Late-onset Sarcoidosis After Liver Transplantation for Primary Biliary Cirrhosis

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Abstract: Primary biliary cirrhosis (PBC) and systemic sarcoidosis are granulomatous diseases of unknown etiology whose hepatic manifestations may infrequently be imitative of one another. Described herein is the first reported case in the medical literature of systemic sarcoidosis developing after liver transplantation for PBC. The presented patient, who suffered from typical clinical, laboratory, and pathologic manifestations of PBC, developed decompensated liver cirrhosis within a course of 8 years, necessitating orthotopic liver transplantation. A year and a half after transplantation, the patient developed diffuse, biopsy-proven, dermatologic and pulmonary manifestations of systemic sarcoidosis, which promptly responded to corticosteroid treatment. In retrospect, the patient's longstanding liver disease was probably caused by an unrecognizable, isolated hepatic form of sarcoidosis or an overlap between PBC and sarcoidosis. This patient illustrates the complexity that may be rarely encountered in differentiating between PBC and hepatic sarcoidosis. Discussed are the clinical, laboratory, and pathologic overlaps between hepatic sarcoidosis and PBC, and clues that may aid in the diagnosis and differentiation between the 2 disorders. Hepatologists and liver transplantation specialists should be aware of the rare possibility of hepatic sarcoidosis imitating PBC, and exacerbating systemically after liver transplantation.

Key Words: liver transplantation, primary billiary cirrhosis, sarcoidosis

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CASE REPORT

A 50-year-old former liver transplant recipient was admitted for evaluation of progressive dry cough and skin rash from 6 weeks before her admission. Nine years earlier the patient was diagnosed with primary biliary cirrhosis (PBC), manifesting as cholestatic liver enzyme disturbance (alkaline phosphatase 716 units/L and γ-glutamyl transpeptidase 207 units/L), positive serology for antimitochondrial antibodies (4/4), and liver biopsy demonstrating bile ductular proliferation, portal space fibrosis with mixed inflammatory infiltrate, vanishing bile ducts, and a single granuloma. The patient denied the use of prescribed, over-the-counter or natural medications and alcohol and drug abuse. Evaluation for vascular, infectious, metabolic, and drug-induced hepatitis was unremarkable.

During the following 8 years, despite treatment with ursodeoxycholic acid (15 mg/kg), the patient gradually developed pruritus, weakness, fatigue, and jaundice. Subsequently she manifested signs of cirrhosis, including esophageal varices, splenomegaly, mild encephalopathy, and synthetic liver dysfunction and was referred for liver transplantation. Pretransplantation evaluation included a normal lung function test and total body computed tomography scan that was only remarkable for hepato-splenomegaly.

Orthotopic liver transplantation was complicated with a single episode of acute cellular rejection that promptly responded to intravenous corticosteroid treatment, a single episode of cytomegalovirus (CMV) infection that was successfully treated with Gancyclovir, and an episode of acute idiopathic inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome) that resolved after a short course of corticosteroid and plasmapharesis treatment. A month after liver transplantation, the patient was discharged with cyclosporine (300 mg b.i.d.), mycophenolate mophetyl (500 mg b.i.d.) and prednisone (20 mg q.d.) treatment. The patient regained full activity and was gradually weaned off steroid treatment. Liver function tests have remained unaltered since.

A year and a half after liver transplantation, the patient presented with a purpuric rash that gradually spread within 3 weeks from the extensor surfaces of the legs to the arms, abdomen, and back. In addition, she developed a dry cough that was unresponsive to empiric cephalosporin and macrolide antibiotic treatment. On admission, the patient seemed well with normal vital signs. Head, neck, pulmonary, cardiac, abdominal, and neurologic examination was unremarkable. Throughout the legs, arms, buttocks, abdomen, and back was a purpuric rash, characterized by psoriaticlike lichenification (Fig. 1A), most prominent around the surgical scar (Fig. 1B).

The patient's laboratory results were notable for pancytopenia with Hb 9.5 g/L, white blood cells 2.9×10^3 cells/μL, platelets 122×10^6 cells/μL and relative lymphocytosis of 44%. Also noted were hyperglobulinemia of 4.8 g/dL, elevated erythrocyte sedimentation rate of 88 mm/h, and mildly elevated C-reactive protein of 1.04. Liver function test results were

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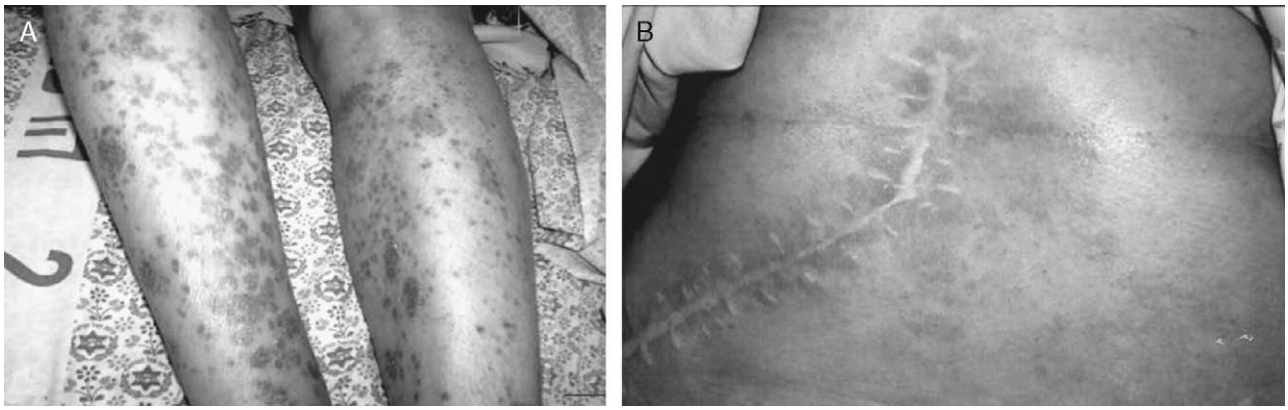

FIGURE 1. A, The patient's purpuric rash at the lower extremities, characterized by psoriaticlike lichenification. B, The rash was most prominent around the surgical scar.

unremarkable, antimitochondrial antibodies were again strongly positive (4/4), and serum cyclosporine levels were within normal ranges. CMV polymerase chain reaction and PP65 antigen were negative. Chest radiography was notable for increased interstitial lung markings in both bases. Pulmonary function tests demonstrated a moderate restrictive pattern, with moderate reduction in diffusion capacity of carbon monoxide (46% of predictive value). High-resolution computed tomography showed lymph nodes of up to 7 mm in the mediastinal region, and diffuse multiple bilateral small nodules measuring 1 to 3 mm. Significant interlobar septal beading and mild thickening of the peripheral septa were also noted (Fig. 2). Bronchoalveolar lavage was negative for CMV, adenovirus, influenza, parainfluenza, respiratory syncytial virus, and acid-fast bacilli. Transbronchial lung biopsy revealed multiple noncaseating epithelioid granulomata in the lung parenchyma and bronchial cartilage (Fig. 3A). Periodic acid-Schiff and Ziehl-nielssen stains were negative. Multiple skin punch biopsies disclosed similar noncaseating granulomas with mononuclear and eosinophil infiltrate, with negative staining for periodic acid-Schiff, Ziehl-nielssen, Giemsa, and CMV (Fig. 3B). Bone marrow biopsy revealed normocellular marrow without granulomas. The clinical, laboratory, imaging, and pathology results were highly consistent with the diagnosis of sarcoidosis. Corticosteroid treatment (prednisone 30 mg/d) was associated with rapid resolution of pulmonary symptoms and rash within 2 months. Clinical improvement was accompanied by reduction of erythrocyte sedimentation rate and C-reactive protein to normal levels, and normalization of pancytopenia and relative lymphocytosis.

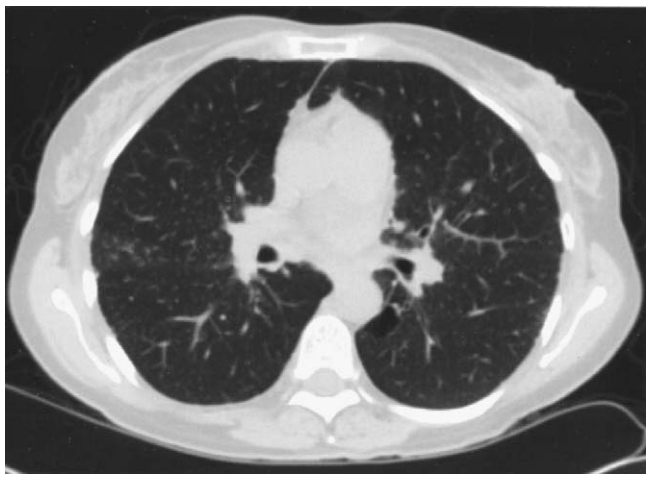

FIGURE 2. High-resolution computed tomography in lung window demonstrating diffuse multiple small lung nodules, with interlobar septal beading.

DISCUSSION

Presented herein is a patient who was initially diagnosed with PBC, underwent orthotopic liver transplantation owing to hepatic decompensation, and a year and a half later developed clinical signs of systemic sarcoidosis. To the best of our knowledge, this is the first described case in the medical literature of systemic sarcoidosis presenting after liver transplantation for presumed PBC.

PBC and sarcoidosis are two distinct granulomatous disorders that may share some clinical and pathologic similarities. The diagnosis of PBC is often based upon a combination of characteristic symptoms (including pruritus and profound fatigue), cholestatic liver enzyme disturbance, an elevated titer of antimitochondrial antibodies (> 1:40), and characteristic liver biopsy.[1–4] In contrast, the diagnosis of systemic sarcoidosis necessitates clinical signs of involvement of commonly affected organs such as the lungs, reticuloendothelial system, skin, eyes, and the central nervous system, as well as histopathologic confirmation demonstrating noncaseating granulomas in involved organs.[5–8]

Infrequently, differentiating between PBC and systemic sarcoidosis may be challenging. On the one hand, rare extrahepatic manifestations of PBC have been described.[9–17] These include interstitial and granulomatous lung disease, an association of PBC with scleroderma (CREST syndrome standing for **C**alcinosis, *R*aynaud phenomenon, *E*sophageal dysmotility, *S*clerodactyly,

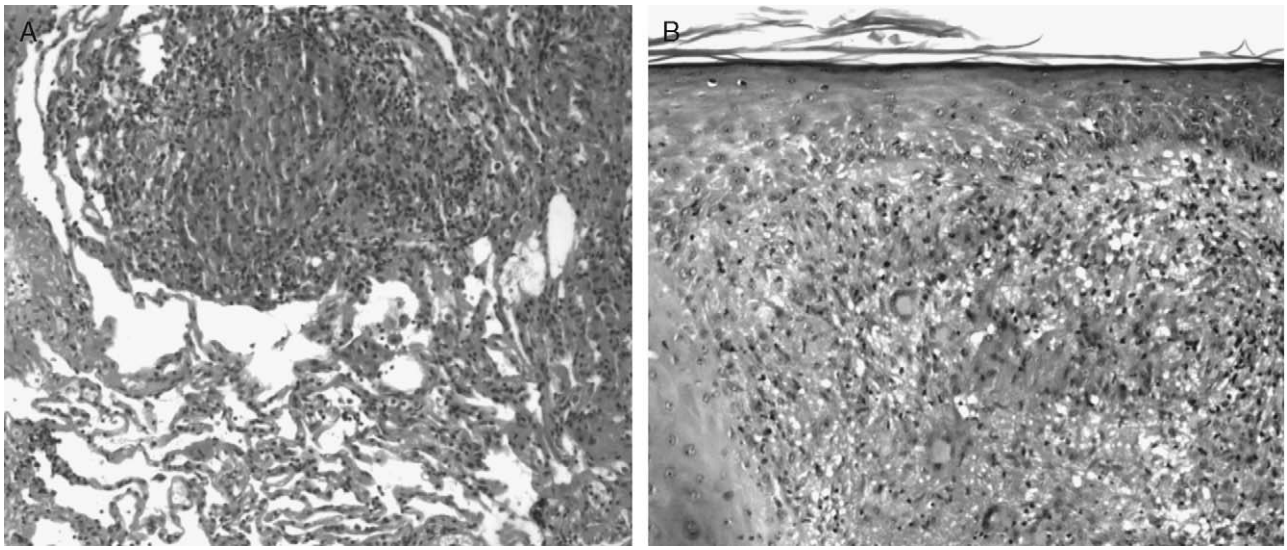

FIGURE 3. A, Lung showing large noncaseating granuloma, surrounded by normal lung parenchyma (hematoxylin and eosin, original magnification: × 100). B, Skin showing collections of epitheloid histiocytes, some multinucleated, with few lymphocytes, in the upper dermis (hematoxylin and eosin, original magnification: × 200).

and *T*elangiectasia), and granulomatous cutaneous involvement similar to that noted in systemic sarcoidosis. On the other hand, cholestatic liver disturbance is the third most common systemic manifestation of systemic sarcoidosis, noted in an estimated 11.5% of affected individuals.[18–20] In most cases of sarcoidosis, clinical hepatic involvement is minor and is discovered incidentally as part of a disease process that primarily affects the lungs.

Some rare cases, however, may feature a more prominent hepatic involvement, ranging from cholestatic hepatitis to rare complications such as hepatic vein thrombosis secondary to granuloma-induced impingement of the hepatic veins, diffuse intrahepatic biliary strictures, and portal hypertension. The marked similarities between hepatic PBC and sarcoidosis led some researchers to believe that the two diseases may represent two ends of a spectrum of granulomatous disorder that spans from isolated hepatic to a multiorgan systemic disease. Others suggested that the two disorders are discrete, but may coexist in the same patient.[21,22]

In such overlapping cases, distinguishing between hepatic PBC and sarcoidosis may be extremely challenging. Histologically, liver granulomas of sarcoidosis are usually better organized with less surrounding fibrosis and are not as closely related to the bile ducts as those in PBC. Florid duct lesions, which are considered typical of PBC, are usually not seen in hepatic sarcoidosis. Anergy to a wide range of antigens is a hallmark of systemic sarcoidosis, whereas it is restricted to tuberculosis-related antigens and dinitrocholobenzine in PBC.[23] Sarcoidosis is characterized by peripheral T-cell lymphopenia and reduced CD4/CD8 lymphocyte ratio, although the CD4/CD8 ratio is increased in lung parenchyma, skin, and liver granulomas.[24] In PBC, the peripheral T lymphocyte count and CD4/CD8 ratio in peripheral blood and in involved tissues are variable.[25]

At the time of liver transplantation, the presented patient fulfilled all clinical, imaging, and histopathologic criteria for the diagnosis of PBC and featured no extrahepatic manifestation suggesting an alternative diagnosis. However, the pulmonary and dermatologic manifestations that developed a year and a half after transplantation are highly consistent with the diagnosis of sarcoidosis. Thus, in retrospect, it is likely that the entity causing the original disease was an isolated, unrecognizable hepatic form of systemic sarcoidosis, or an overlap between sarcoidosis and PBC.

Sarcoidosis-induced end-stage liver disease is an extremely rare indication for liver transplantation (0.3%).[26,27] Survival rates were comparable to those of patients transplanted for other indications, although recurrent hepatic sarcoidosis was identified in only a single patient after 5.6 years of follow-up. In another report, recurrence of pulmonary sarcoidosis after liver transplantation was suggested to have been precipitated by weaning of immunosuppressive medication.[28] In our presented case, weaning-off of corticosteroids, completed shortly before the appearance of symptoms of sarcoidosis, may have contributed to the clinical presentation. Although some reports have suggested a linkage between cyclosporine use and sarcoidosis exacerbation,[29] the fact that the presented patient was asymptomatic throughout a year of treatment with constant doses of cyclosporine makes this possibility unlikely in our opinion.

In conclusion, we present the first case in the medical literature of a patient who underwent orthotopic liver transplantation for PBC, but subsequently developed pulmonary and dermal manifestations of systemic sarcoidosis. Treatment with systemic corticosteroids led

to rapid resolution of her disease. Awareness by hepatologists and liver transplant specialists should be raised to the rare possibility of an overlap between PBC and isolated hepatic sarcoidosis before liver transplantation, as well as to the possibility of systemic sarcoidosis arising after liver transplantation for PBC.

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