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Necrotizing Granulomatous Hepatitis as an Unusual Manifestation of Lyme Disease

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Introduction

Lyme disease is the most common vector-borne infection in the United States and is caused by *Borrelia burgdorferi*, a spirochete that is transmitted from the ixodid tick. Abnormal liver chemistry is a rare, but well-described phenomenon in Lyme disease infection [1]. There have been several postulated theories as to the cause of hepatitis with *B. burgdorferi* infection. These include direct toxicity from the spirochete, systemic cytokine release, and, possibly, an immune-mediated event [2]. Although elevated aminotransferase has been seen, there has been only one case reported of granulomatous hepatitis from Lyme infection [3]. We describe here the first case of a patient with acute Lyme disease who was found to have necrotizing granulomatous hepatitis with eosinophilic infiltration of the liver.

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Case report

A 22-year-old African-American female presented to her primary care physician with the abrupt onset of lower back and epigastric pain, accompanied by fever and chills. These were worse in the evening. A chest x-ray was negative and the initial laboratory results revealed a mild increase in aminotransferase levels. The patient was diagnosed with viral syndrome and was treated symptomatically with ibuprofen for pain and fever.

Her symptoms persisted, and the patient made two subsequent visits to the emergency room of her local hospital. She was prescribed trimethoprim/sulfamethoxazole for presumed urinary tract infection at the first emergency room visit, and she was given ciprofloxacin for possible "pyelonephritis" during her second visit. Several days after her second visit to the emergency room, the patient was admitted to another hospital for persistent fever and body aches. The patient reported no history of tick bite or any rash.

Laboratory tests revealed the folllowing: alkaline posphatase, 225 U/L; ALT, 90 U/L; AST, 40 U/L; white blood cell count, 11,200; erythrocyte sedimentation rate, 114 mm/hr; lactate dehydrogenase, 294; and a CRP of 202. Total complements level was 194 (normal: 48–153); C3, 248 (normal: 75–140); and C4, 38.2 (normal: 10–34).

Serologic tests for hepatitis A, B, and C and HIV were all negative, as was a Monospot test. A tuberculin skin test and sputum for acid-fast bacilli were negative, as was a cryptococcal antigen and urinary histoplasma antigen. The RPR was nonreactive and syphilis IgG antibodies were negative. Blood and urine cultures for gonorrhea and chlamydia were also negative. Tests for ANA, anti-double-stranded DNA, and rheumatoid factor were all negative. The family history

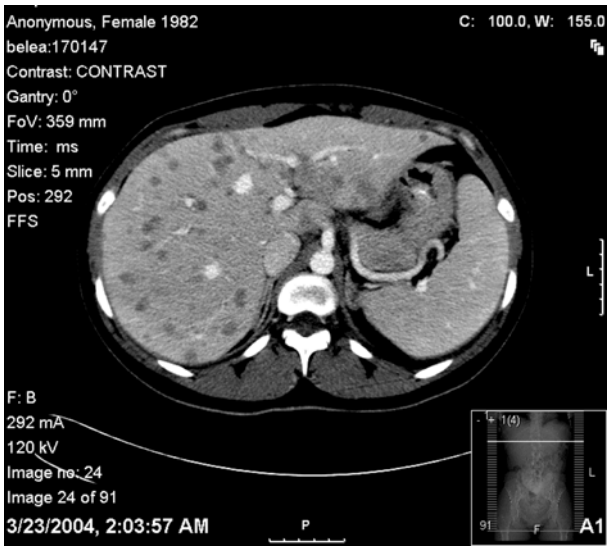

Fig. 1 Numerous low-density lesions involving the liver on CT scan

was significant for maternal sarcoidosis, but the patient's angiotensin converting enzyme level was normal.

The chest x-ray was unremarkable. Abdominal computed tomography (Fig. 1) revealed innumerable round, low-density lesions throughout the liver parenchyma, most of them <1 cm, with the biggest lesion being 1.7×1.2 cm, and a borderline enlarged spleen. The intra- and extrahepatic bile ducts, kidneys, and adrenal glands were normal, and no retroperitoneal or pelvic lymphadenopathy was noted.

Following a liver biopsy, the patient was discharged home with the diagnosis of fever of unknown origin. She was given acetaminophen for fever control, and all antibiotics were discontinued.

Her liver biopsy (Fig. 2) revealed numerous necrotizing granulomas with marked eosinophilic infiltrates. Though there were also large, multinucleated giant cells, as may be seen in sarcoid, the extensive caseous necrosis, the negative chest x-ray, and the normal ACE levels were felt to exclude that diagnostic possibility. There were no features of chronic liver disease or significant injury to the biliary tree. The special stains were negative for microorganisms. The granulomas were felt likely to reflect either infection or a drug/toxin-mediated injury.

As Lyme disease was part of our differential diagnosis for this granulomatous liver disease, serum was sent for antibodies to *Borrelia burgdorferi*. The patient reported no history of tick bite or erythema chronicum migrans rash. The serum came back positive for antibodies to *B. burgdorferi,* with two bands of the 23- and 41-kD proteins on IgM Western blot. IgM Western blots which have two or more of the three (23-, 39-, and 41-kD) significant bands are considered positive for specific antibodies to *Borrelia burgdorferi*.

A clinical diagnosis of Lyme disease was made, and the patient was treated with 8 weeks of doxycyline. The patient's

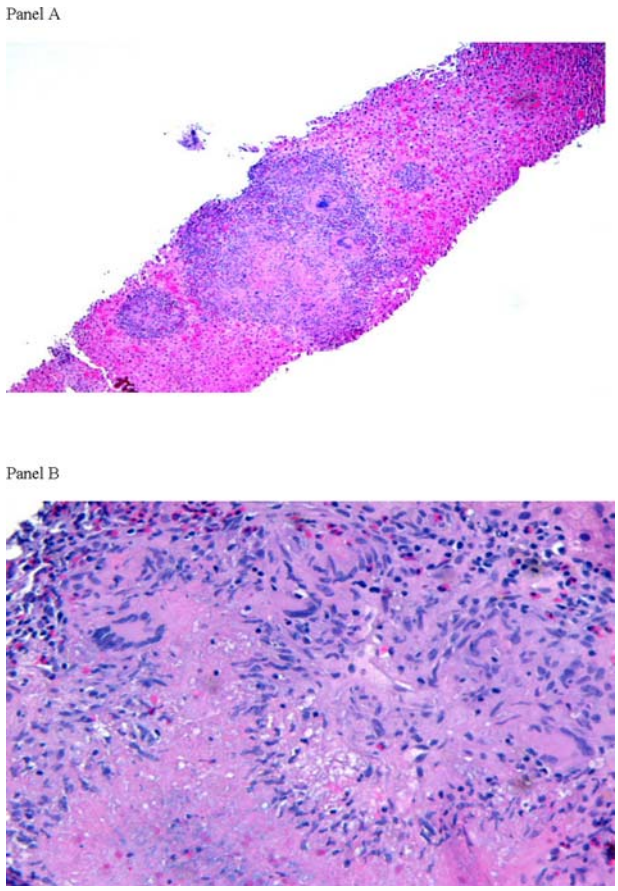

Fig. 2 (A) Necrotizing epithelioid granuloma with eosinophils. (B) A cluster of epithelioid cell granulomas. (H&E.)

symptoms improved, and a follow-up MRI confirmed complete resolution of the multiple liver lesions (Fig. 3). She has remained asymptomatic 6 months later.

Discussion

Hepatitis, as a sequelae of Lyme disease, is well documented. Although there is a previously reported case of granulomatous hepatitis associated with Lyme disease, to our knowledge, this is the first documented case of Lyme disease with necrotizing granulomas and eosinophilic infiltration of the hepatic parenchyma [4]. Goellner *et al*. in 1988 reported a case of a patient with recurrent Lyme disease and hepatitis. In this particular case, along with hepatitis, there was marked ballooning of hepatocytes, prominent inflammation, and increased mitotic activity as a late complication of the disease, with a few Dieterle silver-staining spirochetes identified in hepatic sinusoids and parenchyma. In that case, no granulomas were reported on liver biopsy, but a few *B. burgdorferi* spirochetes were cultured. Although it is possible to see spirochetes on liver biopsy in patients with Lyme disease and hepatitis, in the majority of these cases, no

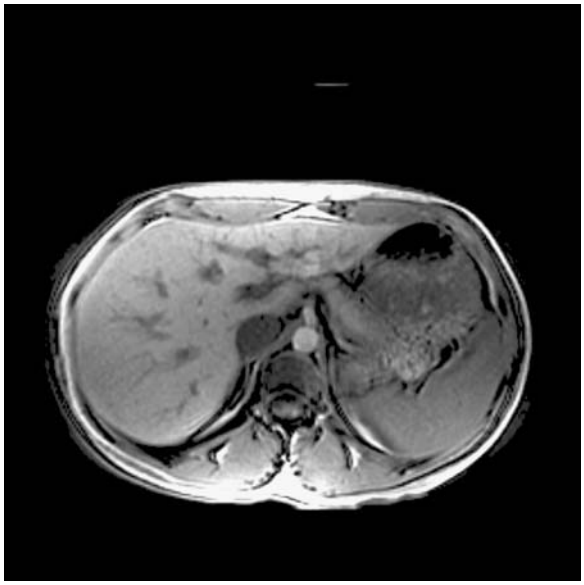

Fig. 3 MRI of the liver after treatment showing complete resolution of the lesions

organisms are identified [4]. In these cases, the diagnosis must be established by the presence of *B. burgdorferi* titers in the serum and/or an appropriate response to the correct antibiotic treatment as seen in our case.

Lyme disease can follow many different stages of evolution: an early stage, characterized by erythema migrans and/or clinical symptoms of early disseminated disease (severe headaches, multiple skin lesions, cranial palsies, cardiac arrhythmias), and a late stage which may include arthritis, acrodermatitis chronica atrophicans, or chronic neurological manifestations [1]. In African-American patients, such as ours, the skin lesion may not have been recognized, probably due to the location on the back or behind the knee or due to the dark skin. In the classic presentation of erythema migrans with a characteristic expanding annular lesion at the port of entry, making the clinical diagnosis is not difficult. However, those patients presenting without erythema migrans or with atypical skin lesion may need laboratory confirmation. Laboratory tests for detection of *B. burgdorferi* include direct methods (light microscopy, polymerase chain reaction, culture) and serology testing (indirect fluorescent antibody assay, enzyme-linked immunosorbent assay, Western immunoblots) [5].

Since *B. burgdorferi* shares some antigens with testing other bacteria, and the test can detect nonspecific antibodies, the CDC recommends a two-step approach. The first test should include a sensitive enzyme immunoassay or indirect fluorescent antibody assay, followed by a second step consisting of Western immunoblots, as a confirmatory exam for those with a positive exam on initial testing [5]. The immunoblot was confirmatory for our patient.

Gastrointestinal signs and symptoms are common in the early stages of the disease, with approximately 10% of patients having symptoms suggestive of hepatitis in one study of 314 patients [1]. Another study of 124 patients showed that 27% of the patients had subclinical hepatitis [2]. Patients with early-disseminated Lyme disease are more likely to have abnormal liver chemistry than patients with localized disease. Some of the elevation in aspartate aminotransferase and alanine aminotransferase levels could indicate Lyme disease–associated myositis and not necessarily be related to hepatic injury.

Rarely, *B.burgdorferi* infection can result in granulomatous hepatitis. Lyme disease should be included in the differential diagnosis of any febrile granulomatous hepatitis. It is possible that granulomatous hepatitis may be a more frequent occurrence than originally believed. Perhaps, with improved laboratory technologies available to physicians and increased awareness of the less common causes for this condition, this diagnosis may be made more frequently in the future.

In our case, the presence of eosinophils in the granulomas also raises the possibility of either a different diagnosis or, more likely, a second diagnosis. Bjornsson *et al.* in 2000 reported a case of necrotizing granulomatous hepatitis with eosinophilia following norfloxacin administration [6]. Similarly to their case, our patient was also taking a quinolone antibiotic, ciprofloxacin, several weeks before her hospital admission, for a presumed urinary tract infection. However, in our case, there was no peripheral eosinophilia seen, as reported by Bjornson *et al.* and usually seen in cases of drug allergies. While we acknowledge that the eosinophilic infiltration seen in the liver in our patient may be due to the ciprofloxacin treatment, the positive *B. burgdorferi* antibodies and prompt response of liver lesions to, and normalization of liver chemistry with, doxycycline make Lyme disease the more likely etiology of these granulomas.

In the case of a classic presentation of Lyme disease, the diagnosis and treatment are simple. However, if a tick bite and an erythematous rash are not recalled by the patient and granulomatous hepatitis is found on liver biopsy, it is important for the clinician to include Lyme disease as part of the differential diagnosis, especially when at least 5%–10% of these patients do not have a specific diagnosis and are regarded as having idiopathic granulomatous hepatitis [7].

References

1. Zaidi SA, Singer C (2002) Gastrointestinal and hepatic manifestations of tickborne diseases in the United States. Clin Infect Dis 34:1206–1212
2. Horowitz HW, Dworkin B, Forseter G, *et al.* (1996) Liver function in early Lyme disease. Hepatology 23:1421–1417
3. Chavet P, Pillon D, *et al.* (1987) Granulomatous hepatitis associated with Lyme disease. Lancet 330:623–624

4. Goellner MH, Agger W, Burgess J, Duray P (1988) Hepatitis due to recurrent Lyme disease. Ann Intern Med 108(5):707–708
5. Aguero-Rosenfeld ME (2003) Laboratory aspect of tick-borne diseases: Lyme, human granulocytic ehrlichiosis and babesiosis. Mt Sinai J Med 70 No(3):197–199
6. Bjornsson E, Olsson R, Remotti H (2000) Norfloxacin-induced eosinophilic necrotizing granulomatous hepatitis. Am J Gastroenterol 95:3662–3664
7. MacSween RNM, Burt A, Potmann B, *et al*. (2002) Pathology of the liver. Churchill Livingstone, Edinburgh, p 833