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Case Report

CASE REPORT

Myeloma-associated systemic amyloidosis masquerading as NASH-associated cirrhosis and diabetic microvascular complications

Partha Pal[1], Sayantan Ray[2,*], Sisir Kumar Patra[3], Anjan Kumar Das[3], Subhasis Dey[1], and Rintu George[1]

[1]Department of General Medicine, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India, [2]Department of Endocrinology and Metabolism, Institute of Post Graduate Medical Education & Research (IPGMER) and SSKM Hospital, Kolkata, West Bengal, India, and [3]Department of Pathology, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India

*Correspondence address. Department of Endocrinology, IPGMER and SSKM Hospital, 244, AJC Bose Road, Kolkata 700020, West Bengal, India. Tel: +91-9231674135; E-mail: sayantan.ray30@gmail.com

Abstract

Authors describe the case of a 60-year-old diabetic man who presented with jaundice, ascites and significant weight loss over a period of 2 months. Physical examination revealed firm hepatomegaly with ascites. On evaluation, nephropathy, axonal neuropathy, carpal tunnel syndrome and decompensated cryptogenic liver disease with portal hypertension were found fitting with the diagnosis of diabetic nephropathy and neuropathy and nonalcoholic steato-hepatitis-associated cirrhosis, respectively. It was only after tissue diagnosis and serum protein electrophoresis that a definitive diagnosis of myeloma-related amyloidosis was made. This case emphasizes the fact that due to nonspecific initial presentation and multisystem involvement, a high index of suspicion and prompt use of appropriate tests including tissue diagnosis may be required to diagnose amyloid light-chain amyloidosis, which may be a rare presenting feature of myeloma. It should be differentiated from a commoner multisystem disease like diabetes and its complications.

INTRODUCTION

Myeloma-associated systemic amyloidosis may involve kidney, heart, liver and peripheral nervous system in the form of nephrotic syndrome and/or renal impairment, hepatic amyloidosis and sensorimotor axonal polyneuropathy with carpal tunnel syndrome (CTS), respectively [1]. Hepatic involvement as presenting complaints is uncommon and includes hepatomegaly-related right upper quadrant discomfort and even more rarely as severe cholestasis, hepatic encephalopathy or intractable ascites [1–3]. On the other hand, type 2 diabetes may lead to microvascular complications such as diabetic nephropathy with variable proteinuria and diabetic sensorimotor polyneuropathy, and diabetes-associated nonalcoholic steato-hepatitis (NASH) which may lead to advanced liver disease with portal hypertension [4]. Diabetes can also cause CTS. We report a case of myeloma-related amyloidosis masquerading as NASH-associated cirrhosis and diabetic microvascular complications.

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CASE REPORT

A 60-year-old man presented with jaundice, ascites and weight loss over 2 months along with tingling and numbness in all extremities. He had been diagnosed with type 2 diabetes 6 years back and was fairly controlled with oral hypoglycemic agents. There was no history of fever, abdominal pain, alcoholism, hepatotoxic drug intake or any past or family history of jaundice. Physical examination revealed mild pallor, icterus, bipedal edema, firm non-tender hepatomegaly and ascites. There was no orthostatic hypotension and fundoscopy was normal. Complete blood count showed normocytic anemia (hemoglobin 10.2 g%, normal iron studies) and a raised erythrocyte sedimentation rate: 62 mm/first hour. Liver function test revealed a cholestatic pattern of liver involvement: conjugated hyperbilirubinemia (total bilirubin 2.9 mg/dl and direct 2 mg/dl), markedly raised alkaline phosphatase (1223 U/l), hypoalbuminemia (2.2 g/dl) with a globulin level of 3.5 mg/dl, mildly increased INR (1.5) and mildly raised transaminases (aspartate transaminase 54 U/l and alanine transaminase 44 U/l). Renal function tests showed azotemia and thyroid function tests were unremarkable. Serological tests for hepatitis B and C were negative. On ascitic fluid study, total cell count was 280 cells/cmm, most of them were lymphocytes. Serum ascites albumin gradient (SAAG) was 1.64 g/dl, indicating high SAAG ascites. Ultrasound of abdomen showed hepatomegaly with coarse echo-texture, ascites without any biliary obstruction and altered cortico-medullary differentiation in the kidney with normal kidney size. Stool for occult blood test was negative and upper gastrointestinal endoscopy revealed grade 2 esophageal varices. A contrast CT scan abdomen showed ascites and heterogeneously enhancing enlarged liver but no detectable mass lesion. Serum alpha fetoprotein was normal. So, NASH-associated cirrhosis on the background of type 2 diabetes was suspected. Echocardiography was normal. Urine examination revealed nephrotic range proteinuria (3 g/24 h) without any active sediment. Nephrotic range proteinuria in the absence of diabetic retinopathy prompted us to perform renal biopsy, which showed amyloid deposits (Fig. 1). Systemic amyloidosis was diagnosed and percutaneous liver biopsy was done to rule out other potential pathologies of cholestatic liver disease with portal hypertension considering the rarity of ascites and other stigmata of portal hypertension in hepatic amyloidosis and to complete the diagnostic assessment of cholestatic liver involvement. It revealed marked deposition of acellular amorphous eosinophilic deposit within the hepatic sinusoids (Fig. 2A), suggestive of hepatic amyloidosis. It was subsequently confirmed with Congo red staining (Fig. 2B). Serum protein electrophoresis showed hypoalbuminemia with monoclonal spike in gamma-globulin region. Serum immunofixation electrophoresis showed monoclonal IgG kappa light chain para-protein. Flow cytometric immunophenotyping of bone marrow aspirate specimen showed a population CD138 cells (Fig. 3A–C). Serum beta-2 microglobulin was raised: 10 600 µg/l. Bone marrow aspiration and later biopsy were performed which showed 20% plasma cells (Fig. 4A and B). Electro-diagnostic study of all four limbs showed absent sensory nerve action potentials and low amplitude compound motor action potentials with preserved motor conduction velocities suggestive of axonal neuropathy along with prolonged distal median motor latencies suggestive of CTS. The patient was referred to hematology department where he was started on combination induction therapy with thalidomide, dexamethasone and bortezomib. Unfortunately, after 6 weeks of

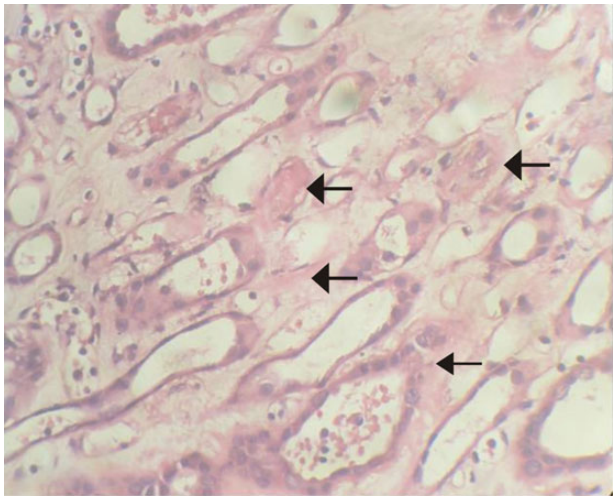

Figure 1: Kidney biopsy specimen showing amyloid deposit between renal tubules seen as amorphous hyaline material (black arrows) [H&E, ×100].

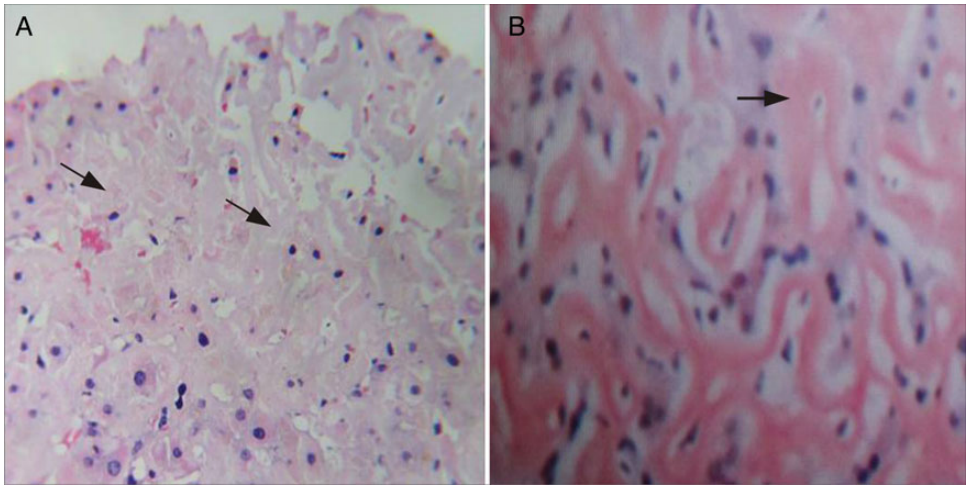

Figure 2: (**A**) Liver biopsy specimen showing amorphous eosinophilic deposit within the hepatic sinusioids (black arrows) [H&E, ×100] and (**B**) photomicrograph showing eosinophilic acellular material (arrow) positive for amyloid on Congo red stain (×200).

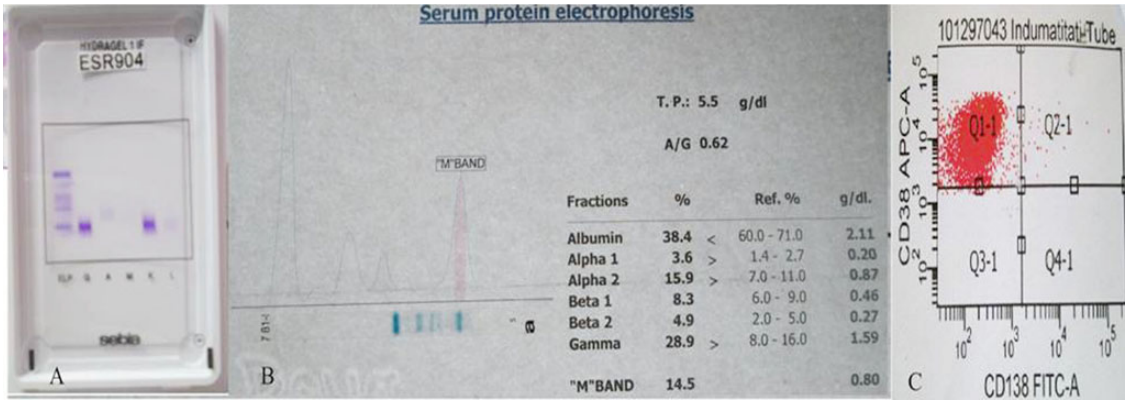

Figure 3: (**A**) Serum immunofixation electrophoresis showing κ light chain; (**B**) Serum protein electrophoresis showing M band and (**C**) Flow cytometric scatter plot: positive for CD138 cells.

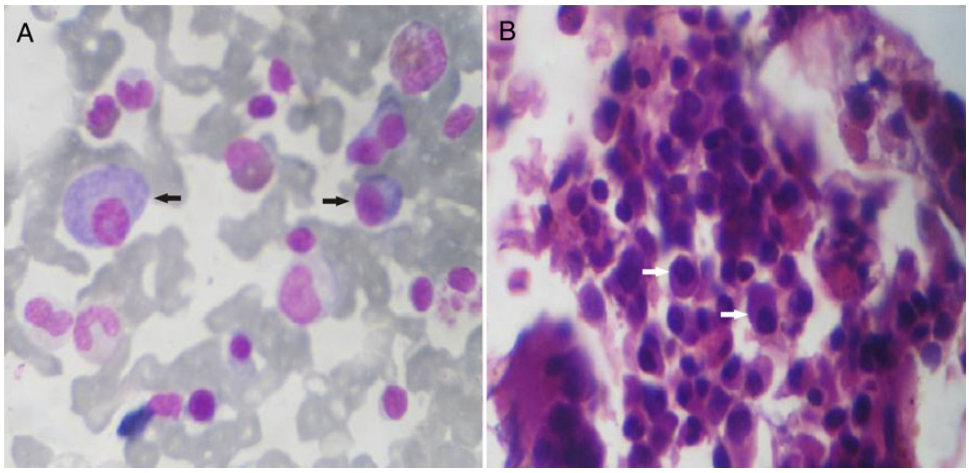

Figure 4: (**A**) Photomicrograph of bone marrow aspiration specimen showing plasma cells (black arrows) [H&E, ×100] and (**B**) bone marrow trephine biopsy specimen showing plenty of plasma cells (white arrows) suggestive of multiple myeloma.

treatment, the patient succumbed due to sepsis and progressive liver failure inspite of all supportive measures.

DISCUSSION

Earlier descriptions suggest that primary systemic amyloidosis mainly involves tongue, heart, gut, muscle nerve and skin, whereas secondary amyloidosis involves liver, spleen, kidney and adrenals predominantly [1]. But, now it is recognized that liver is commonly involved in primary amyloidosis. The amyloid proteins in primary and secondary amyloidosis are amyloid light-chain (AL) and amyloid-associated protein (AA), respectively [1, 5]. The basic patterns of hepatic amyloid deposits are (i) parenchymal involvement (prominent hepatomegaly), (ii) vascular and periportal (less prominent hepatomegaly) and (iii) mixture of 1 and 2. Deposits may be typical non-globular or less common globular deposits (5–40 μm in diameter) with amorphous eosinophilic appearance on hematoxylin and eosin staining and apple-green birefringence on Congo red staining. Recent reports show that AA amyloidosis exhibit frequent vascular and less parenchymal involvement, and AL amyloidosis have near universal parenchymal involvement [6].

Multiple myeloma usually presents with anemia and skeletal manifestations [7]. Rarely, it may manifest as AL amyloidosis. In any dyscrasia of monoclonal B lymphocytes, unique monoclonal unfolded immunoglobulin light chains (more commonly from λ rather than κ), which lose their tertiary or higher order structure, can readily aggregate retaining their β-sheet secondary structure into amyloid fibrils [8]. Systemic AL amyloidosis typically presents after fourth decade predominantly involving male and outnumbers AA amyloidosis. Commonly presenting symptoms are nonspecific and include fatigue, weight loss and edema (40–70%) and paresthesias (25%). Systemic involvement includes heart (50% usually restrictive cardiomyopathy), kidney (33%), gastrointestinal system (involvement from mouth to anus), liver (hepatomegaly and rarely severe cholestasis, portal hypertension, intractable ascites and peripheral edema, subacute or fulminant hepatic failure, hepatic encephalopathy, spontaneous hepatic rupture and focal intrahepatic mass), peripheral nervous system (painful sensory neuropathy followed by motor deficits, autonomic neuropathy and CTS) and skin [1, 9, 10]. The non-specific clinical manifestations of AL amyloidosis underlie the need for prompt appropriate investigations such as biopsy of the affected organ, serum immunofixation electrophoresis and serum-free light chain assay to identify underlying plasma cell dyscrasia [8].

Systemic amyloidosis should be suspected in the setting of monoclonal gammopathies, chronic inflammatory diseases and typical manifestations of systemic amyloidosis. Multiple myeloma primary manifesting as systemic amyloidosis in the

background of confounding multisystem disease such as diabetes which can lead to nephropathy, neuropathy, CTS and hepatocellular dysfunction with portal hypertension made the diagnosis difficult. However, the presence of nephrotic range proteinuria in the absence of diabetic retinopathy prompted us to perform renal biopsy which clinched the diagnosis. Finding of hepatic amyloidosis on liver biopsy can explain jaundice, cholestasis, ascites, hepatomegaly and portal hypertension.

CONCLUSION

The present case highlights that high index of suspicion and prompt use of appropriate tests are necessary to diagnose myeloma-associated amyloidosis, which can present with features of various organ involvement that may mimic manifestations of other more common multisystem disease such as diabetes. Secondly, hepatic amyloidosis should be kept in the differential diagnosis of hepatomegaly and portal hypertension in which case the pattern of amyloid deposition in liver biopsy may be helpful in differentiating primary and secondary amyloidosis to some extent.

AUTHORS' CONTRIBUTIONS

All authors had access to the data and a role in writing the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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