# An unusual presentation of primary amyloidosis

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## ABSTRACT

A 65-year-old male patient presented with right upper-quadrant abdominal pain. Ultrasonography revealed hypoechoic lesion in the perihepatic and intraparenchymal area. Computed tomography (CT) showed hypodense lesion in the same localization. A fine needle biopsy specimen of the perihepatic lesion was hemorrhagic. On abdominal CT, the liver showed enhancement, but the spleen did not enhance. The spleen could not be detected by scintigraphic imaging using $Tc^{99}m$ sulfur dioxide. A diagnosis of primary amyloidosis was made by renal biopsy. Melphalan 10mg/day for 4 days/month was started. The clinical and radiological follow up demonstrated a resorption of the hematoma. The patient is still alive at the eighth month of therapy.

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Primary amyloidosis constitutes most of the systemic amyloidosis cases in Western countries. It is usually seen during the sixth decade and more commonly in men than women. The most common presenting features are weakness, fatigue and marked weight loss in over half of the cases. Peripheral edema, paresthesia, orthostatic dizziness, syncope, purpura and other skin lesions may be observed.[1] Hepatic involvement usually presents with hepatomegaly, and rarely with liver enzyme abnormalities. A limited number of cases with spontaneous hepatic rupture have been presented in the literature.[1,2,5,7,12] A spontaneous isolated hepatic subcapsular hematoma, without intraperitoneal hemorrhage has been reported only in one case.[11] Functional hyposplenism and asplenism are frequently seen in the primary amyloidosis.[15] We present a rare case demonstrating spontaneous subcapsular and intraparenchymal hematoma in the liver together with functional asplenia.

Case Report. A 65-year-old Caucasian man presented fatigue, tiredness, dizziness and right upper abdominal discomfort. There was no history of abdominal trauma. Physical examination indicated pale conjunctiva, fullness and sensitivity on the right hypochondrium and epigastrium. Hepatomegaly (3 cm) and splenomegaly (2 cm) were present. The blood analysis demonstrated hemoglobin: 8 g/dL, leukocyte count: 11 x $10^3$/µL and platelet count: 500 x $10^3$/µL. Peripheral blood smear revealed Howell-Jolly bodies, serious poikilocytosis with achantocytes and burr cells. Erythrocyte sedimentation rate: 110 mm/hour, blood urea nitrogen: 63 mg/dL (range 8-20), creatinine: 2.1 mg/dL (range 0.6-1.2), alkaline phosphatase: 288 IU/L (range 41-133) gamma-glutamyltranspeptidase: 99 IU/L (range 9-50), alanine aminotransferase: 30 IU/L (range 0-35), aspartate aminotransferase: 41 IU/L (range 0-35), total bilirubin: 1.5 mg/dl (range 0.2-1.0), lactate dehydrogenase: 437 IU/L (range 88-230), globulin: 5.1 g/dL (range 2.6-3.7), albumin: 2.6 g/dL (range 3.4-4.7), calcium: 8.2 mg/dl (range 8.5-10.5), creatinine clearance: 29 mL/minute (range 90-140) and proteinuria: 0 g/day.

Bence-Jones protein was not found in the urine. There was no κ and λ light chain in urine

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immunofixation electrophoresis. Plasma cell was 8% in the bone marrow aspirate. The other blood tests were as follows: bleeding time was 1 minute (N<7), prothrombin time was 12.4 second (range 11-15), activated partial thromboplastin time was 29 second (range 26-40) and factor X level was 108% (range 70-120). Serologic tests for hepatitis B virus and hepatitis C virus were negative. Serum C-reactive protein was 61 mg/L (range 0-5). A tall narrow spike in the gamma band was found in the protein electrophoresis (**Figure 1**). The immunoglobulin results were as follows; IgG: 3546 (N: 583-1761) mg/dL, IgA: 235 (N: 78-367) mg/dL, and IgM: 86 (N: 52-335) mg/dL. Skeletal radiography was normal. Abdominal ultrasonography showed a hypoechoic area (6 cm maximum diameter) containing internal echoes in the right lobe of the liver extending from anterior to posterior at the subdiaphragmatic localization (**Figure 2**). The size of the spleen was 140 mm at ultrasonography. At abdominal computed tomography (CT), the liver was enlarged, and there were 3x5 cm hypodense areas (subcapsular hematoma) in the right lobe anterolaterally and posteriorly. A hypodense area, 6x3 cm in diameter, was detected in the posterior part of the right lobe of liver. The spleen was enlarged, and did not enhance following an intravenous injection of iodinated contrast medium (**Figure 3**). Scintigraphic imaging using $Tc^{99}m$ sulfur dioxide showed a non-uniform radiotracer uptake in the liver, whereas there was no uptake in the area of the spleen (**Figure 4**). Upper and lower gastrointestinal tract endoscopy was normal. Chest radiography revealed cardiomegaly and dilatation of aortal conus. Echocardiography showed an enlargement of the left atrium and ascending aorta, and left ventricular hypertrophy. Cytological examination of the perihepatic collection showed an "erythrocyte rich base". There was no hemorrhage on abdominal paracentesis. Renal biopsy revealed that many glomerular structures had disappeared and there was an accumulation of eosinophilic material. In the same areas, there was a more nodular and diffuse homogeneous eosinophilic substance accumulation. Additionally, there was a mononuclear cell infiltration in the tubular structures. The levels of β2-microglobulin were <0.81 (N: 2-3) mg/L, carcinoembryonic antigen were 3.0 (N: <4.3) ng/mL and alpha fetoprotein were 2.0 (N: <14) ng/mL. The serum immune electrophoresis demonstrated a marked increase in IgG-l (**Figure 5**). The patient was discharged with a good health following a treatment including melphalan (10mg/day for 4 days/month during 8-months) and blood transfusion. We offer taking of oral penicillin upon the onset of symptoms and not to wait for office visits or culture results.

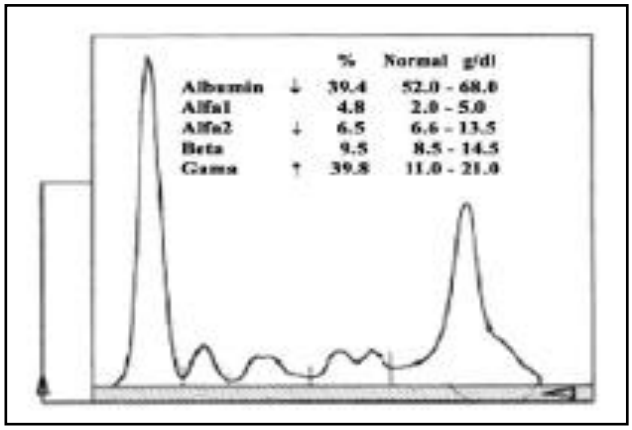


Figure 1 - The serum protein electrophoresis demonstrated a marked increase in gamma band.

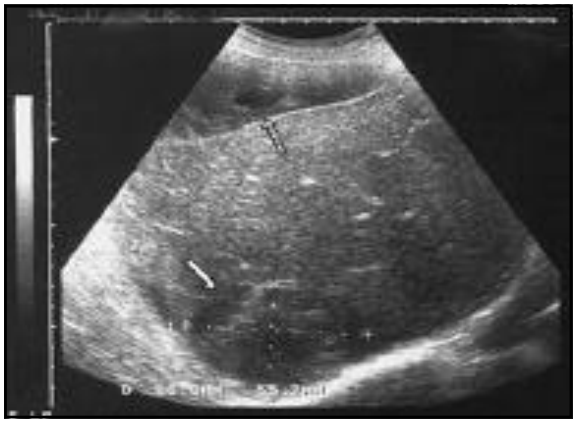

Figure 2 - Ultrasonography revealed intrahepatic (white arrow) and perihepatic (black arrow) hypoechoic lesions.

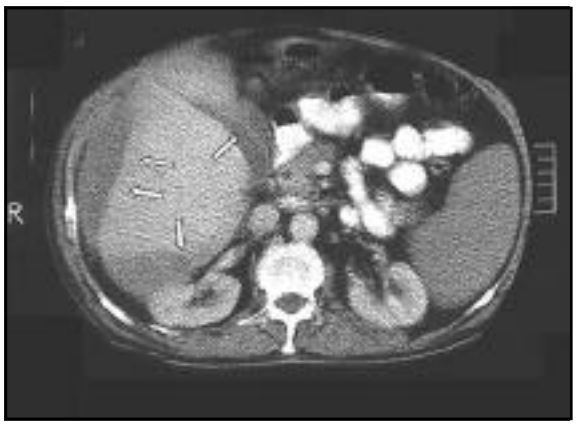


Figure 3 - Computerized tomography showed hypodense areas in the perihepatic regions. The spleen showed no enhancement.

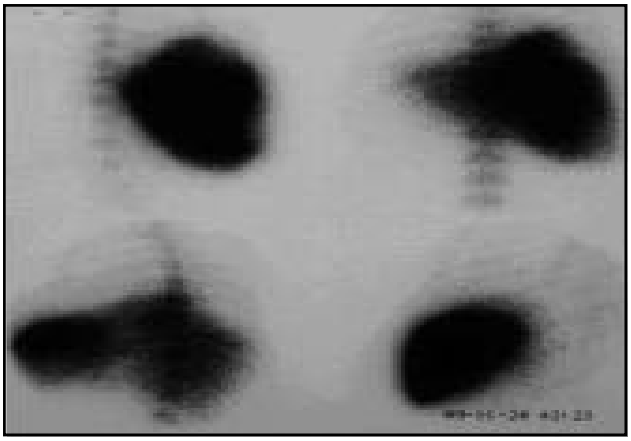

Figure 4 - Liver-spleen Tc99m sulfur colloid scintigraphy. The spleen cannot be detected.

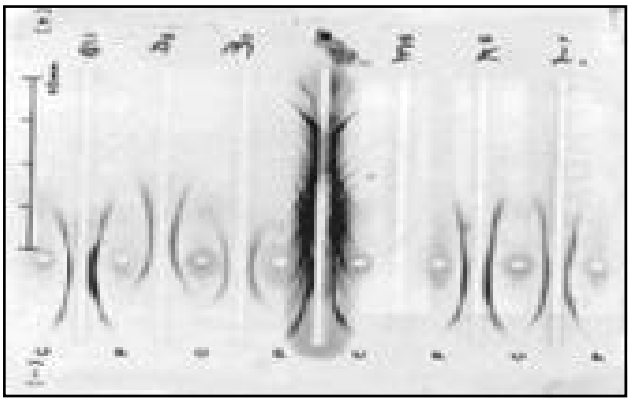

Figure 5 - The serum immune electrophoresis demonstrated an increase in IgG-λ

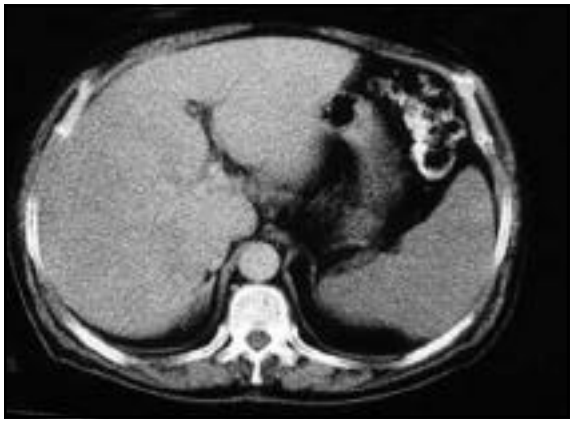

Figure 6 - Computerized tomography showed resorption of the perihepatic hematoma after 8-months of therapy. The spleen still did not opacify.

The clinical and radiological follow up revealed a resorption of the hematoma. The spleen still shows no uptake of contrast medium on CT (**Figure 6**). The serum M-spike decreased with therapy. Eight months passed over the treatment, and the patient is still alive.

Discussion. Systemic amyloidosis comprises a group of diseases characterized by the extracellular deposition of amyloid fibrillar proteins in one or more organs. The primary form is characterized by extracellular amyloid deposits composed of light chain fragments in the absence of multiple myeloma. Hepatic infiltration is frequently found in patient with systemic amyloidosis, but significant liver disease is rare. Mild hemostatic failure is a relatively common complication of amyloidosis, usually manifested by pinch purpura and easy bruisability. Liver hemorrhage is a recognized but uncommon complication of hepatic amyloidosis. The spontaneous rupture of the liver is uncommon and amyloid is extremely rare among the reported associated conditions, which include hydatid cyst, pregnancy, peliosis hepatis, the primary carcinoma of the liver, systemic lupus erythematosus.[13,14,16,17] Eleven patients with spontaneous hepatic ruptures from amyloidosis have been reported,[1,2, 4, 5, 7, 9, 12] and only in one case with a spontaneous hepatic subcapsular hematoma without intraperitoneal hemorrhage has been reported.[9] Spontaneous rupture of the liver associated with a universally poor prognosis often leads to death in 1-2 weeks. As far as we know, long-term survival has only been reported in one patient in whom there was a hepatic rupture,[7] and in another patient who had a subcapsular hematoma.[9] Kacem et al[7] reported that their case had a recurrent hepatic rupture, and that the second rupture had been conservatively treated without any surgical intervention. In the patient with subcapsular hematoma who reported by Levy-Lahad et al,[9] conservative treatment was instituted alone. The most important factors involving the pathogenesis of hemorrhage caused by amyloidosis include an abnormality in the synthesis of hemostatic factors, especially deficiency of factor X, and an accumulation of amyloid fibrils in the vascular wall.[2,18] It is always not easy to demonstrate the hepatic and splenic involvement in the primary amyloidosis. Although it is important to show hepatomegaly and splenomegaly as an indication of organ involvement, this is not sufficient. In such cases, liver biopsy is not considered a routine test, since it may lead to hemorrhage in 5% of cases.[3] In such circumstances, non-invasive techniques including anatomical imaging techniques (CT and MRI) may play an important role. In CT, an enlarged liver with homogeneous decrease in attenuation, a focal low-density lesion, poor enhancement, delayed

enhancement and extensive visceral calcification may remind the observer of amyloidosis.[6,10,11] However, these findings are non-specific for amyloidosis. On the other hand, scintigraphy gives more information to show organ involvement as compared to anatomical imaging techniques.[11] A functional hyposplenia is seen in most cases of primary amyloidosis. Functional hyposplenia has a bad prognosis. In some cases, changes may be seen in the morphology of erythrocytes due to the functional asplenia.[5] There is no certain consensus about the prophylaxis in the functional asplenia. Some author advises oral penicillin. Other physicians advise all asplenic patients that no febrile infection should be considered trivial. They instruct these patients to take penicillin upon the onset of symptoms and not to wait for office visits or culture results. The hepatic involvement of amyloidosis is sometimes mixed with cirrhosis. In such cases, scintigraphy is important in the differential diagnosis. In contrast to amyloidosis, there is an increased splenic uptake in the cirrhosis.[15] Lymphoplasmacytic disorders, such as multiple myeloma, may be associated or confused with systemic amyloidosis. In this case, it is excluded due to clinical and laboratory findings.

Melphalan and prednisone with or without colchicine are the first combination therapy of amyloidosis, but several case reports suggest occasional benefit. For patients who respond to chemotherapy, there are no data defining the optimal duration of the treatment. Liver transplantation and stem cell transplant can be used as other options in the selected patients. In addition, other potential novel therapeutic strategies that include stabilization of the native fold or precursor proteins, reversion of misfolded proteins to their native state, inhibition of fibril propagation and enhancement of amyloid clearance, either through immunotherapy or by reducing the stability of deposits.

To our knowledge, this is the second case who presented with an isolated subcapsular hematoma without frank hepatic rupture. Furthermore, it is the third case who showed a long-term survival with conservative treatment. The other interesting finding of our patient was the presence of functional asplenia.

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