Case report of arthritis caused by *Legionella anisa* and review of the literature

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**Abstract**

**Background**: *Legionella* spp. is recognized as a common cause of community acquired pneumonia, with *Legionella pneumophila* serogroup 1 being the most prevalent. At least 70 species are described so far but few are identified in pathogenic conditions. Data on extrapulmonary infections are scarce.

**Case presentation**: A 73-year-old male with chronic lymphoid leukemia was hospitalized for an insidious wrist arthritis. Ultrasound of the wrist showed a carpal and radiocarpal fluid effusion with positive Doppler signal. While routine bacterial cultures remained sterile, 16S rRNA PCR identified *Legionella anisa*. Ciprofloxacin 500 mg twice a day for a period of six weeks improved arthritis with full recovery at the end of the treatment.

**Conclusion**: *Legionella non pneumophila* are a rare cause of septic arthritis especially found in immunosuppressed patients and identification of species could help clinician to adapt antibiotherapy.

**Keywords**: Arthritis, *Legionella non pneumophila*, Case report
ribosomal RNA (rRNA) polymerase chain reaction (PCR) identified *Legionella anisa* at day 4. The manufacturer of the equipment was Diagenode. Blood cultures were sterile.

Ciprofloxacin 500 mg twice a day for a period of six weeks improved arthritis with full recovery at the end of the treatment. Interestingly, C-reactive protein showed spontaneous normalization before any treatment.

The source of infection was presumably gardening. The patient had a well in his garden. Chest X-ray was normal. No environmental exploration was performed according to the national reference center guidelines.

**Discussion and conclusion**

*Legionella* spp. are ubiquitous, aerobic, gram-negative rods naturally found in freshwater environments and are usually transmitted to humans in aerosols. They are regarded as fastidious bacteria as they do not grow on routine bacteriologic media. The clinical manifestations of *Legionella* infections are primarily respiratory (Legionnaires’ disease), but several extrapulmonary infections has been described. *Legionella* spp has been implicated in arthritis, meningitis, sinusitis, endocarditis, pericarditis, myocarditis, pancreatitis, peritonitis and soft tissue infections [2].

While *L. pneumophila* is responsible to the vast majority of human infections, data on *L. anisa* pathogenicity are scarce. Despite being one of the most frequent species of *Legionella* in the environment, only eight articles reported infections secondary to *L. anisa* [3–10] (Table 1). In a French study, this strain was the most frequent non-pneumophila species in the environment (13.8%), but only accounted for 0.8% of the clinical isolates [11]. It has been responsible of hospital water system contamination, as well as nosocomial infections. Besides, there are concerns that *L. anisa* could mask *L. pneumophila* water contamination [12]. Clinical manifestations described are mainly respiratory with eight reported pneumonia (seven immunocompromised (IC) patients) [8, 9] and 34 Pontiac fever during an outbreak in California [10]. Other manifestations included one pleural infection with probable pneumonia (IC) [5], one osteomyelitis secondary to pneumonia (IC) [4], one chronic endocarditis [6] and one mycotic aortic aneurysm [3] in both immunocompetent patients.

Immunologic response to *Legionella* infection is complex. *L. pneumophila* activates an important inflammatory response in hosts, with innate and adaptive responses. IFN-γ and TNFα are primarily responsible for immune clearance while CD4+ and CD8+ T cells additionally contribute to host defense [13]. Humoral response is considered feeble and does not provide prolonged immunity against the pathogen.

Arthritis caused by *Legionella* spp are rare, with only twelve cases previously described (Table 2). Seven were immunocompromised and two had kidney insufficiency (one moderate and one presumably non-severe given the arthritis antibiotic management). Median age at diagnosis was 71, range (51–90). Inoculation occurred most frequently through skin wound which are nonetheless rarely found at diagnosis. Some reports mentioned potential inoculation through corticosteroid injections [14–16]. However, acute arthritis following such injection could be unrecognized *legionella* infection potentiated by the induced local immunosuppression. Final, reactive arthritis has been a concern in one article and present with positive 16S RNA PCR with inflammatory fluid [17].

The patients often presented few symptoms amid localized pain. Fever is rarely described (two cases with polyarthritis) [18, 19]. Delayed diagnosis is frequent with a median of 21 days, range (2–90). Polyarthritis seems to be a concern of *L. pneumophila* serogroup 1 (Lp1).
Non-pneumophila strains are more frequently isolated in monoarthritis which is consistent with the direct mode of transmission [20]. Blood samples usually showed increase C-reactive protein, median 147 mg/L, range (5–254 mg/L). Fluid aspirate was hemorrhagic in two cases [20, 21], as our patient, with median neutrophil count of 80%, range (23–90).

Patients with significant immunosuppression (no isolated humoral deficiency as discussed previously) were older (median 80 vs 56 years) and had longer delayed diagnosis (median 32 vs 16 days).

Diagnosis was performed by 16S RNA PCR in each case except three. The other means of diagnosis were urinary antigen test for Lp1, serology, NGS and cultures. Legionella spp. require non-routine culture media for growth, especially BCYE. Successful cultures with chocolate agar and mycobacteria specific medium have been reported [22, 23]. Microbiologist must be aware of Legionella suspicion to perform such culture, which may lead to under-recognize diagnosis. Wide spreading of PCR might fill this gap. MALDI-TOF can be helpful for species identification [24].

There is no standard for antimicrobial therapy. Treatment consisted of fluoroquinolones in the majority of cases (9/11). Five patients had combination therapy (four rifampicin, one azithromycin). Data was missing in one patient. Median duration of antibiotic therapy for native septic arthritis was 42 days, range (21–90). One patient with knee prosthesis infection and was successfully treated with levofloxacin and rifampicin for five months. All strategies were effective.

We present the first case of septic arthritis caused by L. anisa. Legionella spp. should be suspected in arthritis, especially involving extremities and knee, with sterile standard culture, insidious evolution and compatible exposition. Concomitant pneumonia is uncommon but immunosuppression is not. Older age is probably a risk factor for Legionella arthritis.

| Reference | Cases (n) | Sex | Age | Medical history | Significant IS | Presumed route of infection | Presentation | Diagnosis methods | Treatment |
|-----------|-----------|-----|-----|-----------------|----------------|----------------------------|--------------|--------------------|-----------|
| Tanabe et al. [3] | 1 | M | 79 | Y-graft replacement for an abdominal aortic aneurysm (3 years ago) | No | Unknown | Mycotic Aortic Aneurysm | PCR | LNZ, PFX 21d followed by LFX, CTM |
| Sanchez et al. [4] | 1 | M | 51 | Stage IV angioimmunoblastic T-cell lymphoma | Yes | Pneumonia (two months before) | Osteomyelitis of the patella | PCR, culture | MFX 56d |
| Bornstein et al. [5] | 1 | M | 32 | Lymph node carcinoma | Yes | Nosocomial pneumonia | Pleural infection | Culture | Deceased |
| Compain et al. [6] | 1 | F | 58 | Type 2 diabetes mellitus and grade II obesity | No | Unknown | Chronic endocarditis | PCR | LFX 21d |
| Thacker et al. [7] | 1 | F | 65 | Type 2 diabetes mellitus | No | Pneumonia | Pneumonia | Culture | ERM |
| Vaccaro et al. [8] | 1 | F | 36 | – | No | Pneumonia | Pneumonia | PCR | LFX, CFX 10d |
| Head et al. [9] | 6 | 3F, 3 M | 31a | VHI (tuberculosis or pneumocystosis co-infections) | Yes | Pneumonia | Pneumonia | PCR, culture | NA |
| Fenstersheib et al. [10] | 34 | NA | NA | NA | NA | Pneumonia | Pontiac fever | Serology | 0 |
| Current case | 1 | M | 73 | CLL | No | Direct inoculation | Arthritis | PCR | CPX 42d |

F female, M male, IS immunosuppression, LNZ Linezolid, PFX Pazufloxacin, LFX Leflofoxacin, CTM Clarythromycin, MFX Moxifloxacin, ERM Erythromycin, CFX Cefixime, CPX Ciprofloxacin, NA not available

a Median
Table 2  Characteristics of the case reports of Legionella arthritis, including the current case

| Reference        | Sex | Age | Medical history | Significant IS | Joint(s) | Delay before diagnosis (days) | Strain          | Diagnosis methods | Treatment          |
|------------------|-----|-----|-----------------|----------------|---------|-------------------------------|----------------|------------------|-------------------|
| Dugar et al. [19]| M   | 56  | RA, diabetes (CS, MTX) | Yes            | L foot | 2                             | L. longbeachae | Culture          | AZM, MFX 42d     |
| Just et al. [24] | F   | 71  | Dermatomyositis (CS, MTX) | Yes           | L knee | 16                            | L. bozemanii   | PCR, culture, serology | CPX 21d          |
| Fernández-Cruz et al. [16] | F   | 83  | RA (CS, MTX) | Yes           | R knee | 16                            | L. micdadei    | PCR, culture     | LFX, RFP 150d    |
| Flendrie et al. [15] | F   | 58  | SLE like disease (CS, MTX) | Yes          | R knee | 16                            | L. dumoffii     | PCR, culture     | CPX, RFP 90d     |
| Huang et al. [21] | M   | 54  | SLE (CS) | Yes           | R MCP joints | 16 | L. micdadei | PCR, NGS, culture | LFX 60d          |
| Ibranosyan et al. [20] | F   | 56  | Anti-synthetase syndrome (CS, MTX, TCZ) | Yes | L wrist | 16 | L. bozemanii | PCR, culture | LFX, RFP 90d    |
| Bemer et al. [22] | M   | 51  | Thymoma (chemotherapy one year before) | Yes | R wrist and ankle, knees | 30 | L. pneumophila S1 | UAT, culture, serology | OFX, RFP 21d |
| Naito et al. [18] | F   | 80  | Kidney disease | No            | Ankles | 14 | L. pneumophila S1 | UAT, PCR | CPX         |
| Thurneysen and Boggian [25] | M   | 70  | Thymoma—hypogammaglobulinemia | No | R knee, L ankle | 16 | L. pneumophila S1 | PCR, culture | CPX 90d       |
| Linscott et al. [23] | F   | 80  | None | No            | R MCP joints | 90 | L. pneumophila S4 | Culture, serology | Surgery       |
| Bandet et al. [14] | F   | 90  | Grade 3A kidney diseasea | No | L wrist | 21 | L. cincinnatiensis | PCR, culture | AZM 21d       |
| Current case     | M   | 73  | CLL | No            | R wrist | 42 | L. anisa | PCR | CPX 42d     |

a According to KDIGO

Abbreviations
NSAIDs: Non-steroidal anti-inflammatory drugs; RNA: Ribonucleic acid; PCR: Polymerase chain reaction; NGS: Next generation sequencing; BCYE: Buffered charcoal yeast extract; MALDI–TOF: Matrix assisted laser desorption ionisation/time of flight; F: Female; M: Male; LNZ: Linezolid; PFX: Pazufloxacin; LFX: Levofloxacin; CFX: Cefixime; CPX: Ciprofloxacin; LCF: Lefloxacin; CTM: Clarithromycin; MFX: Moxifloxacin; FRM: Erythromycin; CS: Corticosteroids; MTX: Methotrexate; TCZ: Tocilizumab; UAT: Urinary antigen test; AZM: Azithromycin, CPX ciprofloxacin, LFX levofloxacin, RFP rifampicin, MFX moxifloxacin

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Author contributions
EM and MR participated to conception of the work; acquisition, analysis, and interpretation of data, drafted the work and substantively revised it. EM and MR to have approved the submitted version (and any substantially modified version that involves the author’s contribution to the study); EM and MR agreed both to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. All authors read and approved the final manuscript.

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Consent for publication
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Competing interests
None.

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