ORIGINAL ARTICLE

The occurrence of antibodies against *Legionella pneumophila* in patients with autoimmune rheumatic diseases

Agnieszka Sikora[1], Arkadiusz Koszarny[2], Maria Kozioł-Montewka[1], Maria Majdan[2], Jolanta Paluch-Oleś[1], Małgorzata M. Kozioł[1]

1 Department of Medical Microbiology, Medical University of Lublin, Lublin, Poland
2 Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Lublin, Poland

KEY WORDS

antibodies, autoimmune rheumatic disease, *Legionella pneumophila*, risk factors

ABSTRACT

INTRODUCTION Patients with autoimmune rheumatic diseases are more susceptible to infection, owing to the underlying disease itself or to its treatment. Most commonly, infections affect the respiratory and urinary tracts. One of the etiological factors of infections in these patients is the bacteria of the genus *Legionella*.

OBJECTIVES The aim of the study was to assess the prevalence of anti-*Legionella pneumophila* (*L. pneumophila*) antibodies in patients with autoimmune rheumatic diseases and to analyze individual and environmental risk factors for the development of *Legionella* infection in patients with positive antibody results.

PATIENTS AND METHODS The study group consisted of 165 patients with autoimmune rheumatic diseases and 100 healthy subjects. Serum samples were tested for the presence of specific antibodies in the immunoglobulin (Ig) M and IgG classes against *L. pneumophila* serogroups 1 to 7 (SG 1–7) and the IgG class for serogroup 1 (SG 1).

RESULTS Antibodies against *L. pneumophila* were found in 7 patients (4%): 5 cases with antibody positivity only in the IgG class and 2 cases with antibody positivity in both classes. In patients with positive IgG antibodies for SG 1–7, specific antibodies for *L. pneumophila* SG 1 were not detected. In the control group, positive results were obtained in 9 cases (9%): IgM positivity in 6 (6%) and IgG positivity in 3 (3%).

CONCLUSIONS The frequency of antibodies to *L. pneumophila* in our patients is comparable to that in healthy individuals. *L. pneumophila* should be recognized as a potential pathogen in patients with autoimmune rheumatic diseases. Primary disease condition, immunosuppressive therapy, and other risk factors should not be ignored in these patients.

Correspondence to:
Agnieszka Sikora, PhD, Katedra i Zakład Mikrobiologii Lekarskiej, Uniwersytet Medyczny w Lublinie, ul. Chodźki 1, 20-093 Lublin, Poland, phone: +81 448 64 05, fax: +81 448 64 00, e-mail: agnieszka.sikora@umlub.pl
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INTRODUCTION Patients with autoimmune rheumatic diseases are at increased risk of systemic and generalized infections, which result in increased morbidity and mortality rates in this patient group. Most commonly, infections affect the upper and lower respiratory tract as well as the urinary tract. Patients with autoimmune rheumatic diseases are also susceptible to infections of the skin, soft tissues, and central nervous system.[1]

Infections in patients with autoimmune rheumatic diseases are related to immune defects associated with the disease (eg, impaired phagocytosis, defects of cellular immunity, and reduced CD4-cell counts, cytokine production, and immunoglobulin and complement levels) or are induced by therapy (eg, the use of immunosuppressive drugs, glucocorticosteroid, antitumor necrosis factor α [anti-TNF-α], or other biological agents).[1,2]

The most common etiological factors of infections are *Mycobacterium tuberculosis*, *Mycobacterium fortuitum*, *Salmonella* spp., *Listeria monocytogenes*, *Legionella* spp., *Coccidiodes immitis*, *Histoplasma capsulatum*, *Aspergillus* spp., *Nocardia* spp., and *Pneumocystis jiroveci*.[1,3] The bacteria of the genus *Legionella* may cause infections of mild, influenza-like syndrome known as Pontiac fever or severe pneumonia

(Legionnaires disease, pneumonic form of legionellosis). The infection occurs through the inhalation of aerosol or consumption of water contaminated with *Legionella pneumophila* (*L. pneumophila*).[4,5] *Legionella* is ubiquitous in water environments worldwide. The bacteria may colonize hot and cold water distribution systems, fountains, air-conditioning systems, cooling towers, nebulizers, and medical equipment containing water.[5]

L. pneumophila species are responsible for the majority of diagnosed cases of Legionnaires disease (about 80%–90%), including from 60% to 90% of the most virulent *L. pneumophila* belonging to serogroup (SG) 1. The serogroups other than *L. pneumophila* SG 1 are involved in about 20% to 30% of infections (mainly SG 4 and 6). Only from 10% to 20% of the infections are caused by species other than *L. pneumophila* ("*Legionella*-like").[4-6]

From 2009 to 2014, 98 cases of legionellosis were reported in Poland.[7] It should be emphasized that legionellosis is detected in Poland relatively rarely, but according to some experts, the disease is much more prevalent. This is due to the lack of studies investigating the etiological factors of pneumonia.

The virulence and number of microorganisms penetrating into the lungs, as well as the immune status of an individual exposed to contact with the pathogen, play a major role in the development of the infection.[5,8]

So far, there have been no studies in Poland investigating the prevalence of *Legionella* antibodies in patients with autoimmune rheumatic diseases. Therefore, the aim of the study was to assess the prevalence of anti-*L. pneumophila* antibodies in patients with autoimmune rheumatic diseases. Moreover, we analyzed the generally accepted risk factors (individual and environmental) for the development of clinical infection in patients with positive antibody results.

PATIENTS AND METHODS The study group consisted of 165 patients with autoimmune rheumatic disease (117 women [70.9%] and 48 men [29.1%], aged from 18 to 83 years [mean age, 49.3 ±14.7 years]), hospitalized at the Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Poland. The group included 79 patients with rheumatoid arthritis (47.9%); 19, with spondyloarthropathy (11.5%); 12, with systemic lupus erythematosus (7.3%); and 37, with other recognized autoimmune rheumatic disease (22.4%, including 6 patients with systemic sclerosis; 2, with Sjögren syndrome; 6, with psoriatic arthritis; 8, with other types of arthritis; 2, with polymyositis; 8, with vasculitis; 1, with mixed connective tissue disease; and 4, with undifferentiated connective tissue disease). There were 18 patients (10.9%) with suspected autoimmune rheumatic disease without the final diagnosis at the time of hospitalization.

The control group consisted of 100 healthy volunteers (72 women [72%] and 28 men [28%], aged from 17 to 74 years [mean age, 36.6 ± 15.2 years]).

Serum samples were used to assess the prevalence of antibodies against *L. pneumophila*. The serum was obtained from 5 ml of venous blood collected into tubes containing no anticoagulant (MEDLAB-PRODUCTS, Raszyn, Poland). The blood was centrifuged for 10 minutes at 1500 revolutions/minute. Then, 500 μl of the serum was collected into sterile plastic Eppendorf Safe-Lock tubes (Meranco, Poznań, Poland) and stored at –70°C until further testing.

Immunoglobulin (Ig) M and IgG anti-*L. pneumophila* serogroups for SG 1–7 were identified by an enzyme-linked immunosorbent assay (ELISA), using commercially available kits (EUROIMMUN, Lübeck, Germany): ELISA IgM SG 1–7 against *L. pneumophila* and ELISA IgG SG 1–7 against *L. pneumophila*. The diagnostic antigen in these kits is specific for *L. pneumophila* SG 1–7 lipopolysaccharide (SG 1, Philadelphia-1; SG 2, Togus-1; SG 3, Blommington-2; SG 4, Los Angeles-1; SG 5, Dallas 1E; SG 6, Chicago 2; SG 7, Chicago 8). IgG antibodies against *L. pneumophila* SG 1–7 were tested in all patients with autoimmune rheumatic diseases, while IgM antibodies were tested in all patients who were positive for IgG (SG 1–7).

In order to specify the factor inducing a humoral immune response in patients with positive antibody results for IgG class SG 1–7, antibodies for the most pathogenic serogroup (SG 1) *L. pneumophila* were marked using a commercially available ELISA kit, anti-*L. pneumophila* SG 1 ELISA IgG (VIRCELL$_{\text{MICROBIOLOGISTS}}$, Granada, Spain). All tests were performed according to the manufacturers' instructions. The absorbance measurement of each well of the 96-well microplates was performed using Multiscan RC Labsystem (Helsinki, Finland). The test protocols were prepared using the Genesis program, version 3.03.

The potential risk factors for *L. pneumophila* infection were analyzed in patients with positive results. Patients were interviewed using a questionnaire. The risk factors were divided into 2 groups: individual and environmental. The first group included cigarette smoking, alcohol abuse, chronic obstructive pulmonary disease, diabetes, cancer, immunosuppressive therapy, and steroid therapy. The second group included a visit to the dentist, sanatorium treatment, travel, and the use of jacuzzi, water massage, inhalation, or air conditioning within the 2 months preceding the study.

Patients with autoimmune rheumatic diseases and the control group with positive results for antibodies against *L. pneumophila* had no history of *Legionella* spp. infection or infection of any other etiology in the 2 months preceding the study.

Data were presented as means ± standard deviations and analyzed using the χ^2 test. A P value of less than 0.05 was considered statistically significant. A statistical analysis was performed using STATISTICA version 9.0 (StatSoft, Inc., Kraków, Poland).

TABLE 1 Indicators of inflammation in patients positive for *Legionella pneumophila* antibodies

Patient	Clinical diagnosis	CRP, mg/l (0–10)	ESR, mm/h (0–15)	WBC $10^3/\mu l$ (4.8–10.8)	Neutrophils, % (45–70)	Eosinophils, % (0–5)	Basophils, % (0–1.5)	Ferritin, ng/ml (22–322)
1	polymyositis	47.11	41	17.28	93.1	0.5	0.1	not done
2	systemic lupus erythematosus	0.31	21	5.1	43.8	0.3	0.7	136
3	inflammatory spondyloarthropathies	9.33	33	8.05	72.4	1	0.6	not done
4	rheumatoid arthritis	11.68	25	10.52	83	0.4	0.2	not done
5	rheumatoid arthritis	18.79	46	5.11	50.9	2.5	0.6	not done
6	rheumatoid arthritis	4.8	16	4.69	49.6	1.3	0.1	12
7	undifferentiated systemic connective tissue disease	0.1	8	3.86	59.6	4.6	0.3	not done

Reference ranges for inflammatory markers are given in brackets.

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cells

RESULTS In patients with autoimmune rheumatic disease, positive results for antibodies (IgM or IgG or both) against *L. pneumophila* SG 1–7 were obtained in 7 patients (4%), and borderline results—in 18 patients (11%). IgM and IgG antibodies against *L. pneumophila* SG 1–7 were found in 2 patients (1%). IgG antibodies were found in 5 patients (3%). In patients with positive IgG antibodies for *L. pneumophila* SG 1–7, specific antibodies against *L. pneumophila* SG 1 were not detected. Among patients with positive results, 3 had rheumatoid arthritis; 1, spondyloarthropathy; 1, systemic lupus erythematosus; 1, polymyositis; and 1, undifferentiated systemic connective tissue disease. The indicators of inflammation in patients with positive *L. pneumophila* antibodies are shown in TABLE 1.

In all patients with positive antibody results, the potential individual and environmental risk factors for *Legionella* infection were found. Individual risk factors were as follows: immunosuppressive therapy in 5 patients, glucocorticosteroid therapy in 5, diabetes in 1, chronic obstructive pulmonary disease in 1, and cigarette smoking in 1. Environmental factors were as follows: a history of sanatorium treatment in 2 patients, a visit to the dentist in 1, and the use of inhalers in 1 (TABLE 2). In the control group, positive results were obtained in 9 cases (9%): IgM antibodies were detected in 6 (6%), and IgG—in 3 (3%). The borderline results were obtained in 17 cases (17%): IgM in 4 (4%), and IgG—in 13 (13%). The antibodies against *L. pneumophila* SG 1 were not detected in the control group with positive antibody results for *L. pneumophila* SG 1–7. The results of the study and control groups are presented in TABLE 3. The prevalence of IgG antibodies against *L. pneumophila* SG 1–7 in patients with autoimmune rheumatic diseases was comparable to that in the control group (4.2% vs 3%; $P = 0.45$).

DISCUSSION Patients with autoimmune rheumatic diseases are at higher risk of *Legionella* infection because the key mechanisms involved in the immune response to this infection are impaired. This impairment is caused by an underlying disease, comorbidities, and the use of immunosuppressants (including anti-TNF-α).[1]

The bacteria of the genus *Legionella* are intracellular pathogens. A host immune response to these pathogens is significantly different than that directed against extracellular pathogens, and depends on the cell-type-specific response. A minor role is attributed to the humoral response because of the ability of *Legionella* to proliferate inside macrophages, which makes the bacteria resistant to the neutralizing effect of antibodies. Cytotoxic T lymphocytes and TNF-α, interferon γ, interleukin (IL) 1, IL-6, and IL-12 play the key role in cellular response.[6]

The risk of *Legionella* infection in patients with autoimmune rheumatic diseases is also largely determined by environmental factors, which are difficult to avoid owing to the chronic character of the disease, and, what follows, frequent hospitalizations, use of nonpharmacological treatment (such as physical therapy), or stays in sanatoria.[5]

Most of the literature data indicate that *Legionella* infections in immunocompromised patients are characterized by severe clinical course and high mortality rates of up to 30%.[8] Therefore, in all cases of severe pneumonia, especially those with the presence of risk factors, *Legionella* etiology must be considered when choosing an antibiotic therapy. Empirical treatment of pneumonia in patients with autoimmune rheumatic diseases should always include an antibiotic/chemotherapeutic agent with activity against *Legionella* spp. Currently, in the treatment of *Legionella* infections, the use of newer macrolides (azithromycin, clarithromycin), fluoroquinolones

TABLE 2 Diseases and risk factors of infection in patients positive for *Legionella pneumophila* antibodies

Patient	Clinical diagnosis	Anti-*L. pneumophila* antibodies SG 1–7	Age, y	Immunosuppressive therapy	Steroid therapy	Other risk factors
1	polymyositis	IgM(+), IgG(+)	24	azathioprine, cyclophosphamide, immunoglobulin	high-dose methylprednisolone IV, prednisone PO	type 1 diabetes, multiple hospitalizations
2	systemic lupus erythematosus	IgM (–), IgG(+)	37	azathioprine, chloroquine	high-dose methylprednisolone IV, methylprednisolone PO	multiple hospitalizations, visit to the dentist
3	inflammatory spondyloarthropathies	IgM(–), IgG(+)	35	–	–	–
4	rheumatoid arthritis	IgM(–), IgG(+)	63	methotrexate	prednisone PO	chronic obstructive pulmonary disease, cigarette smoking, multiple hospitalizations, previous sanatorium treatment, use of inhaled
5	rheumatoid arthritis	IgM(–), IgG(+)	55	methotrexate, cyclosporine, chloroquine	prednisone PO	multiple hospitalizations, previous sanatorium treatment
6	rheumatoid arthritis	IgM(–), IgG(+)	47	methotrexate, cyclophosphamide, azathioprine, chloroquine	prednisone PO	–
7	undifferentiated systemic connective tissue disease	IgM(+), IgG(+)	43	–	–	–

Abbreviations: IV, intravenous; PO, per os; (+), positive results; (–), negative results

TABLE 3 Percentage and number of positive, borderline, and negative results for IgM and IgG antibodies against *Legionella pneumophila* SG 1–7

Study groups	N	IgM *L. pneumophila* SG 1–7						IgG *L. pneumophila* SG 1–7					
		+		±		–		+		±		–	
		n	%	n	%	n	%	n	%	n	%	n	%
patients with autoimmune rheumatic diseases	165	2	1.2	4	2.4	159	96.3	7	4.2	14	8.4	144	87.2
control group	100	6	6	4	4	90	90	3	3	13	13	84	84

+, positive results; ±, borderline results; –, negative results; n, number of studies, %, percentage of studies

(ciprofloxacin), and rifampicin in combination therapy is required.[9]

So far, there have been no studies investigating the exposure of patients with autoimmune rheumatic diseases to *Legionella* by measuring the levels of specific antibodies. According to the PubMed database, there have been reports of *Legionella* cases in patients with various rheumatic diseases who were treated with anti-TNF-α.[10-16]

In our study, in patients with autoimmune rheumatic diseases, positive results of IgM or IgG anti-*L. pneumophila* SG 1–7 were obtained in 7 patients (4%). Two patients had both classes of antibodies (IgM and IgG). We did not observe specific antibodies for the most virulent anti-*L. pneumophila* SG 1 in any of the study participants. In patients with positive results, there was no history of influenza-like symptoms or pneumonia, indicating the presence of immune response to *Legionella*. The frequency of antibodies against *L. pneumophila* in our patients was comparable to that in healthy individuals, but the results might have been biased by the selection of the study population and methods.

A number of studies have shown that the administration of glucocorticoids or immunomodulatory drugs increases the risk of infection in patients with autoimmune rheumatic diseases. It should be emphasized that the risk of infection increases with an increase in the dose and duration of treatment.[17,18] Moreover, the host's underlying disease state, which influences the dose and duration of treatment, largely determines variability in the risk of infection in clinical practice.[19]

In our study, 5 of 7 patients positive for antibodies against *L. pneumophila* were treated with glucocorticoids. The fact that a single patient with antibodies had received glucocorticoids is not sufficient for risk calculation.

In contrast to the reports suggesting the association of anti-TNF-α therapy with *Legionella*,[10-16] patients with positive results in our study were not treated with anti-TNF-α. A study conducted by Tubach et al[11] showed that the relative risk of Legionnaires disease in patients receiving anti-TNF-α therapy was between 16.5 and 21 compared with the overall population.

In conclusion, the frequency of antibodies against *L. pneumophila* in our patients is comparable to that in healthy individuals, but the *L. pneumophila* should be recognized as a potential pathogen. A positive test result indicates that *Legionella* occur in the environment. This also confirms the existing infection hazard. Primary disease condition, immunosuppressive therapy, and other risk factors should not be ignored even if patients are asymptomatic. Although the incidence of *Legionella* infection is low, its early detection and treatment in patients at risk are clinically important because of high mortality rates.

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ARTYKUŁ ORYGINALNY

Występowanie przeciwciał przeciw *Legionella pneumophila* u pacjentów z autoimmunizacyjnymi chorobami reumatycznymi

Agnieszka Sikora[1], Arkadiusz Koszarny[2], Maria Kozioł-Montewka[1], Maria Majdan[2], Jolanta Paluch-Oleś[1], Małgorzata M. Kozioł[1]

1 Katedra i Zakład Mikrobiologii Lekarskiej, Uniwersytet Medyczny w Lublinie, Lublin
2 Katedra i Klinika Reumatologii i Układowych Chorób Tkanki Łącznej, Uniwersytet Medyczny w Lublinie, Lublin

SŁOWA KLUCZOWE

autoimmunizacyjne choroby reumatyczne, czynniki ryzyka, *Legionella pneumophila*, przeciwciała

STRESZCZENIE

WPROWADZENIE Pacjenci z autoimmunizacyjnymi chorobami reumatycznymi są bardziej podatni na zakażenia, co wynika z choroby podstawowej lub zastosowanego leczenia. Infekcje najczęściej dotyczą dróg oddechowych oraz układu moczowego. Jednym z czynników etiologicznych zakażeń u tych pacjentów są bakterie z rodzaju *Legionella*.

CELE Celem pracy była ocena częstości występowania przeciwciał anty-*Legionella pneumophila* (*L. pneumophila*) u chorych na autoimmunizacyjne choroby reumatyczne oraz analiza osobniczych i środowiskowych czynników ryzyka zakażenia *Legionella* u pacjentów z dodatnimi wynikami.

PACJENCI I METODY Grupę badaną stanowiło 165 pacjentów z autoimmunizacyjnymi chorobami reumatycznymi oraz 100 osób zdrowych. W surowicy oznaczono obecność swoistych przeciwciał w klasie immunoglobulin (Ig)-M i IgG anty-*L. pneumophila* dla serogrup od 1 do 7 (SG 1–7) oraz klasy IgG dla serogrupy 1 (SG 1) metodą immunoenzymatyczną.

WYNIKI Przeciwciała przeciw *L. pneumophila* stwierdzono u 7 pacjentów (4%): u 5 badanych wykryto tylko jedną klasę przeciwciał – IgG, natomiast u 2 badanych wykryto jednocześnie obie klasy przeciwciał. U pacjentów z dodatnimi wynikami przeciwciał w klasie IgG dla SG 1–7 nie stwierdzono obecności swoistych przeciwciał dla SG 1 *L. pneumophila*. W grupie kontrolnej pozytywne wyniki uzyskano u 9 (9%) osób – przeciwciała IgM wykryto u 6 (6%), a IgG u 3 (3%).

WNIOSKI Częstość występowania przeciwciał przeciwko *L. pneumophila* u naszych pacjentów jest porównywalna z ich występowaniem u osób zdrowych. *L. pneumophila* powinna być brana pod uwagę jako potencjalny patogen u pacjentów z autoimmunizacyjnymi chorobami reumatycznymi. Choroba podstawowa, leczenie immunosupresyjne oraz inne czynniki ryzyka nie powinny być lekceważone w tej grupie pacjentów.

Adres do korespondencji:
dr n. med. Agnieszka Sikora, Katedra i Zakład Mikrobiologii Lekarskiej, Uniwersytet Medyczny w Lublinie, ul. Chodźki 1, 20-093 Lublin, tel.: 81 448 64 05, fax: 81 448 64 00, e-mail: agnieszka.sikora@umlub.pl
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