Postoperative Lyme Arthritis in the Orthopaedic Patient

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Context: Lyme disease is the most common tick-borne illness in North America and Europe, and Lyme arthritis is a frequent late-stage manifestation in the United States. However, Lyme arthritis has rarely been reported as a postoperative complication.

Evidence Acquisition: The PubMed database was queried through June 2018, and restricted to the English language, in search of relevant articles.

Study Design: Clinical review.

Level of Evidence: Level 3.

Results: A total of 5 cases of Lyme arthritis as a postoperative complication have been reported in the literature.

Conclusion: These cases highlight the importance for providers practicing in Lyme-endemic regions to keep such an infection in mind when evaluating postoperative joint pain and swelling. We propose herein an algorithm for the workup of potential postoperative Lyme arthritis.

Strength of Recommendation Taxonomy (SORT): C

Keywords: Lyme arthritis; Lyme disease; *Borrelia burgdorferi*; postoperative complication

Arthritis is a known late-stage manifestation of infection with the bacterium *Borrelia burgdorferi*, which is transmitted by the *Ixodes* tick, usually occurring months after initial inoculation^{17,20} (Figure 1). Lyme arthritis was first recognized in the United States in a clustering of children and adults near Lyme, Connecticut, who presented with recurrent attacks of oligoarticular arthritis, mostly in large joints.¹⁹ The incidence of Lyme disease in the United States has been reported by the Centers for Disease Control and Prevention to be over 30,000 cases annually. In approximately one-third of cases the first manifestation of the disease is arthritis.^{5,17} While orthopaedic surgeons are frequently the first clinicians to encounter a patient with Lyme arthritis, it has rarely been reported as a postsurgical complication.

METHODS

A review of the literature through June 2018 for relevant cases was conducted using a PubMed search with the following search terms: “Lyme arthritis and surgery,” “Lyme arthritis and risk factors,” “Lyme disease,” “Lyme arthritis and (surgery or

postoperative or operative),” “perioperative and Lyme arthritis,” “Lyme arthritis and periprosthetic joint infection,” “Lyme disease and (joint disease or arthritis or knee or surgery)” and restricted to the English language. The search yielded 4 relevant articles describing Lyme arthritis as a postoperative complication.

RESULTS

In 2004, Marlovits et al¹⁴ reported on a case of Lyme arthritis in a 38-year-old woman who had undergone a bone-patellar tendon-bone reconstruction of her anterior cruciate ligament along with a staged autologous chondrocyte transplantation to repair a traumatic cartilage lesion of her medial femoral condyle. She presented 5 weeks after chondrocyte transplantation with diffuse swelling and pain in the operative knee. They reported that routine bacteriology studies performed on synovial and serum samples were negative. The patient had a normal complete blood count and complete metabolic panel with an elevated C-reactive protein (CRP). Further serum analysis revealed high concentrations of immunoglobulin G (IgG) antibodies to *B burgdorferi* by enzyme immunoassay

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Figure 1. *Ixodes scapularis*. From left to right: larva, nymph, adult male, adult female. From the Centers for Disease Control and Prevention.

(EIA; also termed, enzyme-linked immunosorbent assay, or ELISA). Polymerase chain reaction (PCR) and culture of the patient's synovial fluid were both subsequently positive for *B burgdorferi* sensu stricto. The patient then underwent antibiotic treatment with oral amoxicillin, 500 mg 3 times per day for 3 weeks, with reported improvement of her arthritis. However, failure of the chondrocyte graft 3 months after transplantation was reported to be secondary to the infection. Fifteen years prior, the patient had an expanding rash after a tick bite, which was neither confirmed by a physician nor treated.

Since 2004, 4 cases of Lyme arthritis as a cause of periprosthetic joint infection (PJI) have been reported. In 2016, Wright and Oliverio²³ reported on a case involving a 67-year-old man who presented with a 3-month history of progressive knee pain and swelling. Twelve months prior, he had undergone unicompartmental joint arthroplasty of the medial compartment of the same knee. Diagnosis of Lyme arthritis was confirmed based on positive EIA and IgG Western blot for *B burgdorferi* of serum samples and synovial fluid positive for *B burgdorferi* by real-time PCR. The patient had negative synovial gram stain and bacterial cultures after 7 days. He was initially empirically treated with oral doxycycline, 100 mg twice daily for 1 week. Subsequently, he was transitioned to intravenous ceftriaxone, 2 g daily for 6 weeks. He had clinical resolution of symptoms and repeat synovial fluid PCR 18 days postantibiotics was negative for *B burgdorferi* DNA.

In August 2017, Collins et al⁹ described a similar case in an 83-year-old man who had undergone left total knee arthroplasty (TKA) 6 years prior to presenting with 3 days of fever and a moderate joint effusion. Initial examination and laboratory findings were suggestive of a PJI based on fever, elevated white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and CRP. He underwent resection arthroplasty and insertion of a static antibiotic spacer. However, both emergency room and intraoperative synovial cultures were negative for bacterial growth, so serum Lyme antibody testing and synovial fluid

Lyme PCR were performed. He had a positive serum EIA and Western blot IgG but negative immunoglobulin M (IgM), as well as a positive synovial analysis for *B burgdorferi* by real-time PCR. He was treated initially with 2 weeks of oral doxycycline and then transitioned to 4 weeks of intravenous ceftriaxone. The dosing and frequency of the antibiotics is not known. The patient had negative repeat synovial fluid PCR 8 weeks postoperatively and was noted to be asymptomatic at 1-year follow-up.

Most recently, in June 2018, Adrados et al¹ reported 2 cases of Lyme arthritis PJI. Patient A was an 89-year-old woman who presented to the emergency department with 24 hours of right knee pain, swelling, and stiffness who, 16 years prior, had undergone uncomplicated right TKA. Patient B was an 80-year-old woman who had undergone TKA 4 months prior to presenting with anterior proximal tibia erythema and tenderness. Synovial fluid aspirates from both patients demonstrated elevated WBC counts of 66,100 and 87,830 WBC/ μ L, respectively. Both were negative for gram stain and culture, but a moderate number of calcium pyrophosphate crystals were seen in patient A. Both patients had markedly elevated serum ESR and CRP. Patient A had pyuria and bacteriuria on urinalysis. She was admitted and treated with vancomycin, ceftriaxone, and colchicine for presumed PJI, urinary tract infection, and concomitant pseudogout. Patient B was treated with intravenous cefazolin for presumed PJI.

On hospital day 2 and 3, respectively, patients A and B were taken to the operating room and underwent irrigation, debridement, and polyethylene liner exchange for presumed PJI. At the time of washout, both patients had only a small amount of intra-articular fluid, which was clear in patient A and a mix of fibrinous exudate and purulent material in patient B. Based on clinical suspicion, serum samples were tested for Lyme antibodies, and PCR analysis of synovial fluid for *B burgdorferi* DNA was performed. In both cases, the PCR was positive for *B burgdorferi* as was the EIA. However, the Western

Figure 2. Algorithm for the diagnosis of postoperative Lyme arthritis. ELISA, enzyme-linked immunosorbent assay; I&D, irrigation & debridement; PCR, polymerase chain reaction.

blot was positive for IgM but not IgG in patient A and was negative for both in patient B. In both cases, arthrocentesis and operative cultures were finalized as negative.

Both were ultimately diagnosed with Lyme arthritis as the cause of their symptoms. Patient A was treated with a 4-week course of oral doxycycline, and patient B was treated with a 4-week course of intravenous ceftriaxone followed by 4 weeks of oral doxycycline. Both patients had complete resolution of symptoms at short-term follow-up. Patient B was asymptomatic at 24 months, while patient A died 5 months after hospitalization from heart disease.

DISCUSSION

Borrelia burgdorferi is the primary etiologic agent of Lyme arthritis in the United States. However, the pathogenesis of the disease and the varied phenotypic response seen in mammals is unclear. Current literature supports a complex interplay between multiple *B burgdorferi*-specific antigens; several host chemokines and cytokines, including interleukin-6 (IL-6), IL-10, IL-15, IL-17, interferon- γ , tumor necrosis factor- α ; and a number of innate and adaptive host cells including polymorphonuclear leukocytes, macrophages, natural killer T cells, and B- and T-lymphocytes.^{3,4,7,8,11-13,15,16,18,20,21} Even though the human immune response to *B burgdorferi* is quite robust—and is often capable of clearing the infection without the need of antibiotic therapy—the spirochete, at times, evades complete eradication and lies dormant in host tissue, most notably joint, nervous, and cutaneous sites in humans. This is likely a result of *B*

burgdorferi's ability to alter or minimize surface antigenic expression, and to a lesser extent, through surface proteins, which regulate complement. This results in inhibition of complement-mediated eradication of *B burgdorferi*.¹⁸ The immunologic response to surgical trauma also involves stimulation of the innate and adaptive immune system.¹⁰

Patients may experience hematogenous spread of *B burgdorferi* to a prosthetic joint, if they are outdoors enthusiasts living in a Lyme-endemic region of the United States. Furthermore, *B burgdorferi*'s biofilm product may explain Lyme arthritis in prosthetic joints.^{9,23}

All 4 articles attest that no guidelines currently exist for the diagnosis and treatment of Lyme arthritis in the postoperative setting, as only a few cases have been described to this point. Thus, their workup and treatment were based on current accepted strategies for the management of Lyme arthritis in a native joint, septic arthritis, and PJs. We propose herein the algorithm presented in Figure 2 when considering the diagnosis of Lyme arthritis in the postoperative setting.

Current recommendations from the Infectious Diseases Society of America (IDSA) for the diagnosis of Lyme arthritis call for 2-tier serum testing, first by ELISA. If this result is positive or equivocal, confirmation should then be made with a Western blot IgG immunoblot. For a serum sample to be considered positive for Lyme arthritis, 5 or more IgG antibody bands must be positive. Western blot IgM positivity alone is not considered diagnostic of Lyme arthritis, as Lyme arthritis is a late-stage manifestation of *B burgdorferi* infection. Thus, IgG antibodies should be present in these cases. PCR for nucleic acid

Table 1. Treatment for Lyme arthritis without neurologic complication adapted from the IDSA clinical practice guidelines

Pharmacologic Agent	Adult Dosing	Pediatric Dosing
Preferred oral regimens		
Doxycycline	100 mg BID, for 28 days	Children <8 years not recommended
		Children ≥8 years 4 mg/kg/d, divided BID, max 100 mg/dose, for 28 days
Amoxicillin	500 mg TID, for 28 days	50 mg/kg/d, divided TID, max 500 mg/dose, for 28 days
Cefuroxime axetil	500 mg BID, for 28 days	30 mg/kg/d, divided BID, max 500 mg/dose, for 28 days
Alternative oral regimens		
Azithromycin ^a	500 mg daily, for 7-10 days	10 mg/kg/d, daily, max 500 mg/d, for 7-10 days
Clarithromycin ^a	500 mg BID, for 14-21 days	7.5 mg/kg BID, max 500 mg/dose, for 14-21 days
Erythromycin ^a	500 mg q6h, for 14-21 days	12.5 mg/kg q6h, max 500 mg/dose, for 14-21 days
Preferred parenteral regimen		
Ceftriaxone	2 g IV daily, for 28 days	50-75 mg/kg/d IV, daily, max 2 g, for 28 days
Alternative parenteral regimens		
Cefotaxime	2 g IV TID, for 28 days	150-200 mg/kg/d IV, divided q6-8h, max 6 g/d, for 28 days
Penicillin G	18-24 million U/d IV, divided q4h, for 28 days	200,000-400,000 U/kg/d IV, divided q4h, max 18-24 million U/d, for 28 days

BID, twice daily; IDSA, Infectious Diseases Society of America; IV, intravenous; q4h, every 4 hours; q6h, every 6 hours; q8h, every 8 hours; TID, 3 times daily; U, units; d, day.

^aGiven their lower efficacy, macrolides are limited to those who are intolerant of doxycycline, penicillin, and cephalosporin; careful observation should be made to ensure clinical resolution of symptoms.

amplification and detection of *B burgdorferi* DNA from synovial fluid samples can be done if additional confirmation is desired. However, the IDSA cautions against making the diagnosis of Lyme arthritis based on positive synovial PCR in the face of negative serum immunoblot testing, as these results are often false positives. Culture of *B burgdorferi* provides the most accurate confirmation of active infection. However, its sensitivity is very technique dependent. The process is labor and time intensive, and expensive. As such, culture for confirmation of *B burgdorferi* infection remains primarily used in research settings.^{2,22}

Both patients presented by Adrados et al¹ had clinical resolution of their symptoms after surgical debridement, liner exchange, and antibiotic therapy. However, in neither case was there a positive Western blot IgG or positive culture, questioning the diagnosis of active infectious Lyme arthritis.

Moreover, while commercial laboratories offer immunoblot testing on nonserum samples, such testing is not recommended. A small retrospective review of 11 patients at Johns Hopkins University with arthritic symptoms and positive synovial fluid immunoblot testing failed to respond to antibiotic therapy. Ten

of the 11 patients had negative serum ELISA and IgG immunoblot testing, suggesting that antibody testing of synovial fluid lacks adequate sensitivity or specificity to be a reliable test.⁶

While a thorough review of the antimicrobial management of Lyme arthritis is beyond the scope of this article, it is important for clinicians to be familiar with the initial choice of antibiotics (Table 1).²² Recommendations for initial antimicrobial therapy for Lyme disease typically advocate for a 14- to 28-day course, with a 28-day course being most recommended for Lyme arthritis. Doxycycline 100 mg orally twice daily is the current first-line treatment of Lyme disease, except for in pregnant or nursing women and children younger than 8 years, for whom amoxicillin 500 mg 3 times daily is recommended. Macrolides are second-line agents, appropriate only for patients with intolerance or contraindications to the use of tetracycline and beta-lactam antibiotics. Ceftriaxone 2 g intravenous daily is the preferred parenteral drug when parenteral antibiotics are necessary.²² Collaboration or consultation with infectious disease experts can be particularly useful.

CONCLUSION

Lyme arthritis as a postoperative complication is a rare phenomenon. Alterations to immune surveillance as a result of surgery or mechanical exposure of dormant *B burgdorferi*

spirochetes during surgery with influx of immune cells into the joint are possible explanations for such a condition. Lyme arthritis PJI is also possible and may be related to *B burgdorferi*'s biofilm.

Clinical Recommendations

SORT: Strength of Recommendation Taxonomy Grade

A: consistent, good-quality patient-oriented evidence

B: inconsistent or limited-quality patient-oriented evidence

C: consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Clinical Recommendation	SORT Evidence Rating
Lyme arthritis should be considered as a possible cause of postoperative pain and swelling in the appropriate clinical setting.	C
Diagnosis of Lyme arthritis should be confirmed by 2-tier testing including ELISA and IgG immunoblot.	C
Doxycycline 100 mg by mouth twice daily for 28 days is the preferred oral agent for the treatment of Lyme arthritis.	B
Ceftriaxone 2g IV daily for 28 days is the preferred parenteral agent for the treatment of Lyme arthritis when parenteral antibiotics are required.	B

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