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CASE REPORT

A patient with Lyme arthritis presenting in general practice

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FIGURE 1
Lyme disease: erythema migrans

What causes Lyme disease?

LYME DISEASE, ALSO KNOWN AS LYME BORRELIOSIS, IS THE MOST COMMON tick-borne infectious disease in Europe and North America. Infection in humans often takes place in woodland or heath areas where animals that carry the ticks such as deer and mice are found.

The Health Protection Agency estimates that there are 2,000 to 3,000 cases of Lyme disease in England and Wales each year (see box 1, right) and that around 15% of infections are acquired abroad.[1] It is caused by infection with *Borrelia burgdorferi sensu lato* (*B. burgdorferi s.l.*) complex. Borrelia is a Gram-negative spirochaete bacterium.

In Europe *B. burgdorferi sensu stricto*, *B. afzelii*, *B. garinii*, *B. bavariensis* and *B. spielmanii* can cause Lyme disease, whereas in the USA *B. burgdorferi sensu stricto* is the sole culprit.[2]

In principle, Lyme disease may affect every organ of the body and may manifest in different stages. Early localised or disseminated stages are characterised by erythema migrans (see figure 1, above), lymphadenosis benigna cutis, facial palsy and arthritis and the later stages by arthritis, acrodermatitis chronica atrophicans or encephalomyelitis.[3] Not all these features occur in every case. The incubation time of the earlier stages varies from several days to months, and that of the later stages from weeks to months, and even years.[4]

Lyme arthritis commonly manifests mono- or oligoarticularly (< 5 joints). Most frequently the knee joint is affected, followed by the ankle, the wrist and the elbow.[5]

According to epidemiology data, there were around 16,500 reported cases of Lyme disease in Germany from 2007 to 2009. The presence of Lyme arthritis in Lyme disease cases ranges from around 2% to 8%.[4,6] However, a figure of almost 25% was reported by primary care physicians in a nationwide survey in Germany.[7]

A prospective US study from the 1980s suggests that not treating erythema migrans with antibiotics results in an increase in Lyme arthritis. During the six-year follow-up, more than half of the 55 patients included with erythema migrans suffered from Lyme arthritis.[5]

The work-up of Lyme arthritis should include a careful history including residence in, or time spent visiting, an endemic region, previous history of tick bite(s), and erythema migrans. Clinical examination for arthritis, serology and other laboratory investigations are also key, see below. As immunity after infection with *B. burgdorferi s.l.* cannot necessarily be assumed, reinfections are possible.[8] We report a case history »

How should Lyme arthritis be diagnosed?

What are the recommended treatments?

Box 1

Lyme disease in the UK

There are an estimated 2,000-3,000 cases of Lyme disease in England and Wales each year.

Areas of the UK that are known to have a high population of ticks include:

- Exmoor
- The New Forest, Hampshire
- The South Downs
- Parts of Wiltshire and Berkshire
- Surrey and West Sussex
- Thetford Forest, Norfolk
- The Lake District
- The Yorkshire Moors
- The Scottish Highlands

of a patient with Lyme arthritis presenting in a family practice in Nufringen, Germany.

CASE HISTORY

A 63-year old woman with no pre-existing disorders presented with pain in her left knee, which had begun about two weeks before her first visit. She reported that redness, warmth and swelling of the knee had progressed markedly over the past three days. She also complained of general discomfort and feeling cold.

She had developed two red marks on her tibial skin, each about 2 cm in diameter, several weeks before the knee pain began. The marks were itchy and disappeared after a week. She recalled having a tick bite about three years ago and previous tick bites when she was a young woman. She was taking no medications and had no family history of gout, arthritis or rheumatic diseases.

Physical findings

The patient was only able to walk with the aid of crutches. There was marked swelling and warmth in the left knee, reddening of the distal ventro-lateral thigh and discrete swelling of the popliteal region and calf without reddening. She felt no pain on palpation of the calf. There was a large effusion of the knee joint and no knee flexion was possible.

Examination of the abdomen, skin and lymphatic system, heart, lungs and oral mucosa were normal. She had no fever. Blood pressure was 130/70 mmHg and her pulse regular.

Investigations

Duplex ultrasonography of the deep veins of the legs excluded deep vein thrombosis. Electrocardiogram and X-ray of the knee were normal.

Histology of the synovial biopsy material revealed a marked chronic synovitis with inflammatory phlegmon that was consistent with septic arthritis.

Borrelia was detected by PCR and DNA sequencing of the synovial fluid, and by serology follow-up of Borrelia-induced immune reactions.

The serology findings showed specific IgG antibodies against B. burgdorferi s.l. *The detection of B. burgdorferi DNA by means of PCR and DNA sequencing of the synovial fluid confirmed the diagnosis of Lyme arthritis caused by* B. garinii. *Specific IgM antibodies could not be detected. Key findings are summarised in table 1, right.*

Treatment

At the first visit to the practice, about 50 ml of unclear serous fluid was aspirated from the knee joint and taken to the laboratory immediately. The patient received oral ibuprofen (600 mg tid), and was instructed to cool her knee until the next day when the first laboratory results were expected.

As the cell count of the synovial fluid was 21,200/µl with a high proportion of segmented granulocytes the patient was admitted to hospital for knee lavage because a septic arthritis was suspected. In hospital she also received analgesic and antibiotic therapy and physiotherapy for the knee joint. Antibiotic treatment included cefazoline IV for one week followed by oral cefadroxil (1g bid). For thromboprophylaxis, she received LMW heparin subcutaneously.

After 11 days, she was discharged on cefadroxil. Then, back in the community, the antibiotic therapy was continued with ceftriaxone (2 g/day) IV.

After 14 weeks the patient had completely recovered.

DISCUSSION

Besides the common causes of acute and subacute gonarthritis (i.e. gouty and septic arthritis, activated osteoarthritis and rheumatologic disorders), Lyme arthritis needs to be considered in patients who live in, or have visited, endemic regions. The lack of IgM antibodies and the confirmation of IgG antibodies raised the suspicion of Lyme arthritis.

Synovial fluid/synovial biopsy material

The cytology of the synovial fluid (granulocytes were prevailing) and the histology of the synovial membrane (marked chronic synovitis with inflammatory phlegmon) were consistent with the findings in septic arthritis. However, bacterial growth could not be detected.

The histology findings in Lyme synovitis are associated with an unspecific inflammatory reaction that can also be found in posttraumatic synovitis, rheumatic arthritis and, juvenile idiopathic arthritis.[9,10]

The detection of spirochaete bacteria in the biopsy material is likely to be successful in only a few cases. This procedure is time consuming and work intensive, therefore, it is not recommended for the routine diagnostic work-up in Lyme arthritis.[11]

Rather, diagnosis of Lyme arthritis can be supported by PCR and DNA sequencing of the synovial fluid or synovial biopsy material.[12] The sensitivity of the detection of DNA is about 50-70%; DNA can more often be detected in the synovial membrane than in the synovial fluid.[13] A negative PCR test result does not exclude Lyme arthritis, whereas a positive result practically confirms it.[13] In our patient, DNA of *B. garinii* could be detected.

Serology findings

In order to confirm the diagnosis of Lyme arthritis clinical findings and specific IgG antibodies are necessary. The lack of IgG antibodies practically rules out Lyme arthritis.[11,14,15,16] At the first visit the patient had high blood concentrations of antibodies (by ELISA), after five weeks the parallel testing showed an increase and after 14 weeks a decline. The patient had no IgM antibodies, however IgM antibodies are often not detected in Lyme arthritis.[17,18,19] Several antibodies against recombinant antigens of *B. burgdorferi s.l.* could be detected by Luminex technology (see box 2, p27).

THERAPY

The patient initially, in hospital, received a first-generation cephalosporin. The recommendations from the European Concerted Action on Lyme Borreliosis (EUCALB), however, include second- and third- generation cephalosporins. Therefore, we decided to administer ceftriaxone (2 g/day, IV, for 4 weeks).

Table 1

Key laboratory investigations and findings

- Elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)
- Specific IgG antibodies to recombinant antigens of *Borrelia burgdorferi*, *B. garinii* and *B. afzelii*
- IgM antibodies not detected
- Knee joint aspirate (serous, unclear) with 21,200 cells/µl (94% granulocytes)

The rise in serum IgG antibodies against the highly specific recombinant p18 antigen (serum parallel testing over the course of 14 weeks) and the detection of nucleic acid sequences in the knee joint aspirate confirmed the infection with *B. garinii*

key points

SELECTED BY
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Lyme disease, also known as Lyme borreliosis, is caused by infection with *Borrelia burgdorferi sensu lato* (*B. burgdorferi s.l.*) complex, a Gram-negative spirochaete bacterium. Infection in humans takes place through tick bites.

In principle, Lyme disease may affect every organ of the body and may manifest in different stages. Early localised or disseminated stages are characterised by erythema migrans, lymphadenosis benigna cutis, facial palsy and arthritis and the later stages by arthritis, acrodermatitis chronica atrophicans or encephalomyelitis. The incubation time of the earlier stages varies from several days to months and that of the later stages from weeks to months or even years.

Lyme arthritis commonly manifests mono- or oligo- articularly (< 5 joints). Most frequently the knee joint is affected, followed by the ankle, wrist and elbow. The work-up of Lyme arthritis should include a careful history including residence in, or time spent visiting, an endemic region, previous history of tick bite(s), and erythema migrans. In order to confirm a diagnosis of Lyme arthritis clinical findings and specific IgG antibodies are necessary. A lack of IgG antibodies practically rules out Lyme arthritis. Antibodies can be detected even years after infection(s) in asymptomatic individuals with previous Lyme disease treated with antibiotics.

In general, the prognosis of Lyme disease is assumed to be good, in particular after antibiotic therapy of early manifestations. The therapy recommendations for adults are tetracyclines or aminopenicillin or a third-generation cephalosporin. After infection, immunity against *B. burgdorferi sensu lato* cannot necessarily be assumed, hence, reinfections are possible.

Box 2

Interpretation of key serology and synovial fluid results

The serology findings and the simultaneous detection of B. garinii DNA in the synovial fluid suggests the following interpretation:

- The p100 antibodies as a late infection marker indicate that an infection took place at least several weeks (or months) before the first visit.
- The rising IgG antibody band and – in particular – the specific p18 antibodies against *B. garinii* detected by Luminex technology reflect immune reactions in the context of Lyme arthritis caused by *B. garinii*.
- The p18 antibodies against *B. afzelii* might be interpreted as an immune reaction caused by a previous infection with *B. afzelii* or as a slight cross-reactivity.

The EUCALB therapy recommendations for adults are as follows:[16]

- Tetracycline antibiotic of choice is doxycycline (100 mg bid, except for children under the age of eight years, pregnant women and breastfeeding mothers) or
- Aminopenicillin of choice is oral amoxicillin (500-1,000 mg tid) or
- A third-generation cephalosporin (explicitly mentioned is ceftriaxone, IV, 2 g/day; alternatively cefotaxime, IV, an exact dose is not specified).

For the latter, Nau and colleagues alternatively recommend cefuroxime, a second-generation cephalosporin (500 mg bid).[20]

In general, the prognosis of Lyme disease is assumed to be good, in particular after antibiotic therapy for early manifestations. However, clinical follow-up data after antibiotic therapy in Lyme arthritis are sparse.[20,21]

CONCLUSION

The diagnosis of Lyme arthritis may be complex, especially the interpretation of serology data. As a rule, IgM antibodies are generally not detected in Lyme arthritis, whereas IgG antibodies are mandatory for diagnosis. Antibodies can be detected even years after infection(s) in asymptomatic persons with previous Lyme disease treated with antibiotics. If an assessment of serology follow-up data is considered, at least parallel testing of the sera has to be performed. However, such blood samples need to be stored deep frozen, and in practice this can be rarely managed.

Arthralgia with IgG antibodies persistent from previous infection(s) needs to be distinguished from Lyme arthritis. DNA analysis is a valuable additional method to diagnose Lyme arthritis.

After infection, immunity against *B. burgdorferi sensu lato* cannot necessarily be assumed. Hence, reinfections are possible.

In contrast to the USA, one has to keep in mind that in Europe infections with different endemic species of the *B. burgdorferi sensu lato* complex occur.

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