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Original article

Hepatic amyloidosis: Morphologic spectrum of histopathological changes in AA and nonAA amyloidosis

Banu Sarsik[a,*], Sait Sen[a], Fatma Secil Kirdok[b], Ulus Salih Akarca[b], Huseyin Toz[c], Funda Yilmaz[a]

[a] Department of Pathology, Ege University Faculty of Medicine, Izmir, Turkey
[b] Department of Gastroenterology and Hepatology, Ege University Faculty of Medicine, Izmir, Turkey
[c] Department of Nephrology, Ege University Faculty of Medicine, Izmir, Turkey

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ABSTRACT

In hepatic amyloidosis (HA), the relationships between the pattern and extent of amyloid deposition, morphologic changes, associated diseases and clinical data have not yet been demonstrated. In this study, we sought the correlation between the above mentioned parameters in HA.

Liver biopsies of 34 HA were retrospectively analyzed for the type, distribution, and intensity of amyloid deposition and associated morphologic changes. AA and nonAA types were classified on the basis of immunohistochemistry. Follow-up clinical and laboratory findings were reviewed. Twenty-three out of 34 patients (67.6%) had AA, and 11 out of 34 patients (32.4%) had nonAA amyloidosis. The predominant localization pattern in AA amyloidosis was vascular (91.3%), and in nonAA amyloidosis it was mixed with other patterns (72.7%). We confirmed that nonAA amyloid involves the hepatic artery, as well as the portal and central vein, but deposition occurred more frequently in the sinusoidal areas. We detected a portal stromal pattern only in cases of nonAA amyloidosis with a mixed pattern of amyloid deposition.

The pattern of amyloid deposition in liver differs between the AA and nonAA type amyloidosis. The distribution of amyloid within the liver is not a reliable method for distinguishing AA from nonAA amyloidosis. However, the histological pattern provides strong clues as to the etiology of the amyloid deposits, and could provide information on the clinical status and prognosis of these patients.

Introduction

The kidneys and heart are the most commonly involved organs in amyloidosis; liver and gastrointestinal tract involvement is less frequent, and the symptoms are usually mild [2,7,22,25]. The main constituent of amyloid deposits is the precursor protein fibril [9,12,19]. Hepatic involvement can occur in all types of amyloidosis, and histologically proven liver involvement in systemic amyloidosis is reported to range between 17% and 98% in different series [2,10,13]. Since the symptoms and laboratory abnormalities of hepatic amyloidosis are usually non-specific, the extension of the disease into the liver may be overlooked clinically. On the other hand, regarding liver biopsies performed for indications other than amyloidosis, hepatic amyloidosis can be an unexpected diagnosis. The topographic distribution of amyloid deposition in liver and the forms of deposited protein may vary in different cases. The deposition of amyloid protein in liver can be recognized in two different forms: *linear* and *globular* [1,5,8,11,18]. The linear form manifests in two major topographic distribution patterns; (a) walls of the portal vessels (vascular pattern), (b) deposition in the space of Disse: sinusoidal linear pattern (so-called parenchymal pattern). The round globular form may be found in the space of Disse and/or portal tract stroma. It is difficult to detect in routinely stained sections and is quite rare, with an incidence of 5–9.6% in different series of hepatic amyloidosis [3,18]. Agaram et al. suggested that amyloid globules may be formed as a result of defective secretion of amyloid synthesized by hepatocytes or phagocytosis of amyloid by Kupffer cells or hepatocytes [1]. Also, it has been proposed that globular hepatic amyloidosis may represent the initial stage of the sinusoidal linear type [18]. Recently, the authors concluded that discrete etiologic factors may have a role in globular amyloid formation [4,27]. Vrana et al. reported that in patients with leukocyte chemotactic factor 2-associated amyloid (ALect2) amyloidosis, which was first described in renal amyloidosis patients, liver involvement with the characteristic portal globular pattern is frequently seen. [27]. Since the morphologic changes caused by amyloid deposition may be admixed with histopathologic changes of the associated or underlying diseases, clear relationships between the extent of amyloid deposition and clinical manifestations have not yet been demonstrated. In this study, 34 patients with biopsy-proven

* Corresponding author at: Department of Pathology, Ege University Faculty of Medicine, Bornova-Izmir 35100, Turkey. Tel.: +90 232 3881025; fax: +90 232 3736143.
E-mail addresses: banu.sarsik@ege.edu.tr, bsarsik@yahoo.com (B. Sarsik).

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hepatic amyloidosis were retrospectively analyzed with regard to the topographic distribution and forms, and their correlations with associated morphologic changes, as well as clinical and biochemical features, were investigated.

Materials and methods

Thirty-four cases with hepatic amyloidosis diagnosed between the years 1999 and 2011 were retrieved from the archives of the Pathology Department of the Medical Faculty of Ege University. The biochemical data and serologic tests had been recorded for each patient. Among the patients included in the study, 27 had undergone multiple organ biopsies and 7 had only liver biopsy. Tissue sections which were processed with conventional techniques and stained with hematoxylin and eosin (H&E), Masson's trichrome, Prussian blue for iron, Gomori's reticulum and Congo red were re-evaluated, including polarized light microscopy. Each liver biopsy was systematically reviewed for the type, distribution pattern and presence of portal inflammation, bile duct injury, hepatocyte loss, steatosis, iron accumulation (within the Kupffer cells, endothelia, hepatocytes and macrophages), and fibrosis. Additional histological features were recorded when detected. The distribution patterns of amyloid deposits were evaluated using Congo-red stained sections. Immunostains only for amyloid A were performed using the peroxidase–antiperoxidase method and an antibody against AA protein (M 0759; Dako, Carpinteria, CA) as described previously [24]. According to the immunohistochemical staining patterns and clinical findings, the classification of the type of amyloid protein was categorized as AA and nonAA.

The pattern of hepatic amyloid deposition was categorized as sinusoidal, vascular, and stromal in the portal area as described previously [1,5,8,11,18]. The vascular pattern was subclassified as hepatic arteries, portal and central veins.

The other histopathologic features were scored as 0: absent or 1: present.

Statistical analysis was carried out on a PC-based analysis program SPSS (15.0). When appropriate, Pearson's Chi-square or Fisher's exact tests and Mann–Whitney *U* tests were applied regarding the difference in the incidence of clinical and histologic findings, such as age, gender, serologic and biochemical tests, distribution pattern and type of amyloid protein and presence of portal inflammation, bile duct injury, hepatocyte loss, steatosis, iron accumulation, and fibrosis. Kaplan–Meier survival curves with the log-rank test were used for survival analysis. A p value of <.05 was accepted as significant.

Results

In this series of 34 patients with hepatic amyloidosis, 17 (50%) were males and 17 (50%) were females. The mean and median age of the patients was 42.7 ± 15.7 and 40 years, respectively (range 8–69). According to the immunohistochemical staining patterns and clinical findings, 23 out of 34 patients (67.6%) were found to have AA amyloidosis, whereas 11 out of 34 patients (32.4%) had nonAA amyloidosis.

The indications for liver biopsy were as follows: grading and staging of chronic hepatitis (hepatitis C; 12 patients, and HBV and HCV co-infection: 2 patients) (41.1%), unexplained elevation of liver enzyme tests (19 patients, 55.8%).

Table 1
Patients' clinical findings and distribution pattern of hepatic amyloid deposition.

Case	Type of amyloidosis	Associated disease	Etiology of hepatitis	First biopsies	Others biopsies	Renal tx	Survival	PV	HA	CV	S	PS
1	AA	FMF	CHC	Kidney	Kidney	Present	E	0	1	0	0	0
2	AA	FMF	CHC	Kidney	Thyroid, kidney	Present	E	1	1	1	0	0
3	AA	FMF	None	Rectum	Pituitary gland	Absent	A	1	1	0	0	0
4	AA	FMF	CHC	Kidney	Kidney	Present	E	0	1	0	0	0
5	AA	RA	None	Liver		Absent	A	0	1	0	0	0
6	AA	None	CHC	Kidney	Bone marrow, kidney	Present	E	0	1	0	0	0
7	AA	None	CHC	Liver	Spleen	Absent	E	1	1	1	0	0
8	AA	None	None	Stomach	Stomach	Absent	E	0	1	0	1	0
9	AA	None	CHC	Liver		Absent	A	1	1	0	0	0
10	AA	FMF	CHC	Kidney	Kidney	Present	E	1	1	0	0	0
11	AA	FMF	CHC + CHB	Kidney	Kidney	Present	A	0	1	0	0	0
12	AA	EB	None	Kidney	Heart, kidney	Absent	E	0	1	1	0	0
13	AA	None	CHC	Kidney	Kidney	Present	E	0	1	0	0	0
14	AA	None	CHC	Kidney	Bladder, kidney	Absent	U	0	1	0	0	0
15	AA	FMF	CHC	Kidney	Kidney	Present	A	0	1	0	0	0
16	AA	None	CHC + CHB	Liver		Absent	U	0	1	0	0	0
17	AA	AS	None	Kidney	Stomach, kidney	Absent	E	1	1	0	0	0
18	AA	None	None	Kidney	Kidney	Present	E	1	1	0	0	0
19	AA	None	None	Rectum–liver	Rectum, stomach	Absent	E	1	1	1	0	0
20	AA	None	CHC	Kidney	Small intestine, kidney	Present	A	0	1	0	0	0
21	AA	None	None	Rectum	Rectum	Absent	A	0	1	0	0	0
22	AA	None	CHC	Kidney	Esophagus, kidney	Present	A	1	1	0	0	0
23	AA	None	None	Liver		Absent	A	0	1	1	1	0
24	NonAA	PCD	None	Liver	Rectum, bone marrow	Absent	E	0	0	0	1	0
25	NonAA	None	None	Kidney	Rectum, kidney	Absent	E	1	0	0	1	1
26	NonAA	PCD	None	Liver	Bone marrow	Absent	E	0	1	0	1	1
27	NonAA	None	None	Liver		Absent	U	0	0	0	1	0
28	NonAA	None	None	Kidney	Muscle, kidney	Absent	E	0	1	0	0	0
29	NonAA	PCD	None	Liver–bone marrow	Rectum, bone marrow	Absent	E	0	1	1	1	0
30	NonAA	CKD	None	Liver	Bone marrow	Absent	E	1	1	0	0	1
31	NonAA	CKD	None	Liver		Absent	E	1	1	1	1	1
32	NonAA	DM	None	Liver		Absent	E	1	1	1	1	1
33	NonAA	PCD	None	Liver	Bone marrow	Absent	E	1	1	1	1	0
34	NonAA	MYELOM	None	Liver	Bone marrow	Absent	E	1	1	1	1	1

Abbreviations and reference range: PCD: plasma cell dyscrasia, AS: ankylosing spondylitis, CH: chronic hepatitis, CHC: chronic hepatitis C, CH: chronic hepatitis B, DM: diabetes mellitus, RA: rheumatoid arthritis, EB: epidermolysis bullosa, FMF: familial Mediterranean fever, CKD: chronic kidney disease, PS: portal stromal, PV: portal vein, HA: hepaticartery, CV: central vein, S: sinusoidal, E: exitus, A: alive, (1): present, (0): absent, U: unknown, tx: transplantation.