Primary biliary cirrhosis presenting with granulomatous skin lesions

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Abstract
A case is described of primary biliary cirrhosis in a 59 year old woman who initially presented with a rash over her lower legs 18 months before diagnosis. Skin biopsy examination showed non-caseating granulomas of the sarcoid type. It is believed that this is the first reported case of primary biliary cirrhosis presenting with a granulomatous rash.

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A number of skin conditions have been associated with primary biliary cirrhosis, some of which are immune mediated. Primary biliary cirrhosis is thought to be a systemic disorder and is characterised by granulomatous inflammation of the septal and interlobular bile ducts. Very occasionally extrahepatic granuloma have been found. We report a patient who presented with granulomatous skin lesions and was subsequently shown to have early primary biliary cirrhosis. The question arose as to whether the skin lesions were an unusual complication of this disease or whether she had two disorders, namely, primary biliary cirrhosis and cutaneous sarcoid.

Case history
A 59 year old woman with a previous history of untreated mild hypertension and depression was referred for investigation of a rash, which had initially occurred 18 months previously. It consisted of painless erythematous patches on her shins, which healed spontaneously over the course of four weeks without bruising. This was followed by episodes of severe lethargy, which became continual over the 18 months before her presentation. There were associated limb girdle muscle aches.

On examination her skin and musculature were normal and she was mildly hypertensive. Investigations included a full blood count and erythrocyte sedimentation rate test, a chest x ray, urea and electrolyte tests, a midstream urine and a serum cholecystokinin test, all of which were normal. Her liver function tests were also normal apart from a mildly raised alkaline phosphatase activity of 157 U/l (normal 30–120 U/l) and serum electrophoresis, which showed a polyclonal increase in IgM 3.5 g/l (normal 0.5–2.0 g/l), and IgG 16 g/l (normal 7–14 g/l).

When she was reviewed a month later, she complained of pains in her distal limbs, all of which were normal on examination. Her serum alkaline phosphatase activity was again mildly raised (165 units/l) and her anti-mitochondrial antibody titre was raised (>640). Other auto-antibodies including anti-nuclear, thyroid, and rheumatoid factor were negative. Ultrasound of the liver, gall bladder, common bile duct, and pancreas was normal. For the next year she remained well but had further episodes of lethargy and ankle pain, lasting up to six weeks at a time. She then had a recurrence of her rash, which was very similar to but more extensive than, the original episode. It started on her lower legs and spread to her thighs, arms, and shoulders in a symmetrical distribution over two weeks. It was present on the legs, resolving on the arms, and consisted of discrete erythematous macular lesions, each 2–3 cm in diameter and spherical in shape. Some of these were nodular and blanched with pressure (Fig A).

Histological examination of the skin biopsy specimen showed non-caseating granulomas in a periadnexial and perivascular distribution. These were mainly in the dermis extending down into the subcutaneous fat, consistent with a granulomatous dermatitis (Fig B). Surface marker analysis of the lymphocytic infiltrate showed predominantly CD4 (helper) T lymphocytes but with significant numbers of CD8 (cytotoxic/suppressor) T lymphocytes present (Fig C and D). The peripheral lymphocyte count was 2.2–3.0×10⁹/l (normal 0.8–1.0×10⁹/l), which included a CD4 count of 0.6–1.0×10⁹/l (normal 0.7–1.0×10⁹/l) and a CD8 count of 0.7–1.0×10⁹/l (normal 0.3–0.4×10⁹/l). The CD4:CD8 ratio was therefore 1:4 (normal 1–2:6). Histological examination of the liver biopsy specimen showed some central bile ducts surrounded by collections of epithelioid histiocytes with associated fibrosis and lymphocytic infiltration. This was thought to be consistent with primary biliary cirrhosis.

Serum alkaline phosphatase activity was again mildly raised and anti-mitochondrial antibodies remained positive at a titre of >640. Cell mediated immunity skin tests were positive for tetanus, diphtheria, streptococcus, candida, and trichophyton antigens and the lipid profile was normal. The other auto-antibodies and the angiotensin II converting enzyme assays were normal. The Mantoux skin test was negative as were Mycobacterium tuberculosis cultures from early morning urine and both the liver and skin biopsy specimens.

Discussion
This patient presented with a rash on her legs before the diagnosis of primary biliary cirrhosis was made. Although a biopsy examination was not done initially of the rash, it recurred later and was shown to be granulomatous. Histologically the appearances were similar to those of sarcoid affecting the skin. It is more probable, however, that the rash was the first symptom of her evolving primary biliary cirrhosis, a diag-
The skin lesions: (A) the rash consisted of discrete erythematous macular lesions 2-3 cm in diameter; (B) photomicrograph showing the granulomatous reaction in the dermis. (Haematoxylin and eosin, original magnification ×10); (C) photomicrograph showing perivascular CD4 positive lymphocytes (arrowed). (Immunoperoxidase, original magnification ×40); (D) photomicrograph showing perivascular CD8 positive lymphocytes. (Immunoperoxidase, original magnification ×40.) The CD4:CD8 ratio in the dermal lesions was approximately 4:1. (C) and (D) were adjacent sections through the dermis.

nosis supported by the cholestatic liver function tests, the biopsy findings, the positive anti-mitochondrial antibodies, and the raised serum IgM concentration. This would also support the theory that primary biliary cirrhosis, like sarcoid, is a generalised granulomatous condition. To our knowledge, this is only the second reported case of primary biliary cirrhosis associated with skin granuloma and is unique in that the skin rash was the presenting symptom.

Sherman et al described a 30 year old white woman who presented with epigastric pain and mildly disordered liver function tests. Subsequent liver biopsy examination showed a single non-caseating granuloma but her anti-mitochondrial antibody test was initially negative but became positive two years later. A repeat liver biopsy examination was diagnostic of primary biliary cirrhosis. Six years after her initial presentation she developed a granulomatous rash, which was diagnosed as cutaneous sarcoid.

An overlap syndrome consisting of pulmonary sarcoid and primary biliary cirrhosis has long been recognised. Most of these patients had positive anti-mitochondrial antibodies and hepatic granulomas. They subsequently developed pulmonary sarcoid type granuloma though not all were Kveim test positive. Various clinical criteria were used to decide the disease that was the more dominant in each patient. The authors postulated that primary biliary cirrhosis and generalised sarcoidosis were at opposite ends of the spectrum of granulomatous disease. This would explain the overlap syndromes and implied a common cause for both disorders.

Against this unifying hypothesis, however, are the differing immunopathological characteristics of these diseases. The liver granuloma of sarcoidosis are better organised with less surrounding fibrosis and are not as closely related to the bile ducts as those in primary biliary cirrhosis. Delayed hypersensitivity skin testing shows a lack of response to a broad range of antigens in generalised sarcoidosis whereas in primary biliary cirrhosis, anergy is restricted to tuberculin and dinitrochlorobenzene antigens. Surface marker analysis of peripheral blood lymphocytes in active sarcoidosis shows a T cell lymphopenia with a decreased proportion of CD4 cells and an increased proportion of circulating CD8 cells. Conversely, the lymphocytes in and around the skin and liver granulomas are nearly all CD4 helper cells. In primary biliary cirrhosis, the peripheral T lymphocyte count may be decreased or normal (as in our patient) and the CD4 helper:CD8 suppressor ratio may vary according to the stage of the disease. The T cells affected in the liver granulomas are a mixture of CD8 and CD4 cells, which is a different cell population to that seen in sarcoid. In the patient described by Sherman et al., the surface marker analysis of the skin granulomas showed a considerable predominance of CD4 cells, which is consistent with sarcoid. The skin granulomas in our patient fitted more with primary biliary cirrhosis as there were significant numbers of T 8 cells present. Twenty five per cent of the infiltrating lymphocytes were T suppressor cells. Similarly both the peripheral differential T lymphocyte count and the delayed hypersensitivity skin tests were more in keeping with primary biliary cirrhosis than sarcoidosis. Therefore, we consider this patient to be the first reported case of primary biliary cirrhosis presenting with a granulomatous skin rash as an extrahepatic manifestation.

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