Hepatic amyloidosis increases liver stiffness measured by transient elastography

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Abstract

Liver stiffness values in transient elastography (TE) have to be interpreted with caution. Steatosis, congestion, acute inflammation and extrahepatic cholestasis can indeed influence measurements. Obtained stiffness values in the cirrhotic range can also be present in the absence of fibrosis as in hepatic amyloidosis. Here we report two cases of systemic amyloidosis with hepatic involvement where high stiffness values were measured at TE. In fact, deposits of amyloid may increase the rigidity of the liver parenchyma resulting in higher liver stiffness values.
Therefore, results of TE should always be interpreted in their clinical context and if inconsistent, the performance of a liver biopsy might be necessary. (Acta gastroenterol. belg., **2010**, 73, **52-54**).

Keywords : Transient elastography (TE), hepatitis B virus (HBV), amyloidosis

Introduction

Transient elastography (TE) is a relatively new noninvasive method to assess liver fibrosis and acquired over the past years an increasing importance in the practice of hepatologists to assess hepatic fibrosis in chronic liver diseases. TE has been extensively studied in chronic hepatitis C infection (HCV) and hepatitis B infection (HBV) and data are also available for other liver diseases (1). Data regarding sinusoidal or vascular diseases are however lacking (2). The objective of this report is to describe two patients having systemic amyloidosis and high liver stiffness values at TE.

Case report 1

A 50-year old male patient, with a medical history of chronic HBV infection, was admitted to our hospital for investigation of atypical chest pain since one month. Physical examination revealed slight malleolar edema. Electrocardiography was normal and an enlarged cardiothoracic index was present at chest X-ray. Laboratory work-up showed chronic HBV infection (HBsAg +, HBeAg -, anti-HBe +, HBV DNA 7000 IU/mL) with normal transaminases [ALT 37 U/L (normal 12-50U/L) AST 41 U/L (normal 14-50 U/L) and moderate cholestasis [alkaline phosphatase 187 IU/L (normal 30-125 U/L), gamma-glutamyl transpeptidase 282 IU/L (normal 9-40 U/L)]. Platelets [259,000/µL (normal 150,000-350,000/µL)), and APRI score (0.31) were also normal. Hypoalbuminemia (20 g/L) was present together with important proteinuria (7.15 g/L). At immunofixation a monoclonal immunoglobulin lambda light chain in high concentration (178 mg/L) was detected. Liver parenchyma was slightly heterogeneous at ultrasound and there was no dilation of bile ducts or hepatic veins. Astonishing high stiffness values (median value 36,6 kPa, IQR 9,8 kPa, success rate 91%) were obtained at TE (Echosens, Paris). Cardiac ultrasound showed hypertrophia of the left ventricular with normal ejection fraction. Cardiac MRI showed important symmetric hypertrophic cardiomyopathy with a slight altered function of the left ventricle. There were no signs of myocardial ischemia. A liver biopsy, performed by a transjugular approach due to the suspicion of amyloidosis, showed important deposits of amyloid in the sinusoids and extracellular matrix with sinusoidal dilation (Fig. 1). In regard of the chronic HBV infection, there was only little portal and lobular inflammation without fibrosis. Immunohistochemistry staining revealed 20% of hepatocytes positive for HBsAg. Analysis of a bone marrow biopsy confirmed the presence of a monoclonal plasmacytoma expressing immunoglobulin lamda light chains. The diagnosis of AL amyloidosis with hepatic, cardiac and renal affection was made.

Case report 2

A 53-year old woman, without medical history, was hospitalized because of weight loss (10 kgs in 3 months), severe fatigue and dizziness. Physical examination revealed a distended abdomen with hepatomegaly. Laboratory data showed normal ALT (11 U/L, normal 9-42 U/L), AST 23 U/L, normal 11-42 U/L, and platelets (420,000/µL) but raised alkaline phosphatase (469 IU/L normal 30-125 U/L) and gamma-glutamyl transpeptidase (327 IU/L normal 9-40 U/L) levels and a severe renal insufficiency (creatinine 391 µmol/L, GFR 10 mL/min/1.73 m²) with hypoalbuminemia (15 g/L). Urine analysis showed important proteinuria (8,37 g/L). Serological tests for HAV, HBV, HCV and HIV were negative. The APRI score was 0.13. ECG and chest X-ray were normal. An abdominal ultrasound showed loss of corticomedullar differentiation in both kidneys and hepatomegaly. There was no dilation of bile ducts or

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hepatic veins. For the unexplained hepatomegaly a TE was performed and revealed elevated stiffness values (median value 21.3 kPa, IQR 7,8 kPa, success rate 100%). A liver biopsy, performed by a transvenous approach, revealed massive deposits of amyloid in the sinusoidal space with sinusoidal dilatation, vascular amyloid invasion and absence of fibrosis. In addition, a renal biopsy showed type AA amyloidosis with a glomerular, vascular and interstitial infiltration. Biopsies of the gastric mucosa revealed amyloid deposits in the antrum and fundus. In this way the diagnosis of AA amyloidosis with a renal, hepatic and gastric affection was made without finding any underlying cause.

Discussion

Amyloidosis is a rare metabolic storage disease that results from deposition of insoluble fibrillar proteins or aberrantly folded and assembled protein fragments in the extracellular space (3,4). Deposits can occur in any tissue, are similar in structural conformation and are derived from a variety of unrelated circulating precursor proteins. More than 25 fibrillar proteins have been identified as precursor proteins in amyloidosis (5). The two major types are AL (primary amyloidosis or myeloma-associated amyloidosis) characterized by deposition of fragments of immunoglobulin kapa or lambda light chains, and AA (secondary or reactive amyloid) associated with serum amyloid A as the precursor protein.

Signs and symptoms of amyloidosis are nonspecific including diarrhea, malabsorption, neuropathy, nephrotic syndrome, renal or cardiac failure (3,5). The liver is commonly affected in both, systemic AL or AA amyloidosis with incidences reported up to 98% (6). Typical manifestations of hepatic amyloidosis are hepatomegaly and cholestasis (4,7). Less common manifestations are acute liver failure and liver rupture (8,9). Hepatic involvement does not impact the survival rate in AL amyloidosis but in AA amyloidosis it is associated with a significantly reduced patient survival (10). To confirm the clinical suspicion a liver biopsy should be performed (4,10) but because of increased bleeding risks, a transvenous approach is advised (4,7). The final diagnosis of hepatic amyloidosis is pathological with the presence of green birefringent deposits under polarized light after staining with Congo red.

TE is a relatively new and reliable method for the diagnosis of fibrosis and cirrhosis in patients with chronic liver diseases (11). It has extensively been studied in patients having chronic HCV infection and cut-off values of 12,5 kPa and 14,6 kPa have been proposed for the presence of cirrhosis in this subgroup (12,13). However, cut-off values need to be adapted for each etiology of chronic liver disease hence values for cirrhosis range from 10,3 kPa in chronic HBV infection to 14,6 kPa in patients with HCV-HIV co-infection to 15.2 kPa in cholestatic liver diseases and 22,6 kPa in patients with alcoholic liver disease (1,14,15).

Nevertheless, it is important that stiffness values should be interpreted in each individual case as for example cardiac congestion, steatosis, extrahepatic cholestasis and acute hepatitis (e.g. acute viral or alcoholic hepatitis) influence stiffness measurements (1,2, 15,16). The high stiffness values obtained at TE in our first case suggested the presence of HBV-related cirrhosis. This was, however, discordant with the absence of clinical, biochemical (APRI score) and ultrasound signs of cirrhosis. Similarly, our second case presented stiffness values in the cirrhotic range without clear evidence for a chronic liver disease. Liver biopsy was necessary in both cases to explore the inappropriateness of the TE values and showed important amyloid deposits in the absence of fibrosis.

To date, no data are available in the literature concerning liver stiffness values in hepatic amyloidosis. The high stiffness values measured in the two reported patients might be explained by the massive deposits of amyloid in the extracellular space increasing the rigidity and stiffness of the liver parenchyma with subsequent high velocity of wave propagation at TE. However, to confirm this hypothesis larger numbers of cases are needed.

In conclusion, liver stiffness values in the cirrhotic range are not always consistent with a fibrotic process as it is the case in hepatic amyloidosis. The amyloid deposits in the liver increase the compactness of the parenchyma resulting in high stiffness values. Thus, results of TE should always be interpreted in their clinical context and if unexplainable, a liver biopsy might be necessary to rule out other diseases.

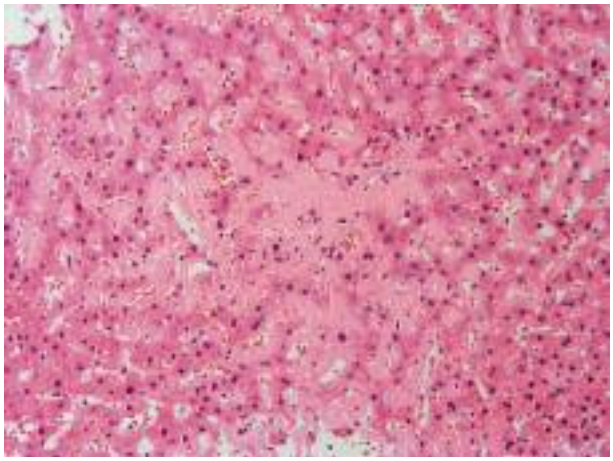

Fig. 1 — Liver histology of case 1: Congo red staining showing the typical extracellular and intrasinusoidal deposits of amyloid in the absence of fibrosis.

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