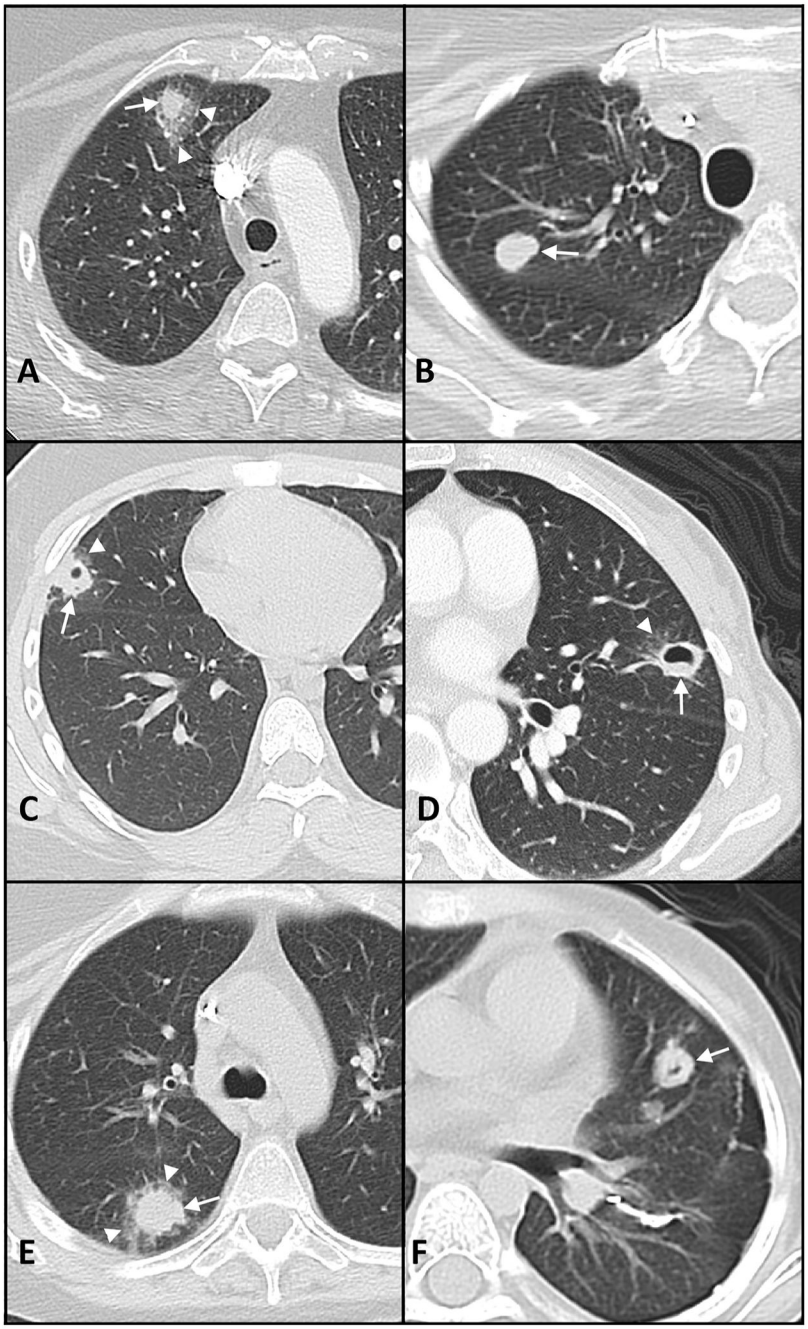

Figure 2.

Coned down axial CT images of *Legionella* lung infection showing nodular pattern. **A**: 70 year old female with a solid right upper lobe nodule (arrow) with a ground glass halo (arrow heads). **B**: 41 year old female with a solid well circumscribed nodule (arrow) in the right upper lobe. **C**: 17 year old male demonstrating a right middle lobe nodule (arrow) with central cavitation. In addition there is a surround ground glass halo (arrow head). **D**: 51 year old female with a lingular nodule (arrow) containing central cavitation and surrounding ground glass halo (arrow head). **E**: 35 year old female with a right lower lobe nodule (arrow)

and a surrounding ground glass halo (arrow heads). **F**: 7 year old female with a lingular nodule (arrow) containing central cavitation.

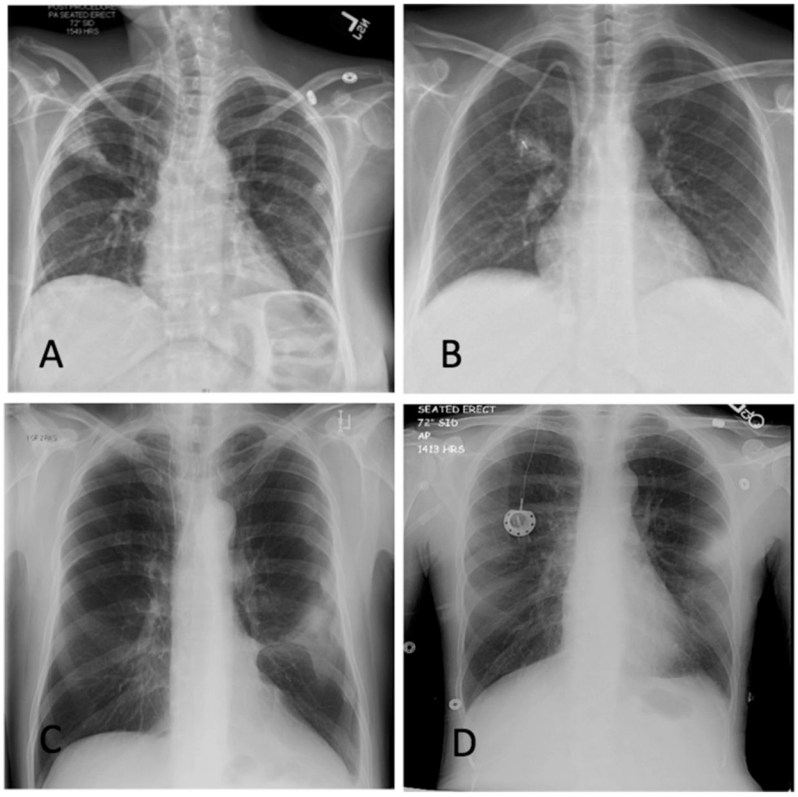

Figure 3.
Chest X-rays of patients with incidental discovery of nodular appearing *Legionella* lung infection.

Table 1

Univariate analysis comparing cases of nodular and non-nodular *Legionella* pneumonia among patients undergoing treatment for cancer at MSKCC from 1999 to 2013.

	Nodular *N* = 8 (%)	Non-nodular *N* = 32 (%)	*P* value
Demographics			
Age in years (mean and range)	44 (7–70)	57 (9–73)	0.17
Male	2 (25)	20 (62)	0.11
Underlying malignancy			0.03
Solid tumor	0 (0)	14 (44)	
Hematologic/SCT	8 (100)	18 (56)	
Neutropenia (ANC <1000/mm^3)	0 (0)	9 (28)	0.16
Legionella species			0.06
L. pneumophila	4 (50)	27 (84)	
Non-pneumophila	4 (50)	5 (16)	
Treatment			1
Quinolones	5 (62.5)	19 (60)	
Macrolides	3 (37.5)	10 (31)	
None	0	3 (9)	
Symptoms (any[a])			<0.001
Asymptomatic	4 (50)	0 (0)	
Symptomatic	4 (50)	32 (100)	
Previous steroid use (within 30 days)	2 (25)	5 (16)	0.61

SCT = stem cell transplant; ANC = absolute neutrophil count.

[a]Including fever, cough, dyspnea, diarrhea, lethargy, headache, and change in mental status.

Table 2

Characteristics of patients with asymptomatic lung nodules.

Patient	Age	Gender	*Legionella* type	Underlying cancer	SCT	Days post-transplant
#1	70	F	*L. micdadei*	Lymphoma	No	NA
#2	7	F	*L. pneumophila*	AML	Yes	231
#3	51	F	*L. pneumophila*	Lymphoma	Yes	91
#4	64	F	*L. micdadei*	Lymphoma	No	NA
#5	35	F	*L. pneumophila*	HLH	Yes	63

SCT = stem cell transplant; AML = acute myeloid leukemia; HLH = hemophagocytic lymphohistiocytosis.

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