CASE REPORT

A rare cause of severe hepatomegaly with an improving outcome

Line Godskesen,¹ Niels Abildgaard,² Jens Kjeldsen,³ Aleksander Krag³

¹Odense University Hospital, Odense C, Denmark

²Department of Hematology, Odense University Hospital, Odense C, Denmark

³Department of Medical Gastroenterology, Odense University Hospital, Odense C, Denmark

Correspondence to

Line Godskesen,
line@napoleon.dk

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SUMMARY

A previously healthy 43-year-old man presented with dyspnoea, 15 kg weight loss, severe hepatomegaly and alkaline phosphatase at 5400 U/L. Examinations seemed to suggest cirrhosis, but blood samples did not show any signs of underlying liver disease. Liver biopsy revealed amyloid light chain (AL) amyloidosis and bone marrow showed multiple myeloma (MM). The patient was treated with drugs of choice cyclophosphamide, bortezomib and dexamethasone. He responded well to the treatment and so far achieved partial response. Previously MM was associated with poor prognosis but due to improved treatment for AL the patient can achieve a progression-free period with good quality of life.

severe universal hypertrophy of the left ventricle, normal systolic function but diastolic dysfunction.

Finally liver biopsy was performed revealing deposits of amorphous solid and staining with Congo red showed the classical apple-green birefringence under polarised light microscopy, diagnostic for amyloidosis.

INVESTIGATIONS

Initial blood test showed haemoglobin 7.1 mmol/L, progressively increasing alkaline phosphatase up to 5400 U/L, alanine transaminase 224 U/L and bilirubin 105 µmol/L. Coagulation factors II, VII, X >1.40 work unit/L. Ferritin was 368 µg/L. Creatinine, carbamide and potassium were normal. Calcium ions were elevated to 1.57.

BACKGROUND

Multiple myeloma (MM) is commonly associated with anaemia, back pain, spontaneous fractures and hypercalcaemia and occurs mostly in elderly people. Between 10% and 30% of patients with MM develop amyloid light chain (AL) amyloidosis. In such cases the excessive amounts of light chains (LCs) produced by the neoplastic plasma cells deposit as amyloid in various organs causing various organ-related symptoms. Most often the amyloid will deposit in the kidneys and heart leading to renal and heart failure. MM and AL amyloidosis is a relatively rare cause of hepatomegaly especially in a young person. The average age of AL amyloidosis is 65 years,¹ with 10% diagnosed before the age of 50 years. Common symptoms are bone pain, back pain and spontaneous fractures.

It is important to recognise and diagnose the condition, because if left untreated morbidity and mortality is very high. In contrast, early aggressive treatment is associated with improved overall survival.

CASE PRESENTATION

A previously healthy 43-year-old man was admitted with fatigue, anaemia, dyspnoea and a weight loss of 15 kg over 6 months. Jaundice had been noticed prior to admission. There was no history of alcohol or drug use. The patient's grandfather died due to liver cirrhosis of unknown origin, and his mother suffers from unspecified scar tissue in the liver. Severe hepatomegaly was noted on admission.

Examinations suggested cirrhosis with enlarged, stiff liver mass and upper endoscopy with gastric varices. But blood samples did not show signs of underlying liver disease. Echocardiography showed

Figure 1 CT scan of the abdomen showing hepatomegaly.

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Figure 2 CT scan of the abdomen showing hepatomegaly.

Antimitochondrial, antinuclear and smooth muscle antibodies as well as Ig were normal. α -1 Antitrypsin was elevated at 2.68 λ/κ chains Ig was 746 mg/L and serum free light κ chains were 4550 mg/L (<25 mg/L), thus highly elevated leading to the suspicion of plasma cell dyscrasia. Screening for chronic hepatitis and HIV was negative. Serum cholesterol was severely elevated to 30 mmol/L.

CT scan of the thorax and abdomen revealed severe hepatomegaly (figures 1 and 2) and slight splenomegaly. Ultrasound of the abdomen revealed a reduced flow in the portal vein and compression on the inferior caval vein without thrombosis. Upper endoscopy revealed pronounced variceal-like elements in the fundic region, on the lesser and larger curvature and sparse diffuse bleeding.

Echocardiography showed severe universal hypertrophy of the left ventricle, less pronounced hypertrophy of the right ventricle, normal systolic function, but diastolic dysfunction. Findings were suggestive of deposition disease.

Fibroscan of the liver revealed a median stiffness of 75 kPa consistent with cirrhosis.

Fluorodeoxyglucose-positron emission tomography/CT was without signs of malignancy.

Liver biopsy showed deposition of an amorphous material in the space of Disse. Staining for κ LCs was positive and staining with Congo red showed the classical apple-green birefringence under polarised light microscopy, diagnostic for amyloidosis (figure 3).

Figure 3 Liver biopsy stained with Congo red viewed under polarised light showing amyloid apple-green birefringence.

Bone marrow biopsy showed 30% κ -clonal plasma cells and positive amyloid and κ staining of small vessels confirming the diagnosis of MM and AL amyloidosis. The patient had hypercalcaemia but no osteolysis.

TREATMENT

After confirmation of the diagnosis the patient immediately started chemotherapy with cyclophosphamide, bortezomib and dexamethasone.

OUTCOME AND FOLLOW-UP

Later the patient developed non-sustained and sustained ventricular tachycardia with a maximum heart rate of 155 bpm. For this reason an implantable cardioverter defibrillator was implanted. Ventricular tachycardia is a common and severe complication of AL with cardiac involvement and a serious prognostic indicator factor.

He responded well to the chemotherapy. Four months later his performance status was improved to WHO Performance Status 0, serum alkaline phosphatase dropped to 1000 and κ -chains dropped to 150 mg/L. However, the liver is still severely enlarged.

DISCUSSION

In MM monoclonal κ and λ LCs are produced by the proliferative plasma cells. Owing to abnormality and misfolding of the LCs they are able to stack to form the amyloid fibrils. The amyloid fibrils deposit in various organs (most common kidney and heart) and tissues causing a variety of symptoms. In the liver amyloid fibrils are found in the space of Disse and in small vessels. Among patients with AL amyloidosis 30% have hepatic manifestation determined by a liver span >15 cm in the absence of heart failure or alkaline phosphate >1.5 times upper normal limits.¹ In rare cases cholestatic hepatitis may occur. Hyperlipidaemia has been described as the first biochemical manifestation of hepatic amyloidosis.² Biopsy from a target organ or abdominal fat aspiration stained with Congo red showing the classical apple-green birefringence under polarised light microscopy is still the gold standard in diagnosing AL.^{1 3 4} Though different biomarkers such as N-terminal of the pro-hormone brain natriuretic peptide (NT-proBNP) for heart involvement and estimated glomerular filtration rate and albuminuria for renal involvement can be used to detect early silent

development in predisposed individuals, that is, patients with monoclonal gammopathy of undetermined significance.⁴

Earlier MM and AL had a bad prognosis especially when involving the heart. Untreated AL has a median survival of 6 months.⁵

Nowadays treatment is improving and there are a variety of new agents. Treatment strategy depends on risk staging according to performance status and organ involvement especially cardiac involvement.⁴ Low-risk patients are treated with auto stem cell transplant. Patients with intermediate risk are treated with cyclophosphamide, bortezomib and dexamethasone. The same treatment is given to patients with high risk with dose-attenuated regimes and close monitoring.⁴ The combination of cyclophosphamide, bortezomib and dexamethasone has initially been used in MM with good results.⁶ Recent studies show a good response rate with cyclophosphamide, bortezomib and dexamethasone in AL as well.⁶ Estimated 2-year progression-free survival was 66.5% for patients treated upfront and the estimated 2-year overall survival was 97.7%.⁷ A longer

observation period is still required to recognise the full long-term effect of the treatment.

Studies show that amyloid deposits can be absorbed and organ function can be restored if the LCs are reduced or completely eliminated. By this patients can achieve a progression-free period with good quality of life.⁸

The prognosis in patients with AL amyloidosis has improved considerably within the last few years, emphasising the importance of early recognition and diagnosis.

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Competing interests None.

Patient consent Obtained.

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Learning points

- ▶ Enlarged and stiff liver is not necessarily liver cirrhosis.
- ▶ Liver biopsy is still considered the standard reference for diagnosis of liver diseases of obscure causes.
- ▶ Prognosis for patients with multiple myeloma and amyloid light chain (AL) is improving nowadays as new treatments develop.
- ▶ Early diagnosis and treatment should be emphasised in AL to improve remission and survival.

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