

The pattern of amyloidosis in Malaysia

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Abstract

Congo red screening of routine biopsies at the University Hospital Kuala Lumpur revealed the following categories of amyloidosis: systemic AL (5.9%); systemic AA (3.2%); isolated atrial (14%); primary localized cutaneous (7.5%); other primary localized deposits (3.2%); localized intratumour (58%); and dystrophic (8.6%). Unlike in the West, AA amyloidosis in this population was usually secondary to leprosy or tuberculosis. Liver involvement in AL amyloidosis was shown to exhibit a sinusoidal pattern and differed from the vascular pattern of AA amyloidosis. Within the category of AA amyloidosis, there were two patterns of renal involvement – glomerular and vascular, with the glomerular pattern carrying a more ominous clinical picture. Notable among the localized amyloidoses were isolated atrial amyloidosis complicating chronic rheumatic heart disease, intratumour amyloidosis within nasopharyngeal carcinomas and dystrophic amyloidosis which occurred in fibrotic tissues.

Key words: Amyloidosis, tuberculosis, leprosy, heart disease, nasopharyngeal carcinoma, osteoarthritis.

INTRODUCTION

It is known that amyloidosis can complicate widely diverse diseases and is of global relevance. However, most studies have been from the West and the pattern of amyloidosis in Asian populations is less well known. This paper reports on an investigation into the various categories of amyloidosis encountered in surgical pathology practice in a Malaysian setting and provides a baseline for comparison with Western studies.

MATERIALS AND METHODS

Over a 5.5 yr period, all surgical biopsies, with the exception of endometrial curettings and products of conception, received by the Department of Pathology, University of Malaya were screened histologically for amyloid by alkaline Congo red staining. Further sections of amyloid positive cases were stained for alkaline Congo red after prior treatment with acidified potassium permanganate, and for human AA protein, human AP protein and human immunoglobulin lambda and kappa light chains using standard immunoperoxidase methods.¹ Electron microscopic examination was carried out when suitable tissue was available.

A clinico-pathologic classification of amyloidosis based on that proposed at the Third International Symposium on Amyloidosis (1979) was adopted.

RESULTS

186 amyloidosis cases were detected on screening 27,052 biopsies from 22,827 hospital patients. A detailed description of these have been published previously.² Their classification and pathological findings are summarised in Table 1.

Systemic amyloidosis carried the most significance clinically because of the involvement of vital organs such as the heart and kidney. Of these, 11 (65%) were AL amyloidosis and largely associated with plasma cell dyscrasias. 6 (35%) were AA amyloidosis and were associated with either tuberculosis or leprosy. These findings were consistent with earlier studies from this centre suggesting that tuberculosis and leprosy are by far the most important underlying diseases for AA amyloidosis in Malaysia.

In an autopsy study of 228 Orang Asli above the age of 10 years, 11 (5%) cases of amyloidosis were detected.³ 36% of subjects without amyloidosis had tuberculosis. In contrast, the prevalence of tuberculosis among subjects with amyloidosis was 82%. In another autopsy study on leprosy subjects at this centre, 7 cases of systemic amyloidosis were detected out of 37 subjects, indicating a prevalence of 19%.⁴ It was noted that amyloidosis started to appear as a complication when the leprosy process had gone on for more than 10 years.

TABLE 1: Classification, immunohistochemical and electron microscopic findings in 186 cases of amyloidosis (reproduced from *Histopathology* 1991; 18: 133-141² with permission from Blackwell Scientific Publications)

Type of amyloidosis	No.	(%)	No. positive/no. tested					
			EM	AA	AP	Lambda	Kappa	KMnO ₄ *
Generalized								
Systemic AL	11	(5.9)	2/2	0/11	10/11	4/11	2/11	0/11
Systemic AA	6	(3.2)	2/2	6/6	3/3	0/4	0/4	6/6
Localized								
Isolated atrial	26	(14.0)	19/19	0/24	22/24	0/24	0/24	0/26
PLCA	14	(7.5)	–	0/7	12/12	0/8	0/8	0/5
Primary localized	6	(3.2)	–	0/6	5/5	2/5	1/5	0/5
Localized intratumor								
NPC	36	(19.4)	2/2	0/11	3/9	3/11	3/11	0/14
Metastatic NPC	14	(7.5)	–	–	–	–	–	–
Basal cell carcinoma	41	(22.0)	3/3	0/11	7/8	3/11	2/11	0/20
Islet cell tumor	4	(2.2)	3/3	0/4	3/3	1/4	1/4	0/4
Medullary thyroid Ca	1	(0.5)	–	0/1	1/1	0/1	0/1	0/1
Misc. other tumours	11	(5.9)	–	–	–	–	–	–
Dystrophic	16	(8.6)	–	0/16	6/16	0/16	0/16	0/16

*No. sensitive/no. tested. PLCA = primary localized cutaneous amyloidosis;
NPC = nasopharyngeal carcinoma

Pattern of liver infiltration

A collaborative study into the pattern of liver involvement in AL and AA amyloidoses³ revealed that AL amyloid tended to infiltrate along liver sinusoids or the space of Disse, forming a "sinusoidal" pattern. This pattern was in sharp contrast to that of AA amyloidosis, where the walls of blood vessels in the portal tract were largely involved, with no deposition in the sinusoids – a "vascular" pattern. These observations suggest that chemically different types of amyloid have affinity for different anatomical structures. This finding may help to differentiate AA from AL amyloidosis and may serve in selecting patients for appropriate therapy.

Pattern of kidney infiltration

In a review of renal AA amyloidosis,⁶ two patterns were observed: a glomerular pattern where amyloid obliterated glomeruli with variable, usually minimal, vascular involvement, and a vascular pattern where amyloid was largely deposited in blood vessel walls and often spared the glomeruli. The glomerular pattern was the more ominous being associated more often with chronic renal failure and severe protein loss. It appears that AA protein is not homogenous, there being different types of AA proteins with

differing affinity for anatomical structures.

Localized amyloidosis

Amyloidoses localised to a single organ or a single location were the most common types. Of these, 3 are unique to the Malaysian setting.

1. *Isolated atrial amyloidosis*: Congo red screening of cardiac biopsies obtained during cardiac surgery from 154 patients revealed 26 instances of isolated atrial amyloidosis (IAA), a prevalence of about 17%.⁷ When correlated against the type of heart disease that brought these patients to cardiac surgery, it was noted that most of them suffered from chronic rheumatic heart disease or atrial septal defect. The prevalence of IAA in chronic rheumatic heart disease was 23% and in atrial septal defect 15%. Table 2 shows the age-distribution of IAA in cardiac patients versus controls. Controls consisted of 247 healthy adults autopsied for traumatic deaths (such as road traffic accidents). The prevalence of IAA in cardiac patients was generally higher than controls. IAA also occurred at a younger age compared with controls.

What is noteworthy is that IAA in Western populations is considered a form of senile cardiac amyloidosis whereas the observations here show its occurrence at a much younger age in persons

TABLE 2: Age distribution of IAA-positivity in cardiac patients and controls
(reproduced from *Human Pathology* 1993; 24: 602-7 with permission from WB Saunders Company)

Age (Yr)	Cardiac patients		Controls	
	Screened	Positive	Screened	Positive
0-9	10	0	0	0
10-19	24	0	11	0
20-29	64	5 (7.8%)	100	0
30-39	32	9 (28.1%)	41	0
40-49	17	8 (47.1%)	32	3 (9.4%)
50-59	7	4 (57.1%)	29	1 (3.4%)
60-69	0	0	16	1 (6.3%)
70-79	0	0	15	1 (6.7%)
80-89	0	0	3	1 (33.3%)
>90	0	0	0	0
Total	154	26 (16.9%)	247	7 (2.8%)

with heart disease. This form of amyloidosis has been shown to contain atrial natriuretic peptide (ANP) and it is likely that the disturbed haemodynamics that occur in cardiac disease have resulted in high levels of ANP which polymerise into amyloid.

2. *Amyloidosis in nasopharyngeal carcinoma (NPC)*: Examination of 497 primary NPC and 113 metastatic NPC revealed amyloid deposits in 65 (13%) primary and 14 (12%) metastatic tumours.⁸ Unusual features of this form of amyloidosis are its radiate, spicular appearance, and its presence both within and outside the tumour cells, as shown by electron microscopy. Nasopharyngeal carcinoma associated amyloidosis is a novel finding first reported from this centre. The composition of the amyloid fibril is still not clarified and its nature and significance are being investigated.

3. *Dystrophic amyloidosis*: Dystrophic amyloidosis have been described in scarred heart valves and damaged joints. In addition, we have demonstrated that it can occur in scarred tissues in any part of the body such as scarred cyst walls and the fibrous tissues of longstanding ulcers.⁹ This heterologous distribution of dystrophic amyloidosis and its link to tissue damage may provide clues to the mechanism of amyloid formation.

DISCUSSION

This study serves to provide some basic information regarding the prevalence and types

of amyloidosis occurring among Malaysians. There are notable differences compared with information from the West. Among these are (i) the prominence of leprosy and tuberculosis as underlying factors in systemic AA amyloidosis as against rheumatoid arthritis and other rheumatic diseases, (ii) the high prevalence of isolated atrial amyloidosis among patients with chronic rheumatic heart disease, and (iii) the occurrence of a unique form of localized amyloidosis among nasopharyngeal carcinoma cells.

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