Cutaneous amyloidosis associated with primary biliary cirrhosis

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Primary cutaneous amyloidosis is defined as the deposition of amyloid in the skin in the absence of systemic involvement. The association between primary cutaneous amyloidosis and other diseases, although rare, has been documented for connective tissue disorders such as systemic sclerosis, systemic lupus erythematosus and rheumatoid arthritis. We report the case of a 41-year-old woman who developed primary biliary cirrhosis in association with primary cutaneous amyloidosis. This association has not been reported before in the literature. ***Eur J Gastroenterol Hepatol*** **19:603–605 © 2007 Lippincott Williams & Wilkins.**

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Introduction

Virchow [1] introduced the term amyloidosis to describe a new type of amorphous material found in tissues which could be stained with iodine and sulfuric acid. Over time, this material has been found to be related not only to a single disease, but to a process of deposition of protein fibrillary plaques formed by different mechanisms [1].

Amyloidosis can be divided into primary and secondary forms. Primary amyloidosis is the most common form in the western world and it is associated with immunological disorders such as multiple myeloma and lymphoma, and preferentially affects muscle, heart, gastrointestinal tract and peripheral nerves [2]. In the systemic form, the skin is affected in 29–40% of cases and provides a good indicator for the diagnosis of the disease [1]. Lesions are the result of capillary fragility owing to infiltration of the dermis and vascular wall by amyloid deposits, with petechiae, purple plaques and ecchymoses because of minimal injuries being common [1]. Secondary amyloidosis shows a greater association with chronic infections and inflammatory diseases and preferentially affects the kidneys, adrenal glands and gastrointestinal tract [2].

Primary cutaneous amyloidosis (PCA) is defined as the deposition of amyloid in the skin in the absence of other systemic or skin diseases [3]. The disease is classified into three types: macular, lichen and nodular [3]. In the macular and lichen forms, the amyloid is derived from the degeneration of epidermal keratinocytes, whereas in the nodular form it is associated with a blood disorder (with no evidence of paraproteinemia) [1]. The macular form predominates among women between 30 and 60 years of age, being more common in Central and South America, Asia and the Mediterranean, and manifests as poorly delimited pruriginous and hyperpigmented lesions on the back and limbs [1]. The lichen form affects various ages and produces pruriginous lesions mainly on the extremities [1]. In contrast, the nodular form is peculiar because it may show symptoms overlapping with those of primary systemic amyloidosis during its course [1].

The association between PCA and other diseases, although rare, has been documented for connective tissue diseases such as systemic sclerosis, systemic lupus erythematosus and rheumatoid arthritis [4]. Here, we report a case of a 41-year-old woman with PCA who developed primary biliary cirrhosis. Previous report in the literature about this type of association was not found.

Case report

A 41-year-old Caucasian woman has been followed up at the Dermatology outpatient clinic since 2000 because of the appearance of poorly delimited hyperpigmented macules, which predominated on the trunk and limbs. After a skin biopsy, these lesions were diagnosed as the macular form of PCA. No biochemistry evaluation of liver enzymes was made at that time.

In August 2004, the patient presented with itching, jaundice, choluria and acholia and was referred to the Hepatology Service of the same hospital. During this period, the patient reported no fever, use of medications,

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blood transfusions or contact with individuals with hepatitis. Physical examination showed 3 + /4 + jaundice and a painless liver with a thick edge 14 cm from the right costal margin. Laboratory exams revealed cholestatic jaundice with preserved hepatic function: total bilirubin = 9.7 mg/dl (normal value: 1.0 mg/dl), direct bilirubin = 8.0 mg/dl (0.4 mg/dl), γ-glutamyltransferase = 2649 U/l (30 U/l), and alkaline phosphatase = 2485 U/l (250 U/l). Serology for hepatitis A, B and C was negative, and the iron store profile was normal. Ultrasound of the liver only showed homogeneous hepatomegaly in the absence of biliary lithiasis or dilatation of the bile ducts.

Determination of serum antimitochondrial antibody was positive (1 : 320) by immunofluorescence and the M2 fraction (AMA-M2) was positive by enzyme-linked immunosorbent assay. The patient was submitted to a percutaneous liver biopsy to rule out hepatic involvement with deposition of amyloid material. Although the execution of a liver biopsy in the case of a diagnostic suspicion of liver amyloidosis is controversial due to the increased risk of hemorrhagic complications, in this case diagnostic differentiation was necessary because of the marked hepatomegaly. The liver biopsy revealed biliary-type portal fibrosis with ductopenia and the absence of an amyloid deposit even after staining with Congo red.

The patient was treated with ursodeoxycholic acid (15 mg/kg/day) with improvement of the symptoms and levels of cholestatic enzymes and she was referred to orthotopic liver transplantation. Her model for end-stage liver disease score was 15 and the estimated survival by the Mayo score was 89% within 1 year and 37% within 5 years.

Discussion

Breakdown of organ homeostasis by the deposition of amyloid promotes the clinical manifestations of amyloidosis [2,5]. The kidneys, heart and peripheral nerves are the organs most affected by amyloidotic syndromes, whereas hepatic amyloid is observed in at least 70% of autopsied patients [5].

Liver involvement in amyloidosis is characterized by hepatomegaly in 80–90% of cases and by an increase of cholestatic enzymes, mainly alkaline phosphatase, due to biliary stasis secondary to amyloid fibrils [5,6]. Histologically, the amyloid deposit can be present in three different forms: parenchymatous, sinusoidal and Disse spaces, with vascular and periportal or periportal and parenchymatous involvement [2].

As the clinical manifestations of liver amyloidosis present low specificity, mimicking numerous other liver diseases, accurate diagnostic methods such as scintigraphy, angiography and liver biopsy are necessary. Technetium scintigraphy shows an irregular distribution of the radionuclide in the hepatic parenchyma and the occasional absence of splenic uptake, but is not a usual test [5]. Angiography demonstrates luminal irregularities and abrupt changes in the caliber of hepatic artery branches owing to compression by the sinusoidal amyloid, but these alterations are not specific [5]. Therefore, the diagnosis should be confirmed by a liver biopsy using Congo red staining, with this method representing the gold standard for the diagnosis of liver amyloidosis [2]. Congophilia is the main characteristic of amyloid deposits, revealing an apple-green birefringence under polarized light that is directly related to β-amyloid plaques [1].

In this patient, the diagnosis of primary biliary cirrhosis was confirmed by the presence of AMA-M2 and the suspicion of liver amyloidosis was ruled out by a biopsy. PCA has been associated with collagen diseases, including dermatomyositis and autoimmune cholangitis [7]. Its association with primary biliary cirrhosis has also been reported but in patients with sclerosis as a third concomitant disease [7].

It is possible that PCA, sclerosis and biliary involvement share common immunological characteristics. In PCA, it has been suggested that hyaline bodies (colloid bodies) found in the epidermis result in the degeneration of keratinocytes [1,7]. These hyaline bodies are not destroyed owing to immunotolerance, which inhibits their lysis and elimination and thus permits their transformation into amyloid deposits [1]. The expression of antikeratin antibodies in these tissues has recently been described, suggesting that the process may derive from keratin filaments [1].

One of the hypotheses to explain the simultaneous occurrence of biliary damage and cutaneous amyloid involvement is the presence of epitopes common to keratinocytes and bile duct epithelium [7]. Thus, the autoantibodies formed react against these elements and cause different manifestations of the same spectrum of disease. It remains to be determined whether antikeratin autoantibodies may cross-react with components of the biliary epithelium and thus explain the biliary damage found.

In conclusion, as PCA seems to be related to autoimmunity, the presence of other diseases with the same pathophysiology must be considered and investigated.

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