Amyloidosis in Turkish patients

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Abstract

Amyloidosis is characterized by the systemic or localized extra cellular deposition of amyloid, a proteinaceous fibrillar material in various tissues and organs, mainly classified into primary (AL) or secondary (AA) groups according to the biochemical nature of the fibril forming protein.
The histopathological diagnosis was made on Congo red stained biopsy specimens using polarized light and the subtyping of amyloidosis was made by immunohistochemical analysis. One hundred twenty eight amyloid positive biopsies obtained from 111 patients whose paraffin blocks were available for immunohistochemical analysis were included in the study. 111 patients (70 male) with an average age of 34.2 years (range 6-65 years), were included in the study.
Amyloid deposits were subtyped immunohistochemically in 128 biopsies. The vast majority (90.9 %) of patients in our study presented with AA amyloidosis.
This retrospective study demonstrates that the patient population with amyloidosis in Turkey is significantly different from the western countries. Our results indicate the predominance of AA amyloidosis and also suggest that routine immunohistochemical analysis of amyloidosis cases with certain ethnic background is sufficient to classify the subtype of amyloid fibril protein and the related disease.

Key words: amyloidosis, histopathological diagnosis, immunohistochemistry

Introduction

Amyloidosis is characterized by the systemic or localized extra cellular deposition of amyloid, a proteinaceous fibrillar material in various tissues and organs. Although many types of fibril proteins have been defined, amyloidosis is mainly classified into primary (AL) or secondary (AA) groups according to the biochemical nature of the fibril forming protein. The results of previously published reports on amyloidosis including autopsy series strongly suggested that the frequency and type of amyloidosis and related disease may vary significantly in different patient populations (1-4).
There is not much information in the literature concerning the accuracy of immunohistochemical subtyping in relation to clinical diagnosis (5-7), though classifying primary amyloidosis by immunohistochemistry has been reported to be more difficult (8).
The aim of the present study was, therefore, to classify amyloidosis by means of immunohistochemical subtyping of amyloid fibril proteins and assessing the correlation of immunohistochemistry with clinical diagnosis in order to retrieve useful epidemiological data from these patients.

Patients and methods

The histopathological diagnosis was made on Congo red stained biopsy specimens using polarized light and the subtyping of amyloidosis was made by immunohistochemical analysis. One hundred twenty eight amyloid positive biopsies obtained from 111 patients whose paraffin blocks were available for immunohistochemical analysis were included in the study. Mean patient age was 34.2 years with a range of 6-65 years. There were 70 male, 41 female patients in the study.
Paraffin sections, 4 microns thick, were taken from 128 biopsy specimens comprising 69 renal, 36 rectal, 15 testicular, 5 liver, 2 small intestinal biopsies and 1 bladder biopsy. An antibody panel including monoclonal antibodies to Amyloid A (1:100), lambda (1:50) and kappa (1:50) light chains, transthyretin (1:100), and beta-2-microglobulin (1:50) (DAKO), leaving out the extremely rare forms of amyloid fibrils, was selected for the study. Patient files were reviewed and clinical histories were recorded.

Table 1: The results of immunohistochemical analysis

Biopsy site	# of biopsies	AA	AL	AK	ATTR	β2MG	Mixed
Kidney	69	65					4 (2 AA+A*L*) (2 AA+ATTR)
Rectum	36	35					1 (AA+ATTR)
Testicle	15	10	4				1 (AA+A*L*+ATTR)
Liver	5	0	2			1	2 (1 AA+A*L*) (1 AA+β2MG)
Small Int.	2	2					
Bladder	1	1					
Total	**128**	**113**	**6**	**0**	**0**	**1**	**8**

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Results

Amyloid deposits were subtyped immunohistochemically in 128 biopsies taken from 111 cases. In 17 cases, multiple organ biopsies were taken; 10 cases had renal + rectal biopsies, whereas 7 cases had renal + testicular biopsies.

The results of the immunohistochemical analysis are presented in Table 1. Amyloid deposits were stained by a single antibody in 120 (93.8 %) whereas 8 biopsies (6.2 %) stained positively by more than one antibody.

Table 2: The relation of clinical diagnosis to biopsy site

Disease	# of cases	# of biopsy	Kidney	Rectum	Testicle	Liver	Small Intestine	Bladder
FMF	81	98	48	36	10	2	1	1
Tuberculosis	8	8	8					
Bronchiectasis	4	4	4					
RA	7	7	7					
Crohn's Disease	1	1					1	
Plasma CD	7	7	1		4	2		
Hemodialysis	1	1				1		
Unknown	2	2	1		1			
Total	**111**	**128**	**69**	**36**	**15**	**5**	**2**	**1**

FMF: Familial Mediterranean Fever, RA: Rheumatoid Arthritis, Plasma CD: Plasma cell dyscrasias

The relation between clinical diagnosis and biopsy site is presented in Table 2. The correlation of immunohistochemical subtyping and clinical diagnosis is summarized in Table 3.

Table 3: The correlation of immunohistochemical sub typing and clinical diagnosis

Disease	# of cases	# of biopsy	AA	*AL*	*AK*	ATTR	β2MG	Mixed
FMF	81	98	95					3 (1 AA+AL) (1 AA+ATTR) (1 AA+β2MG)
Tuberculosis	8	8	8					
Bronchiectasis	4	4	4					
RA	7	7	5					2 (2 AA+ATTR)
Plasma CD	7	7		6				1 (1 AL+AA)
Crohn's Disease	1	1	1					
Hemodialysis	1	1					1	
Unknown	2	2						2 (1 AA+AL) (1AA+AL+ATTR)
Total	111	128	113	6	0	0	1	8

FMF: Familial Mediterranean Fever, RA: Rheumatoid Arthritis, Plasma CD: Plasma cell dyscrasias

Discussion

Lachmann et al (8), reported that immunohistochemistry is usually definitive in identifying reactive (AA) amyloidosis, though, it is frequently not diagnostic with respect to AL amyloidosis either due to abnormal fibril conformation of light chain fragments or to the background staining caused by normal immunoglobulins in the tissues. In a recent study, immunofluorescence technique yielded negative staining in 35.3 % of cases with proven AL amyloidosis in renal biopsies (9). Since the vast majority (90.9 %) of patients in our study presented with AA amyloidosis, the technical limitations of immunohistochemistry are not evident in our patients except for two cases (1.8 %) in which no clinical condition related to amyloidosis could be documented. In contrast to the reports from western countries where the majority of cases are AL amyloidosis (8, 9), the few cases with AL amyloidosis in the present study were also accurately diagnosed by means of immunohistochemistry.

Amyloidosis can be diagnosed and classified in any affected tissue sample. Nevertheless, it is still important to define the most suitable diagnostic site to be biopsied and examined for the early detection of amyloid deposition. For systemic amyloidosis, however, no such favorite site has been documented in any of the studies performed so far (2, 3) although rectal biopsy seems to be more commonly used mainly because of its easy access by the clinician (3, 10). Another easy access, abdominal fat biopsy has been reported as insensitive for AA amyloidosis while renal biopsy, probably due to the increase in the number of well-trained nephrologists, is becoming more popular in the diagnosis of amyloidosis (4). Similarly, it was the most commonly used intervention to diagnose amyloidosis in our study. In practice, however, clinical presentation seems to be the main determinant of the biopsy site; i.e. a patient with proteinuria would undergo a renal rather than a rectal biopsy. Renal or rectal biopsies were performed commonly in our cases depending on the presenting clinical symptoms. Though a variety of anatomical sites have been used for the detection of amyloid (3,4), we found only few reports mentioning testicular biopsy despite the high incidence observed in our study (11,12). In one of these reports, testis biopsy was found valuable and more sensitive than rectal biopsy in the diagnosis of systemic amyloidosis (12).

In many developed countries primary amyloidosis is the more common form of systemic amyloidosis (1-3). With the virtual

abolition of chronic infectious diseases, the incidence of secondary amyloidosis has been reduced in such countries. However, it still occurs mainly in patients suffering from RA followed by chronic infectious diseases and Crohn's disease while TBC and FMF were found to be very rare as amyloid related diseases (5,13). On the other hand, secondary amyloidosis is still the more common type of systemic amyloidosis in developing countries (1,3) where TBC together with other chronic infectious diseases are the leading causes of systemic amyloidosis followed by RA which is observed only in a small percentage of patients with amyloidosis (14,15). In the Middle East, however, among patients with different ethnic origins, FMF is the leading etiologic condition in the development of amyloidosis. This ethnically restricted genetic disorder mainly affects populations originated from the Mediterranean-Middle Eastern populations such as Jews, Arabs, Armenians and Turks (16). In a recent report, a lower incidence of amyloidosis was observed in a group of Italian patients with FMF (17). Although the true Figures are not well documented, Turkey is known to have a high prevalence of FMF and FMF-related amyloidosis (18,19).

Not surprisingly, secondary amyloidosis is the main form of systemic amyloidosis in our cases, many with a clinical diagnosis of FMF followed by TBC, RA and bronchiectasis in similar frequencies. This finding seems to be in concordance with previous reports from Turkey (19,20).

Conclusions

This retrospective study demonstrates that the patient population with amyloidosis in Turkey is significantly different from the western countries. Our results indicate the predominance of AA amyloidosis associated with FMF and also suggest that routine immunohistochemical analysis of amyloidosis cases with certain ethnic background is sufficient to classify the subtype of amyloid fibril protein and the related disease. However, detailed clinical information is mandatory before making a definite diagnosis based solely on immunohistochemical observations. Moreover, due to increased rate of immigration affecting the ethnic structure of the developed countries, physicians' awareness of the prevalence of certain diseases related to ethnic origin is essential to prevent long term serious complications such as amyloidosis and improve the quality of patients' lives.

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