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THE NINTH K PRATHAP MEMORIAL LECTURE

Fibrillary deposits: Amyloids and tactoids

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Abstract

Two forms of abnormal fibrillary protein deposition are considered: amyloidosis and fibrillary (immunotactoid) glomerulonephritis. Amyloid is characterised by an antiparallel, beta-pleated configuration which imparts to it a unique apple-green birefringence after Congo red staining. Inspite of its fairly constant physical properties, the chemical composition of amyloid fibrils is amazingly diverse, encomposing AA protein, light chain fragments, transthyretin, procalcitonin, islet amyloid polypeptide, atrial natriuretic peptides, beta-amyloid protein, beta-2-microglobulin, cystatin C, gelsolin, apolipoprotein A1, lyzozyme and their mutant variants. Amyloid P component and heparan sulphate proteoglycan are ubiquitous non-fibrillary amyloid components which have significant roles in the amyloidogenetic process, as do also precursor fibril proteins. Different amyloid fibril proteins relate to different amyloidosis syndromes and different histological patterns, and provide the basis for new diagnostic approaches to this disorder.

Glomerular deposits in fibrillary glomerulonephritis (FGN), although often mistaken for amyloid, differ from it in its negative Congophilia, wider fibril width and highly organised, microtubular-tactoidal appearance ultrastructurally. FGN is essentially a primary glomerulopathy resulting in progressive renal failure.

Despite certain differences, intriguing similarities between both entities of fibrillary deposition pose a challenge to researchers as to the mechanisms of abnormal protein crystallization and fibril formation in tissues.

Key words: Amyloid, tactoid, fibrils, glomerulonephritis.

INTRODUCTION

As' pathologists, we often encounter the phenomenon of organised protein deposition in tissues during routine professional practice. Some of these are organised into fibrils associated with normal structures, such as large protein fibrils (e.g. collagen), small fibrils (e.g. elastin) and thin filaments (e.g. basement membrane). Abnormal protein organisation or crystallization in tissues, however, results in pathological states and functional disturbances and poses a challenging study for diagnostic pathologists and researchers alike. The best known of such highly organised protein deposition is amyloidosis. More recently, another form of pathological fibrillary deposition targetted to the kidneys, known as fibrillary glomerulonephritis or immunotactoid glomerulopathy, has been recognised. This lecture addresses current understanding of these two entities.

AMYLOIDOSIS

Defining characteristics

Amyloid is universally defined by its histological and tinctorial characteristics. It appears as amorphous, eosinophilic, extracellular deposits with the conventional haematoxylin and eosin stain, and expresses an affinity for the Congo red dye which stains it rose-pink to orange-red in colour. Once stained with Congo red, amyloid exhibits *an apple green birefiingence* when viewed under cross-polarized light.

Electron microscopy reveals a *fibrillary ultrastructure.* Amyloid fibrils are non-branching, haphazardly arranged, range from 7 to 10 nm in diameter and are of variable length (Fig. 1). These features differentiate it from other fibrils such as collagen and elastin.

The most unique feature of amyloid fibrils is their *anti-parallel, beta-pleated arrangement,* a characteristic that is revealed by X-ray diffraction crystallographic and infrared spectroscopic studies. It is this tertiary configuration and the right-angled orientation of fibrils to each other

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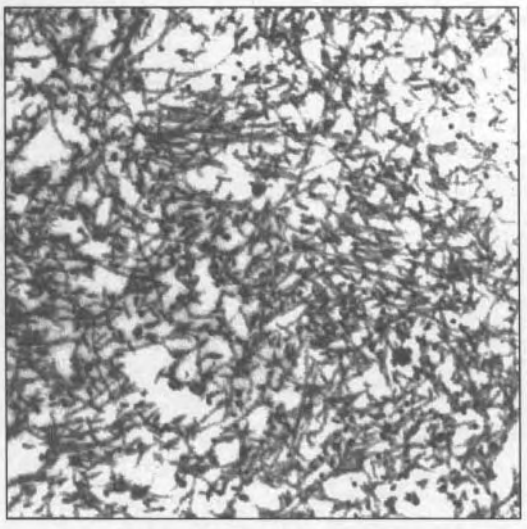

FIG. **1: Electron micrograph of an amyloid deposit showing typical non-branching fibrils in haphazard arrangement.**

that allows Congo red molecules to fit among amyloid fibrils in such a way as to interfere with transmitted light and bring about the diagnostic feature of green birefringence.[1]

Clinical significance

Amyloid deposition causes atrophy and death of adjacent cells, and can severely impair the physiological function of affected organs leading to organ failure. In systemic amyloidosis, resulting from whatever underlying disease, numerous organs are involved, and unfortunately, vital organs such as the heart and kidney are invariably affected. Under such circumstances, the prognosis is poor and the average survival time, from diagnosis, is only about 2 years.[2,3]

Infiltration of blood vessels by amyloid is the basis of bleeding complications encountered in systemic amyloidosis. Apart from that, adsorption of clotting factors by AL amyloid deposits have been known to result in rare but serious clotting deficiencies, particularly of factor X.

Localised amyloidosis poses less clinical complications, which are usually the result of mass effect and obstruction.

Nomenclature and classification

Systemic amyloidosis is known to complicate widely diverse conditions such as chronic inflammatory states, infections, tumours, immunological disorders, heredofamilial syndromes and senile degenerations. This had led in earlier days to a classification based on underlying disease i.e. (1) primary amyloidosis, when there is no obvious underlying disease, and (2) secondary amyloidosis, when there is a recognized predisposing disorder such as rheumatoid arthritis, tuberculosis or leprosy. Successful extraction of the amyloid fibril in the 1960s has pioneered the path to amino acid sequencing of the fibril proteins in the 1970s and 1980s. Today much is known about the amyloid substance and the nomenclature and classification of amyloidosis is now based on the chemical nature of its fibril protein.[4]

Amyloid fibril proteins

The amyloid fibril, which makes up about 90% of the amyloid substance, is amazingly diverse in its possible chemical composition. Table 1 lists some of the common amyloid fibril proteins known and the conditions under which they are deposited.

Fibrils from amyloid associated with immunocyte dyscrasias were first shown in 1970[5] to be composed predominantly of fractions of immunoglobulin light chains, leading to creation of the term "AL amyloid." A year later, it was reported that fibrils from amyloid associated with familial Mediterranean fever, infections and long-standing inflammatory conditions (known today as reactive amyloidoses) yielded a protein with no resemblance whatsoever to AL amyloid.[6] This was designated amyloid associated (AA) protein.

Identification of other amyloid fibril proteins followed swiftly and steadily: In 1976, the fibril protein from amyloid deposits in medullary carcinoma of the thyroid was identified to be a form of prohormone - procalcitonin - a product of the tumour cells? Amyloid in the pancreas of patients with adult-onset (Type II) diabetes mellitus was reported in 1986[8] to be composed of a polypeptide subsequently named "amylin" or Islet amyloid polypeptide. These two forms of apudamyloid have widened concepts in amyloid genesis and the search for other novel tumour-associated amyloid proteins.

By 1980, amyloid from the aging heart and from certain forms of hereditary amyloid syndromes was shown to be composed of prealbumin variants currently known as transthyretin.[9] Beta-amyloid protein was sequenced from amyloid plaques of Alzheimer's disease in 1984,[10] beta-2-microglobulin from dialysis-related amyloidosis in 1985[11] and cystatin C from cerebral amyloid angiopathy in 1986.[4] In 1987, a special form of amyloidosis of the aging heart, isolated atrial amyloidosis, was shown to contain atrial natriuretic factor.[12]

The 1990s saw the identification of mutations in the apolipoprotein A1 gene in familial amyloid

TABLE 1: Types of amyloid fibril proteins and related conditions

AL amyloid	: Immunocyte dyscrasia
AA protein	: Familial mediterranean fever and reactive amyloidosis
Procalcitonin	: Medullary thyroid carcinoma
Transthyretin	: Senile amyloidosis
Beta-amyloid protein	: Alzheimer's disease
Beta-2-microglobulin	: Dialysis-related amyloid
Cystatin C	: Cerebral amyloid angiopathy
Islet amyloid polypeptide	: Type II diabetes mellitus
Atrial natriuretic factor	: Isolated atrial amyloidosis
Apolipoprotein A1	: Familial amyloid polyneuropathy
Gelsolin	: Hereditary amyloid neuropathy with corneal dystrophy
Fibrinogen	: Hereditary renal amyloidosis
Lysozyme	: Amyloidosis of Ostertag
Prion protein	: Hereditary spongiform encephalopathies

polyneuropathy,[13] gelsolin gene in Finnish hereditary amyloidosis,[14] and of fibrinogen and lysozyme genes in hereditary non-neuropathic Ostertag-type amyloidosis.[15,16]

Beta-amyloid protein

One of the most significant of the recent findings is probably the clarification of the molecular origin of amyloid plaques in Alzheimer's disease and Down's syndrome. It is known that intracerebral and cerebrovascular amyloid deposition is the hallmark of Alzheimer's disease, the most common form of presenile dementia. Interestingly, identical amyloid plaques occur in almost all persons with Down's syndrome who live beyond the age of 40 years.[17] The main constituent of these amyloid plaques is the beta-amyloid protein (also known as A4 protein). Deposition of this protein actually occurs in the brains of about 80% of normal persons beyond 80 years of age[18] and presumably accounts for why people become more forgetful as they grow older. However, the production of beta-amyloid protein in Alzheimer's disease and Down's syndrome is 1000 times greater than in normal aging individuals. Beta-amyloid protein is derived from a high molecular weight precursor protein, amyloid precursor protein (APP). The gene encoding APP has been traced to the long arm of chromosome 21. It is an attractive proposition that overexpression of the APP gene, by virtue of its triplication in Down's syndrome and abnormal processing of APP in Alzheimer's disease, leads to increased deposition of beta-amyloid protein resulting in dementia. Recent observations indicate that beta-amyloid protein can be toxic to mature neurons. These findings have opened the path towards understanding the exact mechanism of dementia in Alzheimer's disease and Down's syndrome.[19]

Mutant proteins in hereditary amyloidosis

The last five years have seen an upsurge of interest in the hereditary amyloidosis syndromes. New amyloid proteins have been sequenced and various mutations discovered. Of note are the mutant forms of transthyretin (previously known as prealbumin) associated with the various types of familial amyloid polyneuropathies and cardiomyopathies. A single amino acid substitution - methionine for valine at position 30 - is the unique marker for the Portuguese form of autosomal dominant neuropathy. However, a mutation at position 111 results in the Danish form of familial amyloid cardiomyopathy. At least 40 mutant variants of transthyretin have been identified, each resulting in a different amyloidosis syndrome.[4,20]

It is becoming clear that, besides transthyretin, many other mutant proteins are amyloidogenic. Gelsolin with a substitution of asparagine for aspartic acid at residue 187 is deposited in Finnish hereditary amyloidosis characterised by neuropathy and corneal or vitreous opacity.[14] Cystatin C, with a substitution at position 68, is the protein in the Icelandic type of hereditary cerebral amyloidosis with haemorrhage.[21] More recently, a mutant form of α-fibrinogen has been implicated in a hereditary amyloidosis targetted to the kidneys[15] and mutant lysozyme in systemic hereditary non-neuropathic amyloidosis of Ostertag.[16]

Amyloidogenesis

Amyloidogenecity of proteins

Inspite of mounting research efforts, the pathogenesis of amyloidosis remains far from clear. What is most astounding is how so many completely different proteins come to form the unique beta-pleated configuration that is the unifying feature of amyloid, as reflected in practical terms by its Congophilia and green birefringence. This diversity of proteins is further compounded by the fact that both mutated and non-mutated forms of the same proteins can also be amyloidogenic. For example, mutated transthyretin results in familial amyloid polyneuropathy whereas deposition of non-mutated transthyretin results in systemic senile amyloidosis.[20,22] Mutated beta-protein specifically occurs in the Dutch type of hereditary cerebral amyloid with haemorrhage, whereas non-mutated beta-protein is deposited in senile cerebral amyloid plaques.[10,23,]

Role of non-fibrillary components

In contrast to amyloid fibrils, the non-fibrillary component (which constitutes the remaining 10% of the amyloid substance) is remarkably constant in its composition. It has been shown to consist largely of a glycoprotein known as "amyloid P component" and other minor constituents such as "amyloid enhancing factor" and "heparan sulphate proteoglycan."

Amyloid P *(AP) component* is *a* ubiquitous protein, immunologically identifiable in all forms of amyloid.[24] AP component and its identical serum counterpart SAP, is composed of a pair of pentagonally shaped subunits on electron microscopy, hence the name "P." It has a molecular mass of 230,000 daltons and is antigenically related to alpha-l-serum glycoprotein and C-reactive protein, all classified as pentraxins. AP component is well preserved in evolution, is identifiable in elastin and basement membrane, and acts as an acute phase reactant in animals. The role of the AP component in amyloidosis has long been an enigma and the target of speculation. Its strong association with basement membrane and fibrillary structures suggests that it may serve as a crucial scaffold for fibrillogenesis[25] but whether it is essential for beta-pleated tertiary structure formation remains unclear.[26]

Recently, attention has been drawn to other common amyloid elements, especially *heparan sulphate proteoglycan.* This has been shown to be upregulated early in arnyloid induction and is now a prime candidate being investigated as responsible for beta-pleat formation.[25,27]

Role of precursor amyloid proteins

A number of amyloid proteins are the products of precursor proteins, often carried in the serum. *AA protein* is an example. The amino acid sequence of AA protein in various human diseases is relatively constant. AA protein is a 8,500 dalton, 76 amino acid molecule. However, its precursor protein - SAA - is a 12,500 dalton, 104 amino acid polymorphic protein with multiple isoforms. SAA genes are located on the short arm of chromosome 11. SAA is produced by the liver. Its function is not known but it circulates largely in association with lipoproteins and behaves as an acute phase reactant. In inflammation, it may increase several hundred fold.[28]

In contrast to AA protein, *AL proteins* exhibit tremendous individual variability. The fact that AL fibrils are derived from immunoglobulin fragments is attested to by (1) their sequence homology, (2) the *in vitro* formation of amyloid fibrils on proteolysis of light chains, and (3) the immunologic cross-reactivity of individual AL deposits with kappa or lambda chains. It is noteworthy that lambda chains are more amyloidogenic than kappa chains by the ratio of 2:1, although kappa chains are more commonly produced in immunocyte dyscrasias.[29]

Transthyretin and AP component have been referred to earlier. Both transthyretin and SAP, the precursor of AP, are produced in the liver.

The importance of studying the precursor proteins is that there are known instances where *excessive production of precursor proteins* are associated with systemic amyloid deposition.[28,30] SAA levels are known to be high in systemic AA amyloidosis secondary to many chronic inflammatory conditions, although not exclusively so. Systemic AL amyloidosis is a known complication of myelomatosis where excessive precursor light chains are produced. Excessive transthyretin production is linked with systemic senile amyloidosis.

The mechanism of amyloid deposition

Much in the mechanism of amyloid protein formation remains to be unravelled. However, *proteolysis of precursor proteins,* which are large molecules, to smaller units appears an important step.' These smaller units are presumbably more amenable to structural modification towards fibrils and beta-pleats. However, there are many proteins which are amyloidogenic in the intact form, such as lysozymes, beta-2-microglobulin and particularly transthyretins.[31,32]

Another point of interest is that, experimentally, *high concentrations of amyloidogenic peptides* have been shown to be capable of self-assembly into fibrils and even beta-pleats. Bence-Jones proteins is an example.

There is also increasing evidence that *different amyloid peptides exhibit affinity for different anatomical structures*. Thus AA amyloidosis may show a different morphological pattern from AL amyloidosis.[33] Furthermore, mutants of the same peptide may also differ in anatomical affinity, thus explaining the different syndromes related to different mutants of transthyretin.[4,20]

In experimental amyloidosis, *amyloid enhancing factor* is known to greatly shorten the process of amyloid deposition, presumably by serving as a nidus for amyloid peptide attachment to tissues.[34]

It can be seen that there are many factors which contribute towards fibrillogenesis. Figure 2 proposes an amyloidogenetic scheme based on current understanding.

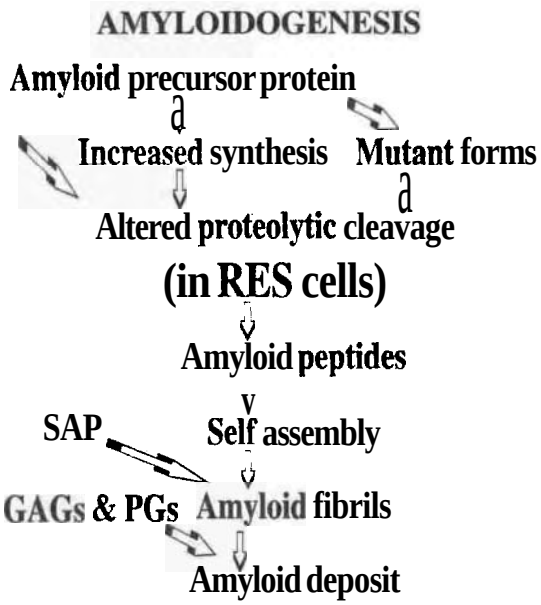

FIG. 2: The amyloidogenetic pathway: a proposition. The first step involves the presence of precursor proteins, either in excess amounts or in particularly amyloidogenic mutant forms. These are cleaved into smaller peptide units, very likely by reticuloedothelial cells. In high concentrations, these peptides may be capable of self-assembly into fibrils, especially with amvloid enhancing factor as a nidus and amyloid P component as scaffolding. After this stage, heparan suplhate proteoglycan and possibly other sulphated glycosaminoglycans, probably have a role to play in the final polymerisation of amyloid fibrils into the crucial beta-pleated configuration i.e. the Congophilic amyloid deposit.

Practical applications

This discourse on amyloid proteins and arnyloid formation need not be of pure theoretical interest. Observations encountered in surgical pathology practice have brought these concepts to a more practical level. New diagnostic approaches to amyloidosis have been developed on the basis of the different amyloid proteins, as annotated below:

(1) The accuracy of detection and classification of amyloidosis in the histopathology Laboratory has been enhanced by applying immunostaining to tissues based on antibodies against various amyloid fibril proteins such as AA, AL and transthyretin.[35] Figure 3 illustrates an example.

(2) In 1988, a collaborative study was published which compared the pattern of amyloid infiltration in the liver in AL and AA amyloidosis using pooled material from the Departments of Pathology of the University of Malaya and the Queen Victoria Medical Centre in Australia.[33] It was found that AL amyloid tended to infiltrate along sinusoids between the liver cells, forming a "sinusoidal" pattern. In contrast, AA amyloid was confined to blood vessels and

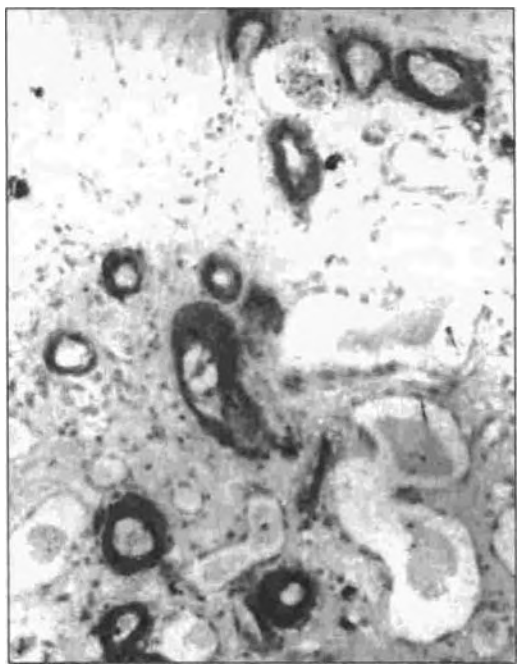

FIG. 3: Using a standard peroxidase-immunoperoxidase method and antibody against AA protein, the amyloid deposit5 within this renal biopsy have been shown conclusively to be of AA type. The deposits are clearly visualised here in blood vessel walls.

spared the sinusoids, forming a "vascular" pattern. These observations, which have since been confirmed by other workers in the USA, are consistent with the notion that chemically different types of amyloid have affinity for different anatomical structures.

(3) In a study conducted to investigate whether patterns of amyloid infiltration could correlate with clinical manifestations, two patterns, designated "glomerular" and "vascular," were observed in renal AA amyloidosis.[36] The glomerular pattern was characterised by severe glomerular infiltration by amyloid and variable, usually minimal, vascular involvement. In the vascular pattern, amyloid was present predominantly in blood vessels with relative sparing of glomeruli. When charted against renal function, the glomerular pattern appeared to be more ominous being associated more often with chronic renal failure and severe protein loss.

From the scientific point of view these patterns were particularly fascinating because they both occurred in AA amyloidosis. What this could mean was that AA protein itself was not a homogenous protein, i.e. there were several different types of AA protein, with different affinity for different structures. This inference has found support in the recent discovery of at least 6 isotypes of AA precursor proteins.[37]

(4) The ubiquitous presence of AP component in all types of amyloid inspite of the varied fibril composition, has also been exploited for the diagnosis of amyloidosis. This has been applied in immunohistochemistry for the detection of amyloid deposits.

(5) More recently, the usage of AP component in radiological localisation and monitoring of the extent of amyloidosis has been investigated. The principle behind this is to inject patients with AP component labelled with iodine-123, which, through dynamic flux between tissue deposits and serum, would be incorporated into amyloid deposits. Whole body scintigraphic images taken of the patient would then indicate the presence and location of such amyloid deposits. Recent trials have shown this to be valuable for assessing amyloid load and monitoring response to treatment.[35,38]

The pattern of amyloidosis in surgical pathology practice

In the minds of many, amyloidosis is a rare disease. However, in recent times, mounting knowledge, improved diagnostic ability and increasing awareness of the condition have led to its recognition in numerous pathological situations. As noted earlier, it complicates widely diverse conditions such that it has been declared to be "associated with more morbid processes than almost any other pathological condition."

With this in mind, a study was carried out to elucidate the pattern and prevalence of amyloidosis that one may expect to encounter in surgical pathology practice in this part of the world.[39] The investigation involved Congo red screening of 27,000 routine biopsies from 22,000 patients at the University Hospital, Kuala Lumpur, a study which essentially meant screening all biopsies (excluding products of conception and endometrial currettings) received over 5.5 years at the Department of Pathology, University of Malaya. All positive cases were classified using histochemistry and immunohistochemistry according to the amyloid protein present.

186 cases of amyloidosis were detected and their distribution is summarised in Table 2: 17 (11 plus 6) (9%) were systemic or generalised amyloidosis while the remaining 91% were localised to one organ system.

Systemic amyloidosis carried the most clinical significance because of involvement of vital organs such as the heart and kidney. 11 (65%) were AL amyloidosis of which a third were associated with immunocyte dyscrasia. 6 (35%) were AA amyloidosis and were associated with either tuberculosis or leprosy. These findings were consistent with earlier studies which suggested that tuberculosis and leprosy were by far the most important underlying diseases for AA amyloidosis in Malaysia.[40,41]

Amyloidoses localised to a single organ or single location were the most common types. These included isolated atrial amyloidosis of the heart,[42] localised arnyloidosis of the skin,[43] and several types associated with tumours, especially nasopharyngeal carcinoma[44] and basal cell carcinoma.[45] A special form categorised as dystrophic amyloidosis was also encountered.[46]

Time constraints prohibit further description of these entities. Suffice it to say that amyloidosis is not uncommon in surgical pathology practice in Malaysia and it can take on several different forms.

TABLE 2: Distribution of 186 amyloidosis cases based on Congo red screening of 27052 biopsies (reproduced from Histopathology 1991; 18: 133-41[39] with permission from Blackwell Scientific Publications)

Type of amyloidosis	No.	(%)
A. Systemic		
AL amyloidosis	11	(5.9)
AL amyloidosis	6	(3.2)
B. Localized		
Isolated atrial amyloidosis	26	(14.0)
Primary localized cutaneous amyloidosis	14	(7.5)
Miscellaneous localized deposits	6	(3.2)
Localized intratumour amyloidosis		
Nasopharyngeal carcinoma	36	(19.4)
Metastatic NPC	14	(7.5)
Basal cell carcinoma	41	(22.0)
Islet cell tumour	4	(2.2)
Medullary thyroid carcinoma	1	(0.5)
Miscellaneous other neoplasia	11	(5.9)
Dystrophic	16	(8.6)
Total	186	(100)

FIBRILLARY GLOMERULONEPHRITIS

Apart from amyloid, there has been recent interest in another form of organised protein deposition. Because it occurs in the kidney, it has been called immunotactoid glomerulopathy or fibrillary glomerulonephritis (FGN). The first documented case appears to be that of Rosenmann and Eliakim in 1977.[47] They reported fibrillary deposition in the glomeruli of a woman with nephrotic syndrome, which appeared similar to arnyloid except for a larger fibril width and negative staining with Congo red. Over 60 similar cases have been reported since, under the terms of "Congo red-negative amyloidosis-like glomerulopathy,"[48] "fibrillary glomerulonephritis"[49] and "immunotactoid glomerulopathy."[50] Although the numbers of documented cases are small, the picture of a progressively worsening proliferative glomerulonephritis is emerging.[51,52,53]

One of the largest known collection of FGN cases is found at the Brigham and Women's Hospital, Harvard Medical School, USA and it is hoped that this account of the first 23 cases in that collection will provide some insight into its pathology:

Demographic profile

The ages of FGN patients ranged from 18 to 81 years with a mean of 50 years. The male:female ratio was 1:2.3 showing a female preponderance.

Clinical features

The majority of patients presented with haematuria (44%), proteinuria (44%), nephrotic syndrome (35%) or hypertension (30%), often with renal insufficiency. There was no association with cryoglobulinaemia, systemic lupus erythematosus (SLE), diabetes mellitus or paraproteinaemia. In general, the patients showed progression towards end stage renal disease. A patient who had undergone renal transplantation developed recurrent disease subsequently. One patient developed pulmonary fibrillar deposition, an unusual outcome because FGN is generally considered to be not a systemic disease.

Renal changes

Renal morphological changes were variable. The majority of renal biopsies revealed a diffuse mesangioproliferative (39%) or mesangiocapillary (26%) glomerulonephritis. Occasional focal proliferative, focal sclerosis, chronic and crescentic features were seen. The classical morphological findings irrespective of glomemlar pattern were:

- mesangial expansion (100%)
- glomemlar capillary thickening with wrinkling and variable splitting of the basement membrane (90%),
- mesangial proliferation (80%),

- mesangial and capillary PAS-positive, trichrome-positive, Congo red-negative globules (70%), and
- hypertensive vasculopathy (>50%).

Immunofluorescence examination was available in 87% of cases. Of these, 90% had positive fluorescence, expressed mainly as an irregular, coarse linear deposition of IgG, kappa and lambda light chains in glomerular capillary walls. Mesangial deposition was less obvious.

Electron microscopy was performed on all the cases and showed diagnostic fibrillary-tactoid deposits (10-20 nm width) within glomerular basement membrane and mesangium. Their highly organised microtubular appearance (Fig. 4) and wider fibril width distinguished them from amyloid fibrils.

Pathogenesis

As in amyloidosis, the mechanism of fibril formation in FGN poses an enigma. The question has been raised as to why some light chains (particularly lambda chains) organise into beta-pleats and condense as amyloid while others, such as those found in light chain nephropathy, form granular deposits. Why immunoglobulins assume 'fingerprint' condensations in SLE, cylindrical or annular bodies in cryoglobulinaemia and microtubular tactoids in FGN is a question that probes into the very heart of protein condensation and crystallization.[54]

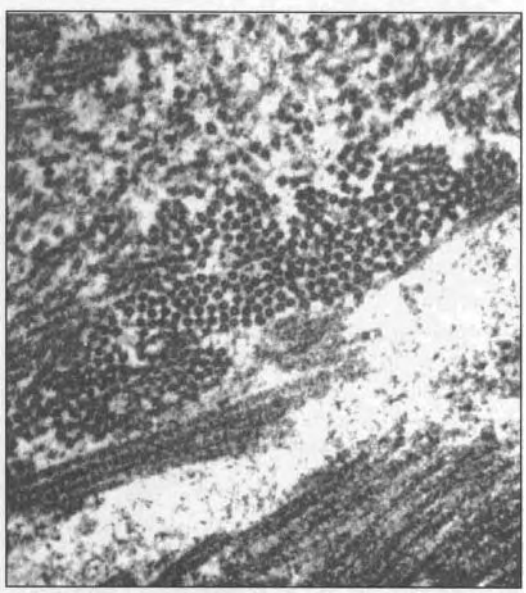

FIG. 4: Electron micrograph showing the highly irganised microtubular configuration of fibrils in fibrillary (immunotactoid) glomerulonephritis (by courtesy of Dr. HG Rennke, Harvard Medical School, USA).

It has been speculated that tactoidal generation in FGN may be analogous to haemoglobin S (Hb S) structure.[51] In Hb S disease, the abnormal haemoglobin forms rings which interact with adjacent molecules to form a nematic (liquid crystal) structure which grows in a unidirectional fashion. It has been postulated that the tactoidal proteins of FGN are immune complexes or abnormal immunoglobulins characterised by a uniform substructure with strong intermolecular attractions, allowing highly organised liquid crystal orientations. However, if abnormal proteins are involved, these are presumably produced in quantities too small for standard serological detection, for none have been documented to this day.

CONCLUDING REMARKS

Although the past two decades have seen tremendous advances in knowledge and insight into the chemical nature of amyloid and amyloid fibril genesis, many questions remain unanswered. Among them would be the factors that determine why some forms of amyloid proteins result in localized disease and others in systemic disease. An extension of this question would be whether there is an analogy between localized amyloidosis and FGN.

The morphological similarities between amyloid and the tactoidal deposits of FGN raise the possibility that they may share similar physical properties and pathogenetic mechanisms. Currently, little is known of the tertiary structure of immunotactoids, and the possibility of a beta-pleated structure has not been excluded. Studies on amyloidosis have shown that elution of proteins and crystallographic studies were needed to reveal the actual tertiary configurations of the arnyloid fibril. Hence, much may be gained if pathologists will draw on the expertise of physicists and chemists to unravel the physicochemical nature of these tactoidal deposits.

It would appear that in both amyloidosis and FGN, the fibrillary nature of the condensed proteins provide effective resistance against easy removal by the body's phagocytic mechanisms. Hence, the fibrils accumulate and eventually lead to organ failure. Until we can understand the mechanisms of such fibril formation and deposition, it would be difficult indeed to contemplate ways to counteract the devastating clinical effects of such deposits.

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