

# A Diagnostic Challenge: The Child with Fever, Rash, and Arthritis

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When a child has a fever, rash, and joint pain, the family physician needs to consider a variety of diseases in the differential diagnosis. Juvenile rheumatoid arthritis, Lyme disease, and streptococcal diseases are all possible causes of this triad of symptoms. An accurate diagnosis, however, might be delayed until serologic studies have been returned and the response of the child to treatment has been observed.

## Case Report

A 5-year-old boy was admitted to the hospital in May with a 12-day history of intermittent fever, rash, and arthralgias. The child's illness began 12 days before admission, at which time he had a temperature of 103.0°F and no other associated symptoms. The fever resolved spontaneously within 24 hours. Nine days before admission he developed an intermittent, erythematous, macular, lacy nonpruritic rash on both thighs. Eight days before admission he had onset of mild intermittent arthralgias involving his knees, hips, and wrists, as well as popping of his knees and intermittent limping. Three days before admission his fever recurred (101.0°F). Two days before admission he was seen by a physician and had a temperature of 100.0°F, normal findings on a physical examination, a white cell count of 23,000/ $\mu$ L with 80 percent granulocytes, and an erythrocyte sedimentation rate of 55 mm/h. The following day on reexamination, he had a temperature of 98.2°F, a new grade 1/6 systolic ejection murmur, and a macular, erythematous, 0.5-cm diameter, blanch-

ing, semicoalescent rash on his inner thighs. Laboratory evaluation that day included an antistreptolysin titer of 578 IU/mL and white cell count 16,900/ $\mu$ L with 70 percent granulocytes.

On the day of admission he had an acute onset of swelling of the right ankle. His temperature was 101.0°F, heart rate 120 beats per minute, respiratory rate 20/min, and blood pressure 90/60 mmHg. He had a tender erythematous area overlying the right medial malleolus, which was surrounded by moderate soft tissue swelling extending 3 to 4 cm in all directions around the malleolus. There was no palpable synovial thickening, and there were no palpable subcutaneous nodules.

His parents reported no history of any upper respiratory tract infection or exposure to streptococcal disease, and the family members had had no recent illnesses, including streptococcal infections. Although the child had no recent history of a tick bite, he had spent time in the past year at his grandfather's farm in Franklin, Mo, an area where Lyme disease had been reported. He had no history of joint problems or recent trauma.

Admitting laboratory results were white cell count 17,800/ $\mu$ L with 73 percent granulocytes, 23 percent lymphocytes, 2 percent monocytes, and 2 percent eosinophils; hemoglobin 10.7 g/dL, and hematocrit 31.3 percent; C-reactive protein 2.9 mg/dL; an erythrocyte sedimentation rate of 38 mm/h; and an antistreptolysin titer of 596 IU/mL. Blood was sent to a reference laboratory to test for Lyme antibody and hidden rheumatoid factor. A bone scan obtained the day after admission showed mild increased perfusion of the right lower extremity without evidence of focal osteomyelitis or arthritis. Electrocardiograms on admission and on the 3rd hospital day were normal with no evidence of heart block. An echocardiogram on the 3rd hospital day was normal, without evidence

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of pericardial effusion or valvular insufficiency. Blood cultures were reported negative at 72 hours.

Intravenous penicillin G and ceftriaxone were prescribed on admission. The patient's rash, fever, and medial malleolar swelling rapidly improved with antibiotic therapy. When discharged 3 days after admission, the child was afebrile, the rash had resolved completely, and the ankle showed only minimal swelling and no redness or tenderness. He had not been prescribed any aspirin, acetaminophen, or ibuprofen during hospitalization. He was prescribed intravenous ceftriaxone to be administered at home.

Findings on repeat bone scan obtained 2 days after discharge (5 days after the initial scan) were normal, and the intravenous ceftriaxone was discontinued; the child was prescribed oral amoxicillin-clavulanate at 40 mg/kg/d. Eleven days after hospitalization the child's white cell count had decreased to 14,500/ $\mu$ L, and his C-reactive protein had returned to normal (0.5 mg/dL), but the antistreptolysin titer was still elevated at 883 IU/mL. Repeat serologic tests for Lyme disease antibodies and hidden rheumatoid factor were ordered. Sixteen days after admission, the child had only minimal swelling of the medial malleolus and no evidence of any pain. Results of the first hidden rheumatoid factor test were reported positive at a titer of 1:128 (normal < 1:16). Results of the admission Lyme disease serologic test, done by enzyme-linked immunosorbent assay at the Laboratory for the Diagnosis of Lyme Disease, State University of New York, Stony Brook, were positive (optical density of patient sample 0.195, and reactive cutoff > 0.137).

Twenty-eight days after admission, results of the second serologic test for Lyme disease were reported positive at 0.267 (positive > 0.097). The child completed 6 weeks of total antibiotic therapy consisting of the initial 6 days of intravenous ceftriaxone, followed by 3 weeks of oral amoxicillin-clavulanate, then 2 weeks of oral amoxicillin. Forty-four days after admission, results of the second hidden rheumatoid factor test were reported negative. Seven weeks after admission the child was again examined, and the findings were normal. Results of the repeat serologic test for Lyme disease showed the titers had decreased to 0.87 (positive > 0.101). One year after the hospitalization, the child was doing well without recurrence of any joint problems.

## Discussion

This 5-year-old boy with fever, rash, and arthritis initially had symptoms and signs compatible with several different diseases, including rheumatic fever, systemic juvenile rheumatoid arthritis, recent streptococcal infection with osteomyelitis or septic arthritis, and Lyme disease. Initial treatment included a broad-spectrum antibiotic to address these possibilities.

Osteomyelitis and septic arthritis were eventually excluded by the two negative bone scans. Because of the impressive erythema, tenderness, and swelling of the right medial malleolus, and because bone scans can occasionally be falsely negative in children with early osteomyelitis, a second bone scan was ordered.

Acute rheumatic fever was considered a possibility; therefore, penicillin G was also included in the initial antibiotic regimen. Although there was serologic evidence of a recent streptococcal infection, it was not sufficient for the diagnosis of rheumatic fever based upon the revised Jones criteria.<sup>1</sup> The only major criterion that the child's condition satisfied was rash, and his rash did not have the characteristic appearance of erythema marginatum. In addition, there was no evidence of carditis, chorea, or subcutaneous nodules. Although the child had impressive monoarticular arthritis, there was no evidence of polyarthritis. The child's condition satisfied three minor criteria—fever, arthralgias, and elevated acute-phase reactants (erythrocyte sedimentation rate and C-reactive protein), and had supporting evidence of antecedent group A  $\beta$ -hemolytic streptococcal infection (elevated antistreptolysin titer). The revised Jones criteria for the diagnosis of an initial episode of acute rheumatic fever require the presence of either two major or one major and two minor criteria, as well as evidence of an antecedent streptococcal infection. Another fact ruling against the diagnosis of acute rheumatic fever was the child's clinical improvement without the use of aspirin.

The diagnosis of systemic juvenile arthritis was considered less likely because of the child's rapid clinical response to antibiotic therapy in the absence of salicylates and the subsequent negative test result for hidden rheumatoid factor. Transiently positive hidden rheumatoid factors have been reported early in the course of Lyme disease. The immunoglobulin M response to the spiro-

chete *Borrelia burgdorferi* can be associated with a polyclonal activation of B cells, which can result in slightly elevated levels of rheumatoid factor.<sup>2</sup>

This child's clinical appearance of fever, arthralgias, rash, and monoarticular arthritis was compatible with disseminated Lyme disease. He had a temperature of up to 103.0°F; fever and other constitutional symptoms are common in early localized and disseminated Lyme disease.<sup>3,4</sup> Our patient had a macular, evanescent rash similar in description to that reported in some cases of disseminated Lyme disease. Forty-five to 85 percent of patients with Lyme disease will have the classic erythema migrans (bull's eye) lesion, and 17 to 50 percent of those patients with disseminated Lyme disease will have multiple erythema migrans lesions or other rashes.<sup>3-5</sup> The child's arthritis appeared 12 days after the onset of the other symptoms; the range of time between disease onset and the development of one or more episodes of arthritis (usually after a period of intermittent arthralgias) has been reported to be 4 days to 2 years.<sup>6,7</sup> Our patient had no known history of a recent tick bite, although he had been in a tick-infested area in the summer before he developed his symptoms. Approximately one half of patients with Lyme disease will not remember a preceding tick bite.<sup>3,4,7</sup>

Lyme disease is a multisystem tick-borne infection of both children and adults that is caused by the spirochete *Borrelia burgdorferi*.<sup>8</sup> The majority of cases of Lyme disease occur in North America and western Europe, but Lyme disease has a worldwide geographic distribution, and it has been reported in 49 states in the United States and in more than 40 countries on six continents.<sup>3,9</sup> The number of cases reported continues to increase, and in 1994, 44 states reported 13,083 cases.<sup>10</sup> Most cases occur in the northeastern, mid- and south-Atlantic, and upper midwestern states.<sup>10</sup> Lyme disease is the most common tick-borne infection in the United States and possibly in the world.<sup>9,10</sup>

Lyme disease is a relatively recently recognized infection and was initially reported and named Lyme arthritis in 1977, when an outbreak of infectious arthritis occurred in Old Lyme, Conn.<sup>11</sup> A new spirochete, named *Borrelia burgdorferi* and transmitted by ixodid bites, was eventually found to be the cause of Lyme arthritis, as well as of several European diseases of previously unknown

causes, including European erythema migrans skin lesions.<sup>3,5</sup> As the multisystem involvement of Lyme arthritis, including dermatologic, cardiac, neurologic, arthritic, and ocular manifestations of the infection, became apparent, it later became known as Lyme disease.<sup>12</sup>

Although the characteristic history of ixodid bite followed by an erythema migrans skin rash at the bite site frequently allows the rapid clinical diagnosis of Lyme disease, the diagnosis is much more difficult in patients lacking this history. Because of the small size of the ixodid (*Ixodes scapularis*, *I dammini*, or *I pacificus* in the United States; *I ricinus* in Europe; or *I persulcatus* in Asia) that serves as the vector of the spirochete, many patients, especially pediatric patients, do not recall a tick bite.<sup>3-5</sup> In addition, many patients with Lyme disease do not recall having the characteristic erythema migrans skin rash.<sup>3,4,7</sup> If left untreated after the initial infection, these patients can later have serious cardiac, neurologic, and musculoskeletal complications.<sup>3,4,7</sup> Adequate antibiotic treatment can successfully prevent the development of both the acute and chronic complications of Lyme disease, including arthritis.<sup>3,7</sup>

Besides being alert to the possibility of Lyme disease in any patient who complains of fever, rash, and arthritis, the family physician needs to consider other systemic disorders and infections. The clinical history is very important, and a history of tick bite, erythema migrans, or other skin rash associated with a tick bite, or a history of an exposure to a tick-infested Lyme-endemic geographical area should raise the level of suspicion for Lyme disease. Currently available diagnostic tests can exclude other diagnoses and support the diagnosis of Lyme disease, and careful observation of the patient's clinical course and response to treatment should then lead the physician to the correct diagnosis.

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