

An unusual cause of abnormal liver function test: hepatic amyloidosis

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ABSTRACT We describe a case of systemic amyloidosis predominantly involving the liver. The patient presented with non-specific symptoms and deranged LFTs. Liver biopsy revealed characteristic findings of amyloidosis. The patient was treated with combination therapy and continues to have a good clinical response at four months' follow-up. We briefly discuss the classification, presentation and management of amyloidosis.

Published online March 2007

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KEYWORDS Abnormal liver function tests, amyloidosis, hepatic, liver

LIST OF ABBREVIATIONS Serum amyloid P (SAP), light chain amyloidosis (AL), amyloid A amyloidosis (AA), familial mediterranean fever (FMF), liver function test (LFT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (γ GT), alkaline phosphatase (ALP), multiple myeloma (MM), gastrointestinal (GI), electrocardiogram (ECG), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)

DECLARATION OF INTERESTS No conflict of interests declared.

CASE REPORT

A 59-year-old male was referred to the gastroenterology clinic with a three-month history of fatigue, malaise and persistently abnormal LFTs. Clinical examination revealed a patient with tattooed arms and firm non-tender hepatomegaly. There were no other stigmata of chronic liver disease. Abdominal ultrasonography showed hepatomegaly with generalised hyper-reflectivity. No splenomegaly or portal vessel abnormality was seen. Initial biochemical profile revealed bilirubin of 18 mmol/l (normal range: 0–17), ALT: 41 IU/l (normal: 0–40), AST: 54 IU/l (normal: 0–40), γ GT: 548 U/l (normal 0–50), ALP: 442 U/l (normal: 39–118). Total protein, albumin and coagulation profile were normal. ESR was elevated at 105 mm/hr and CRP was normal.

Serum creatinine was 119 μ mol/L with an estimated creatinine clearance of 40.6 ml/min. Twenty-four hour urinary protein was 2.34 g. Viral hepatitis and auto-antibody screen were negative; ferritin, caeruloplasmin, copper and α 1-antitrypsin level were all normal.

Serum protein electrophoresis demonstrated increased alpha-2 and beta-globulins, decreased albumin and an abnormal protein band behind the beta-globulin fraction. Urine was negative for paraproteins. Serum immunoglobulins showed an elevated IgM.

The patient underwent a liver biopsy. Histology demonstrated fragments of liver containing acellular,

amorphous, pale extracellular material. It displayed apple green birefringence with Congo Red stain which is characteristic of amyloidosis (see Figures 1 and 2). His ECG showed normal voltage QRS complexes with good R-wave progression. Echocardiography revealed left ventricular hypertrophy with a bright myocardium (a non-specific sign) and diastolic dysfunction. Bone marrow biopsy showed infiltrative amyloidosis but no evidence of MM.

A serum amyloid P scan showed a large amount of abnormal amyloid uptake in the liver and spleen, obscuring the kidneys and adrenal glands. There was abnormal signal from bone marrow which is a pathognomic feature of AL amyloidosis.

The final diagnosis was systemic AL amyloidosis with predominant hepatic involvement, complicating a secreting plasma cell dyscrasia.

The patient was felt to be unsuitable for the usual treatment regime of colchicine and melphalan due to the extent of disease. He was commenced on the CDT regime (cyclophosphamide, dexamethasone and thalidomide). Currently at seven months follow-up he is asymptomatic.

DISCUSSION

Amyloidosis comprises a unique group of diseases that share in common the extra-cellular deposition of insoluble fibrillar proteins in organs and tissues. It is

usually an acquired condition, however there are several hereditary amyloid syndromes.¹ Depending upon the biochemical nature of the amyloid precursor protein, amyloid fibrils can be deposited locally or involve virtually every organ of the body.²

The original attempts to classify amyloidosis were based on apparent aetiology and perceived differences in organ involvement. The most popular classification subdivided amyloidosis into primary, secondary, localised, familial and myeloma-associated amyloidosis. Emphasis was given to apparent differences in organ involvement among the various syndromes. However, a significant overlap between the syndromes became apparent and led to an update of the nomenclature and classification in 2001 by the Committee of the International Society of Amyloidosis.³

The amyloidoses are now classified according to the identity of the fibril-forming protein. The two major forms are designated AL (primary or Light chain amyloidosis) and AA (secondary or Amyloid A amyloidosis), which account for about 90% of all cases.^{1,2,4,5} A wide variety of other types of amyloid have been described (22 in total).

Light chain amyloidosis is the most common form of systemic amyloidosis seen in current clinical practice. It was previously classified as primary idiopathic amyloidosis and the myeloma-associated type. Fewer than 20% of patients with AL have myeloma and about 15% of myeloma patients develop amyloidosis. The amyloid consists of kappa (κ) or lambda (λ) immunoglobulin light chains produced by a monoclonal population of plasma cells.^{1,4,5} Lambda (λ) chain-class predominates over kappa (κ) in AL by 2:1 ratio.^{1,2}

In AA (secondary, reactive or acquired) amyloidosis the fibrils derived from serum amyloid is produced in response to chronic infections or inflammatory processes such as tuberculosis, osteomyelitis, rheumatoid arthritis and FMF.^{5,7}

Amyloidosis often involves the liver (54% in AL vs 18% in AA). Functional abnormalities are minimal and occur late in the disease.^{1,2,4,7-9} Amyloid A amyloidosis predominantly affects the walls of blood vessels in the portal tract thus constituting a 'vascular pattern'^{10,11} whilst, AL amyloid additionally exhibits a 'sinusoidal pattern' of distribution.^{10,11} Hepatic amyloidosis usually manifests with hepatomegaly. Elevated serum ALP has been noted in 5% of patients with AL amyloidosis.^{1,4,7,8,12,13} Twenty percent of patients develop portal hypertension.^{14,15}

Amyloidosis usually presents after the age of 40 with fatigue, weight loss (50%), oedema, paraesthesia, purpura,

bone pain, postural hypotension, gastrointestinal bleeding, and diarrhoea.^{1,2,4} Hepatomegaly is noted in 20% to 40% of patients. Elevated ALP, increased prothrombin time and hypoalbuminaemia are common laboratory abnormalities. Hyperbilirubinemia is rare and transaminases are often normal.^{1,15} There is poor correlation between LFT abnormalities and degree of hepatic involvement.^{1,4,7,8,16} Gross, firm hepatomegaly and tenderness on palpation in the absence of other signs of primary liver disease may be the only presenting finding.^{1,4,7,8,16} Nephrotic syndrome may coexist with liver involvement thus leading to hypoalbuminemia and hypercholesterolemia. I

Diagnosis of amyloidosis requires histological evidence of amyloid deposition.¹⁸ Immunohistochemistry is necessary to determine the true nature of the proteins which form amyloid fibrils. The least invasive diagnostic assay is rectal (or subcutaneous fat) biopsy which is diagnostic in up to 80% of cases of systemic amyloidosis.^{1,4} Patients with confirmed systemic amyloidosis and hepatomegaly do not require confirmation of liver amyloid disease as it rarely causes significant morbidity.¹ Liver biopsy carries an increased risk of bleeding and spontaneous rupture of the liver has been described.²¹ In cases such as ours, with non-specific symptoms and abnormal LFTs, liver biopsy is justified, providing the platelet count and clotting abnormalities are corrected.^{1,7} In these cases transjugular liver biopsy may be a safer approach.

In the liver, amyloid is deposited in the form of amorphous, hyaline material predominantly in the walls of arterioles and in the space of Disse.⁷ Amyloid deposits distort and compress the normal hepatocyte plates thus leaving little normal hepatic parenchyma.

Although there is no specific treatment for AL amyloidosis, studies have shown that treatment with corticosteroids, colchicine and melphalan²¹ prolong survival. Studies have shown no difference in survival of patients treated with colchicine and those treated with corticosteroids and melphalan.²⁰ Mean survival in AL amyloidosis is 12 months following diagnosis and nine months if portal hypertension is present. The main cause of early death is congestive heart failure.^{1,2,4} Patients with marked cholestasis have a mean survival time of only three months. .

CONCLUSION

Cases of systemic amyloidosis have a wide variety of presentations. Hepatic involvement is common but not the main cause of morbidity. Persistently abnormal LFTs that elude diagnosis may warrant further investigation for amyloidosis. Our patient was diagnosed following liver biopsy and continues to have a good response to therapy.

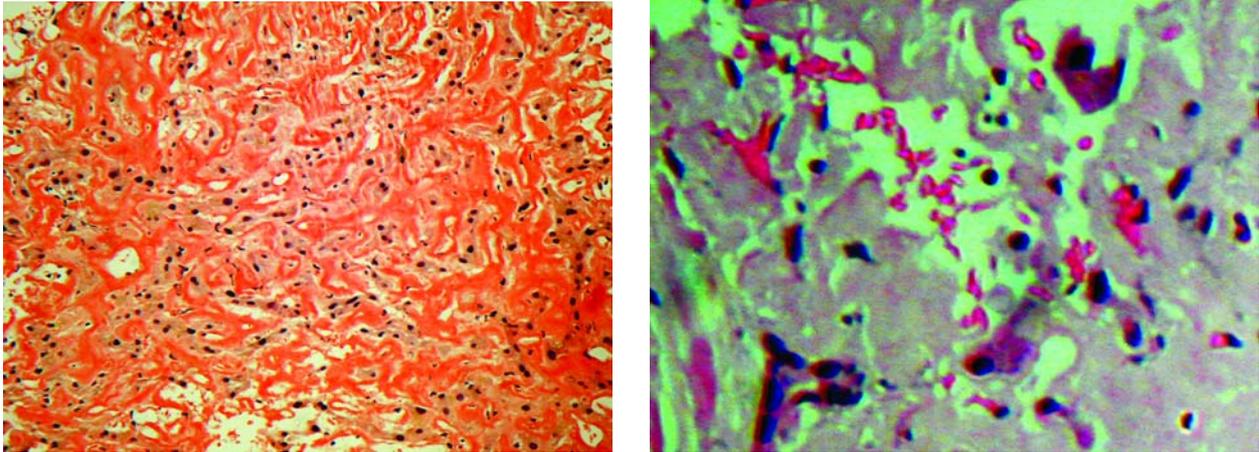


FIGURE 1 AND 2 Liver biopsy of patient showing liver fragments containing acellular, amorphous, pale extracellular material that displays apple green birefringence with Congo Red stain.

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