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Bilateral Knee Septic Arthritis Associated with *Mycoplasma pulmonis* Following Intra-Articular Umbilical Cord-Derived Stem Cell Injection: A Case Report

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Abstract

Background: Stem cell therapy has emerged as a potential treatment for knee osteoarthritis. Infective complications arising from stem cell therapy are uncommon. We report an unusual case of bilateral knee septic arthritis following intra-articular umbilical cord-derived stem cell injections. Case Presentation: A 78-year-old man with a history of degenerative knee disease presented with acute arthritis of both knees after receiving intra-articular umbilical cord-derived stem cell injections into both knees. *Mycoplasma pulmonis*, a murine pathogen, was identified in bilateral knee effusion and granulation tissue. He improved with arthroscopic debridement and combination antibiotic therapy. Conclusion: *Mycoplasma pulmonis* infection involving sterile sites in humans has never been reported. Although a definitive causal relationship between *Mycoplasma pulmonis* and septic arthritis cannot be established from a single case, this report highlights the need for rigorous quality control in stem cell product preparation and the potential for serious complications associated with novel therapies. Further study of the pathogenic role of *M. pulmonis* in humans is warranted.

Keywords

Mycoplasma pulmonis, Septic Arthritis, Intra-Articular Stem Cell Injection

1. Introduction

Knee osteoarthritis is a leading cause of pain and disability in older adults, and its

prevalence is rising with population aging and increasing obesity. Standard management includes analgesia, physical therapy, intra-articular injections, and joint replacement for advanced disease, but many patients seek alternative or adjunctive options. Intra-articular stem cell injections have emerged as a potential therapy for knee osteoarthritis, yet their rapid clinical adoption has outpaced standardized regulation and manufacturing oversight. Most reported adverse events after intra-articular stem cell injections are mild and transient, typically post-injection pain and swelling, and serious infectious complications are considered rare [1]. Mycoplasma species are fastidious organisms, well-known as cell culture contaminants. *Mycoplasma pulmonis* is a common respiratory and genital tract pathogen of laboratory and wild rats and an important biosecurity issue in animal facilities, but it has not been clearly established as a cause of invasive human disease [2]-[6]. We report the first human case of bilateral knee septic arthritis associated with *M. pulmonis*, detected by targeted 16S rRNA sequencing, following intra-articular umbilical cord-derived stem cell injections. This case highlights the diagnostic utility of next generation sequencing in culture-negative septic arthritis and emphasizes the need for stringent sterility assurance and regulatory control in stem cell-based therapies.

2. Case Presentation

A 78-year-old man with a history of degenerative knee disease presented to our hospital with 4 weeks of progressively worsening bilateral knee pain and swelling after receiving intra-articular umbilical cord-derived stem cell injections into both knees at an overseas health care facility on October 22, 2024. Information regarding the origin, preparation, and storage of the stem cells was unavailable. Eight days post-injection, the patient reported new-onset worsening bilateral knee pain, accompanied by warmth, swelling, and difficulty in weight-bearing. He had been taking regular non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief before presentation. He remained afebrile throughout and had no systemic symptoms. The patient is a retired businessman and had no recent rodent or other animal exposure. He had not taken any antibiotics prior to presentation. He was admitted to our hospital, a 480-bed tertiary medical centre in Hong Kong, on November 27, 2024, for evaluation and management of suspected septic arthritis.

Initial blood tests showed a normal white cell count, mild anaemia, markedly elevated inflammatory markers, and acute kidney injury that was likely NSAID-induced: WBC 6.11 × 10^9/L (reference: 4 - 11 × 10^9/L), haemoglobin 11.6 g/dL (13 - 17 g/dL), platelets 284 × 10^9/L (150 - 400 × 10^9/L), creatinine 274 μmol/L (62 - 106 μmol/L), urea 21 mmol/L (2.8 - 8.1 mmol/L), potassium 5.3 mmol/L (3.2 - 4.8 mmol/L), sodium 136 mmol/L (134 - 148 mmol/L), bicarbonate 20 mmol/L (24 - 31 mmol/L), ESR 103 mm/h (0 - 20 mm/h), CRP 190 mg/L (<5 mg/L), procalcitonin 0.13 ng/mL, and uric acid 0.45 mmol/L (0.2 - 0.42 mmol/L). Non-contrast MRI of both knees revealed moderate complex effusions with irregular synovial thickening. Bilateral degenerative changes included marginal osteophytes, carti-

lage thinning, and subchondral marrow oedema. Degenerative tears were observed in the menisci and cruciate ligaments.

Bilateral knee arthrocentesis performed on November 27, 2024 (day 36 post stem cell injection) revealed a small to moderate number of white blood cells in the joint fluid. Gram and acid-fast bacilli (AFB) stains were negative; bacterial, fungal, and TB cultures, as well as TB PCR, were also negative. Bilateral knee arthroscopic debridement was performed on November 28, 2024 (day 37 post stem cell injection). Intraoperatively, a large amount of mucinous granulation tissue was observed in both knees, along with degenerative changes consistent with the MRI findings. The joint fluid and granulation tissue samples underwent the same microbiological workup as before, with no organisms identified. Histological examination of the bilateral knee granulation tissue revealed fibrogranulation tissue with lymphocytic, histiocytic, and neutrophilic infiltrates, but no granulomas. Gram, Grocott's methenamine silver (GMS), periodic acid-Schiff (PAS), and Ziehl-Neelsen stains were all negative.

Bacterial and fungal targeted sequencing was then performed on the joint effusion (from arthrocentesis on November 27, 2024) and granulation tissue (from arthroscopic debridement on November 28, 2024). Briefly, the knee joint fluid cell pellets, minced granulation tissues, and a reagent control were subjected to mechanical lysis using PowerBead tubes (Qiagen GmbH, Hilden, Germany), followed by total nucleic acid extraction using eMAG (bioMérieux SA, Marcy l'Etoile, France). The 515F-1100R and ITS4-ITS5 primer pairs were used to amplify bacterial 16S ribosomal RNA gene and fungal internal transcribed spacer (ITS) region sequences, respectively, followed by sequencing on Oxford Nanopore MinION R9 version flow cells [7] [8]. The base-called sequencing reads from the "fastq pass" folder (minimum QScore: 7) were mapped against the NCBI 16S rRNA RefSeq database (downloaded on 24 April 2020) and the UNITE eukaryotic ITS sequence database (SH general release dynamic version 2 February 2019). *Mycoplasma pulmonis* was identified as the predominant bacterial species in all four specimens (**Table 1**). No fungal pathogen was identified by ITS sequencing.

We attempted to culture the granulation tissue and joint fluid using SP4 glucose broth (in 1:1, 1:10, and 1:100 dilutions). As no colour change was observed after 14 days of incubation at 37˚C, blind subculture onto SP4 agar at 37˚C in 5% CO_2 was performed for an additional 14 days. No mycoplasma colonies were isolated. The negative culture could be due to the prolonged storage (8 weeks) of the joint specimens while awaiting shipment of culture media, which was not locally available.

Empirical intravenous ceftriaxone was started post-debridement on November 28, 2024. The patient's CRP declined from 190 to 152 mg/L with some clinical improvement in pain and swelling. The antibiotic regimen was changed to oral levofloxacin and doxycycline on December 4, 2024, when the 16S sequencing result became available. Subsequently, CRP further dropped to a nadir of 44 mg/L (**Figure 1**). Towards the end of the 6-week oral antibiotic therapy, the patient's right knee pain had resolved, while the left knee remained mildly swollen and

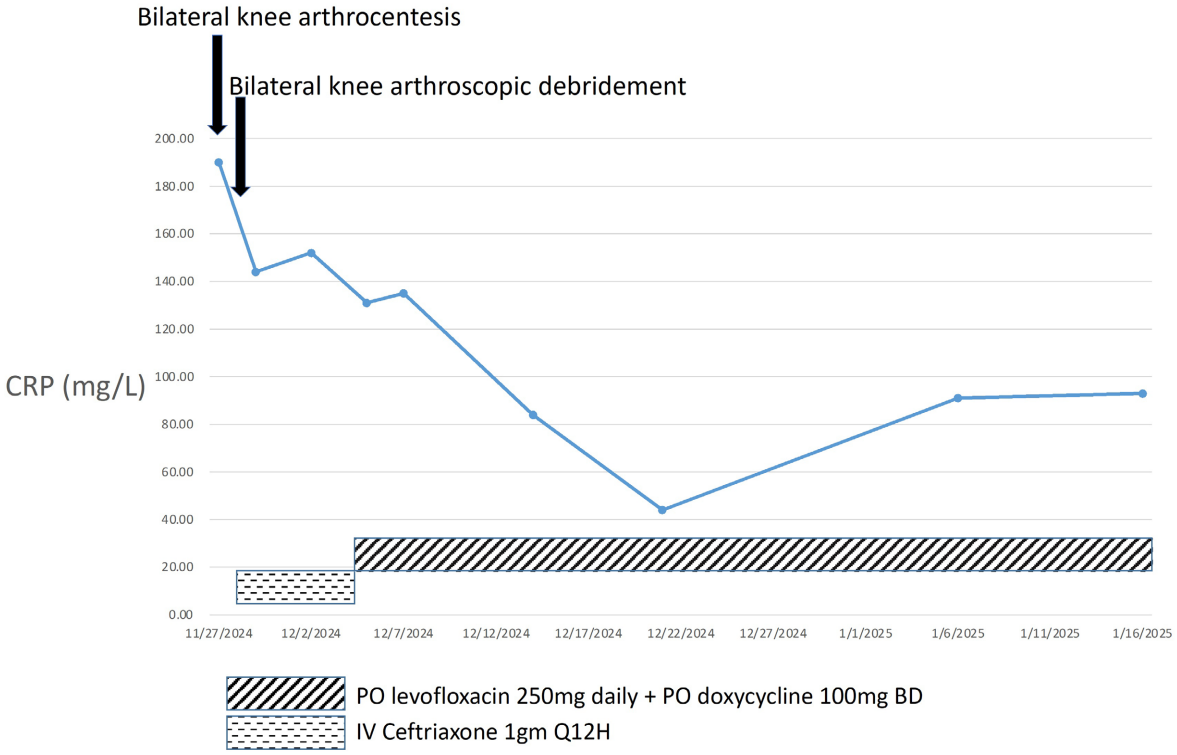
painful. He was able to ambulate with a walking frame. At the same time, a rebound in CRP from 44 mg/L to 93 mg/L was observed, after which it plateaued. As he had been compliant with the two oral antibiotics, which were associated with good clinical response in the initial treatment period, we considered the CRP rebound unlikely to be due to antibiotic failure or persistent infection. Therefore, a therapeutic trial of oral prednisolone 30 mg daily for 3 days was prescribed for presumed flare-up of his chronic arthritis. NSAIDs were relatively contraindicated because of his recent acute kidney injury, and we believed a short course of steroids would not significantly affect his immunity. The plan was to re-evaluate the need for further surgical intervention after completion of antibiotics and steroids; however, the patient was lost to follow-up thereafter.

Table 1. Bacterial 16S ribosomal RNA gene sequencing result of joint effusion and granulation tissue.

	No. of reads					
Genera	**Patient specimen**	**Reagent control**	**Background-subtracted**	**% abundance**	**Patient specimen: background ratio**	**Representative species and comments**
Specimen 1: Left knee effusion collected by arthrocentesis on 27 Nov 2024						
Mycoplasma	44399	3	44396	98.43029443	11099.75	*Mycoplasma pulmonis*; the 3 reads in reagent control were not *Mycoplasma* spp. by BLAST.
Specimen 2: Right knee effusion collected by arthrocentesis on 27 Nov 2024						
Mycoplasma	14461	3	14458	45.91736272	3615.25	*Mycoplasma pulmonis*; the 3 reads in reagent control were not *Mycoplasma* spp. by BLAST.
Burkholderia	11170	9	11,161	35.44637469	1117	*Burkholderia contaminans*
Bradyrhizobium	3023	0	3023	9.600787627	3023	
Ralstonia	1050	0	1050	3.334709563	1050	
Caballeronia	495	4	491	1.55937371	99	
Paraburkholderia	435	4	431	1.368818878	87	
Specimen 3: Right knee granulation tissue collected by arthroscopic debridement on 28 Nov 2024						
Mycoplasma	23,776	3	23,773	66.53512455	5944	*Mycoplasma pulmonis*; the 3 reads in reagent control were not *Mycoplasma* spp. by BLAST.
Ralstonia	6152	0	6152	17.21802407	6152	
Peredibacter	584	0	584	1.634480828	584	

Continued

Specimen 4: Left knee granulation tissue collected by arthroscopic debridement on 28 Nov 2024						
Mycoplasma	11,710	3	11,707	39.7453743	2927.5	*Mycoplasma pulmonis*; the 3 reads in reagent control were not *Mycoplasma* spp. by BLAST.
Bradyrhizobium	7007	0	7007	23.78883042	7007	
Staphylococcus	5826	0	5826	19.77932439	5826	*Staphylococcus cohnii*
Peredibacter	422	0	422	1.43269394	422	



CRP reference range: normal < 5 mg/L.

Figure 1. Response of C-reactive protein to surgical intervention and antibiotics.

3. Discussion

Mycoplasma pulmonis is a cell wall-lacking bacterium in the class Mollicutes, order Mycoplasmatales, and family Mycoplasmataceae [9]. It is primarily a rat and mouse pathogen that can exist as a commensal colonizing the proximal respiratory tract or cause bronchopulmonary infection ("murine respiratory mycoplasmosis") or genital tract infection in murine species [3] [4] [10]. *M. pulmonis* has been isolated from both laboratory and wild urban rats, and colonization in laboratory workers has been reported [2] [5] [6]. In one study, *M. pulmonis* DNA was found in up to 76.32% of oropharyngeal swabs from pet rat keepers, veterinarians,

and technicians; moreover, almost 60% of these healthy individuals were seropositive for *M. pulmonis*, suggesting that asymptomatic human infection is possible [6].

To our knowledge, this is the first case report of human *M. pulmonis* infection involving a sterile site. Given the organism's fastidious nature and poor environmental survival, the prolonged storage of knee specimens likely jeopardized the chance of recovering the organism by culture. We believe the presence of *M. pulmonis* DNA in large abundance in two separate surgical drainages represents a genuine infection with active bacterial replication rather than contamination. Although we cannot ascertain a causal relationship between *M. pulmonis* and septic arthritis from a single case report, the inflammatory cell infiltrate in this patient's knee granulation tissue supports an infective process. Our facility is a clinical microbiology laboratory with no animal studies, which eliminates the chance of cross-contamination. Moreover, *M. pulmonis* DNA has never been detected in our seven years of next-generation sequencing service on clinical specimens, nor is it a known cell culture contaminant [11].

In a recent meta-analysis of complications following stem cell-based injections for knee osteoarthritis, umbilical cord-derived injections had the highest occurrence of adverse events (51.7%) compared with stem cells derived from cultured adipose tissue (29.5%), autologous bone marrow (10.7%), and autologous stromal vascular fraction (8.1%) [1]. The vast majority of adverse events were swelling and pain at the injection site lasting less than 4 weeks, with no cases of infection identified. Our patient's progressive knee symptoms persisted for more than 4 weeks, suggesting an infective process rather than sterile inflammation. As our patient had no rodent or mouse exposure, we speculate that the stem cell product was contaminated by respiratory droplets from rats or colonized laboratory workers during any step of stem cell preparation or during the intra-articular injection.

As there are no antibiotic susceptibility data for *M. pulmonis* and no proven effective treatment regimens for animal infection, we took reference from human mycoplasma infections and treated this patient with a combination of a fluoroquinolone and doxycycline, which inhibit bacterial protein synthesis by interfering with DNA and RNA pathways.

This case highlights the need for rigorous quality control in stem cell product preparation and the potential for serious complications associated with novel therapies. Human umbilical cord-derived mesenchymal stem/stromal cells (UC-MSCs) have emerged as a promising medicinal product for immune and inflammatory diseases. To ensure freedom from microbial contamination, multiple steps in the manufacturing process must be followed, including but not limited to donor/tissue serological testing; avoidance of xenogenic compounds such as fetal bovine serum (FBS) to minimize the transmission of animal spongiform encephalopathy agents; and microbiology, mycoplasma, and endotoxin testing to ensure sterility. Furthermore, the use of good manufacturing practice (GMP) facilities and equipment with environmental control is crucial [12]. In Hong Kong SAR,

stem cell-derived products for medical use fall under Advanced Therapy Products (ATPs), which are regulated as pharmaceutical products under the Pharmacy and Poisons Ordinance (Cap. 138) [13]. All ATPs must be registered with the Pharmacy and Poisons Board before being sold or used. Registration requires meeting safety, efficacy, and quality benchmarks. There are also labelling and record-keeping requirements specific to ATPs to enhance product traceability, as well as a system for reporting adverse drug reactions [14].

4. Conclusion

In conclusion, we reported an unusual case of bilateral knee septic arthritis associated with *M. pulmonis* following intra-articular stem cell injections. The rarity of this case underscores the need for further research on the pathogenic role of *M. pulmonis* in human and monitoring of similar treatment procedures to ensure patient safety.

Declarations

Ethics approval: Not applicable.

Patient consent was obtained for this publication.

The data that support the findings of this study are available on request from the corresponding author.

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Author Contributions

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.
Acquisition of Data: STJ Zee, WSR Chan, WCS Wu.
Analysis or Interpretation of Data: STJ Zee, WSR Chan, WCS Wu.
Drafting of the Manuscript: STJ Zee, WSR Chan.
Critical Revision for Important Intellectual Content: STJ Zee, WSR Chan, WCS Wu.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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