Amyloidosis of Lower Genitourinary Tract: A Review

Sudhanshu Chitalea,*, Mo Morseya, Danielle Peatb, Ralph Webba

a Department of Urology, Norfolk & Norwich University Hospital NHS Trust, Colney Lane, Norwich, NR4 7UY, United Kingdom
b Department of Histopathology, Norfolk & Norwich University Hospital NHS Trust, Colney Lane, Norwich, NR4 7UY, United Kingdom

1. Introduction

Virchow first used the term amyloid [1] meaning “starchlike” to describe tissue deposits that stained with iodine solutions. Although a carbohydrate moiety was rightly identified in the amyloid tissue, it is well established that the principal constituent of the amyloid fibril is protein. Many different proteins (20) may form amyloid under diverse clinical conditions, all characterised by extracellular accumulation of fibrillar protein deposits. Their tissue distribution and consequent clinical manifestations vary widely. A single amyloid protein deposit occurring in different clinical conditions indicates a common pathologic mechanism (e.g. persistent inflammation) but each amyloid protein is usually associated with a unique clinicopathological condition [2]. Thus, amyloidogenesis depends upon whether a single common pathologic mechanism is involved or diverse mechanisms are operational in a given disease process. How different proteins organise themselves into a common structure such as “amyloid” is not clearly understood. There is strong evidence that some derangement in the immune apparatus underlies this process and being a systemic disorder, it cannot be assigned to a single organ [3].

2. Morphology

Amyloid deposition occurs insidiously and its clinical recognition depends upon morphologic identification of this protein in the extracellular space in appropriate biopsy specimens. With progressive accumulation it produces pressure atrophy of adjacent cells [3]. Light microscopy with standard tissue stains shows amorphous eosinophilic hyaline...
material deposited between cells of the respective tissue. Congo red stain under ordinary light imparts pink/red colour to the deposits but under polarised light, the specific green birefringence of the stained amyloid is noted. Transmission electron microscopy (TEM) (Fig. 1) reveals the amyloid to be 95% [3] nonbranching fibrils of 7.5 to 10 nm in diameter. X-ray crystallography and infrared spectroscopy show a characteristic cross beta-pleated sheet configuration. A minor second component called the P component (5%); a pentagonal doughnut shaped glycoprotein seen under EM is always present in addition to the fibrils.

3. Chemistry

Amyloid is not a chemically distinct entity despite the uniform appearance of all amyloids. There are two major and around 13 minor biochemical forms. The two most common or major forms are: AL (amyloid light chain) and AA (amyloid-associated). AL is an immunoglobulin derived from plasma cells and AA is a unique nonimmunoglobulin synthesized by the liver [3].

The amyloid protein of the AL type is associated with monoclonal B cell proliferation such as multiple myeloma, whereas the AA protein is deposited as secondary amyloidosis in chronic inflammatory disorders including rheumatoid arthritis and osteomyelitis.

Apart from AL and AA, other biochemically distinct forms of amyloid have been found in distinct clinical settings: amyloid transthyretin (ATTR; prealbumin) is deposited in familial amyloid polyneuropathies, β₂-microglobulin may be seen in patients on long term haemodialysis and in cerebral amyloid angiopathy; and in Alzheimer’s disease the main protein is Aβ₂. Amyloid in medullary carcinoma of the thyroid is formed from the hormone calcitonin [3].

4. Classification

Amyloids can be classified based on their chemical fibril constituent as AL, AA or ATTR (biochemical classification) or based on clinical syndromes as systemic and localised (clinical classification). A combined biochemical-clinical or clinico-pathological classification is thought to be more practical as a given biochemical form of amyloid may be associated with diverse clinical settings. Clinically, the systemic/generalised and localised patterns could be subclassified into primary amyloidosis when associated with some immunocyte dyscrasias (AL) and secondary amyloidosis when it occurs as a complication of chronic inflammation or tissue destructive process (AA) [3]. Hereditary or familial amyloidosis constitutes a separate group of conditions with distinctive pattern of organ involvement [3].

5. Pathomorphology

In any of the amyloid categories, there are no specific patterns of organ/tissue involvement. As a general observation, primary or immunocyte associated (AL) amyloidosis more often involves heart, gastrointestinal tract, carpal tissue, peripheral nerves, tongue and skin whereas the secondary amyloidosis (AA) tends to involve kidneys, spleen, liver, GI tract, adrenal, thyroid and lymph nodes [2,3]. Familial ATTR amyloid predominantly involves peripheral and autonomic nervous system and carpal tunnel. β₂M amyloid chiefly affects musculoskeletal system. The gross appearance of the involved organ depends upon the volume of amyloid and the site of deposition within the tissue. The affected organ is enlarged, pale and waxy; if there is vascular involvement there may be atrophy. The staining characteristics are shared by all forms of amyloid and are attributable to the cross-beta pleated configuration of amyloid fibrils. Staining dyes include Congo red, potassium permanganate, methyl violet thioflavine and Alcian blue. The specific fibril protein components of the amyloid can be identified by immunohistochemistry or electron microscopy [2,3].

Amyloid is located extracellularly in vessels or parenchyma. Progressive deposition of amyloid follows the stromal architecture of the organ.
Amyloid isolates parenchymal cells and interferes with the intrinsic circulation of the organ causing atrophy in advanced cases. A significant amount of amyloid deposition is needed before the function of the organ is impaired; the kidney is the exception where glomerular function is compromised at an early stage of the disease.

5.1. Renal amyloidosis

The kidney may be normal, enlarged or shrunken in advanced cases due to vascular narrowing induced by amyloid deposits within arterial and arteriolar walls. Deposits are primarily in the glomeruli as a subtle nodular increase in mesangial matrix and widening of capillary basement membrane as well as in the interstitium, arteries and arterioles (Fig. 2). The glomerular vascular tuft may be distorted by masses of amyloid leading to obliteration of capillary lumina.

5.2. Vesical amyloidosis

Deposits of amyloid are found in the arteries, arterioles, veins and suburothelial connective tissue. Foreign body giant cell reaction and calcification may be present. Similar deposits have also been described in the renal pelvis, ureter and urethra.

6. Clinical features and correlation

Amyloidoses are a significant cause of morbidity and mortality in the Western world. Its presentation may vary from an unsuspected anatomic change with no clinical manifestations to causing death. The symptoms depend upon the particular organ/site involved and the magnitude of the deposits. Initial symptoms could be nonspecific such as weakness, weight loss or syncope. Specific symptoms are related to renal, gastrointestinal and cardiac involvement as well as hepato-splenomegaly and altered serum protein levels. Clinical features in an individual are determined by principal site of deposition in that individual. Different types of amyloidosis have certain peculiarities about their organ involvement. Isolated deposits of amyloid can virtually develop anywhere in the body but the most common sites of localized amyloidosis are the genitourinary system, lungs, skin and stroma of medullary carcinoma of the thyroid. These deposits although composed of light chains are rarely a manifestation of systemic AL amyloidosis [2].

6.1. Kidney

The hallmark of renal amyloidosis is heavy proteinuria which may be associated with nephrotic syndrome; there may be progression to chronic renal failure. Bence Jones proteinuria is a feature of AL amyloidosis [4,5]. Renal amyloidosis is one of the dominant features of systemic amyloidosis (AA), the most common being rheumatoid arthritis and other chronic conditions including familial Mediterranean fever (Heredofamilial amyloidosis), ApβM amyloidosis is an important extrarenal complication of chronic haemodialysis, its incidence approaching 100% in patients on haemodialysis for over 15–20 years [6–9].

Diagnosis of renal amyloid is by renal biopsy. Although renal biopsies have a high positive yield in most forms of systemic amyloidosis [10,11], haemorrhage is a significant complication of biopsying amyloidotic organ due to vascular involvement by amyloid and abnormalities of haemostasis associated with amyloidosis [12]. In patients with suspected systemic (AA) amyloidosis, a rectal or gingival biopsy may be helpful [10]. Patients with suspected (AL) amyloidosis should have serum and urine protein electrophoresis performed. Needle aspiration of subcutaneous abdominal fat may be used [13–16].

Treatment of renal amyloid is symptomatic or of its associated complications [17].

Amyloidosis of the pelvicalyceal system without involvement of the renal parenchyma has also been reported as easily confused with urothelial tumour [18]. Diagnosis of urothelial amyloidosis may be possible if presence of amyloid is noted in the urine cytology sample [19].
6.2. Ureter

Primary amyloidosis of the lower ureter has been described in the literature presenting as hydronephrosis secondary to ureteric stricture [20–22] and bilateral involvement presenting as anuria [23]. Treatment with ureteric stenting and occlusive dressing technique using dimethyl sulfoxide (DMSO) for 6 months leading to complete resolution of the lesion has been described [20].

6.3. Bladder

Amyloidosis of the urinary bladder is uncommon [24]. However amongst the various sites in the lower urinary tract, bladder is the most commonly involved organ [26]. Both sexes are equally affected between the fifth and seventh decade. Painless gross haematuria is the main presenting symptoms in most (>75%) cases [24,25]. Both primary and secondary amyloidosis may involve the bladder, isolated primary vesical amyloidosis (Fig. 3) being more common than secondary involvement [32] and the lesions can be easily confused with a tumour [25–32].

Diagnosis depends upon specific staining characteristics of the bladder tissue and immunohistochemical studies identifying the amyloid type. Presence of amyloid light chain (AL) indicates that the protein originated outside the urinary bladder but the protein subtyping by sequence analysis suggests it has no role in restricting the deposited protein to the bladder [26]. Repeated workups for systemic amyloidosis are unnecessary in AL amyloidosis of the bladder [25] but early eradication of the lesion with resection/fulguration/laser ablation is advisable with regular cystoscopic follow up. Prognosis remains excellent in primary amyloidosis [27–31].

6.4. Urethra

Presentation of urethral amyloid deposit (Fig. 4) mimics primary tumour of the urethra or nonspecific urethritis [33]. It has been described in both sexes [34,35]. Isolated amyloid of the penile urethra [36] and corpus spongiosum have also been reported, presenting with painful erection [37] or haemospermia [38]. MRI may be useful in suggesting a diagnosis [39]. Symptomatic and expectant management has been shown to be appropriate in these cases [39,40].

6.5. Prostate & seminal vesicle

Clinical presentation of prostatic amyloid as a part of systemic amyloidosis resembles tumour of the prostate [41]. Localized secondary amyloidosis of the seminal vesicle presenting with chronic perineal pain mimics seminal vesiculitis [41] and although its prevalence is higher in those who had hormonal therapy for prostatic carcinoma, there has been no direct association between seminal vesicle amyloidosis (Fig. 5) and occurrence of prostatic carcinoma [42].

6.5.1. Diagnostic techniques

A definitive diagnosis requires histological identification of amyloid deposits. Identification of the specific subtype of amyloid is important as it has prognostic and therapeutic implications. Biochemists use ancillary techniques such as serum and urine protein electrophoresis and immuno-histochemistry for specific subtype identification of amyloid. Diagnostic molecular genetics has become important for the heredofamilial type of amyloidosis and the data used for genetic counselling and
prenatal diagnosis in affected families [43–46]. An adjunct to amyloid diagnosis is $^{125}$I-SAP scintigraphy [47], which allows identification of the amyloid in vivo in a noninvasive fashion. This technology may contribute to the diagnosis of amyloidosis and monitoring of treated and untreated cases over a long term.

6.5.2. Treatment

Presentation of localised primary amyloidosis of the lower genitourinary tract generally mimics cancer of the respective anatomical site; hence resection of the lesion remains the primary treatment. Following confirmation of histological diagnosis, further treatment remains expectant and symptomatic [28]. Most vesical amyloidosis have been managed with localised endoscopic resection, only one case in a series of 9 required total cystectomy for symptom control [48]. Secondary amyloidosis as a consequence of generalized/systemic amyloidosis has a more aggressive presentation with massive life-threatening bleeding or bladder rupture and will require desperate measures such as arterial embolisation, cystectomy or at times Mickulicz transurethral bladder tamponade [49]. On the whole, treatment of systemic amyloidosis is purely symptomatic, with nephrotic syndrome and congestive cardiac failure needing relevant medical therapy. Treatment of any associated infection or inflammation also needs to be addressed appropriately [17]. Detrusor failure/dysfunction secondary to amyloid polyneuropathy [50] or recently reported detrusor weakness along with impaired bladder sensations secondary to small fibre neuropathy of amyloidosis [51] would need urological attention like any other case of detrusor failure. Involvement of postganglionic cholinergic and afferent somatic nerves seems to be the underlying mechanism. Erectile dysfunction has been reported in patients with familial ATTR amyloidotic polyneuropathy and its successful treatment with sildenafil citrate without altering systemic circulation [52].

6.5.3. Prognosis

The prognosis of generalised (AA) amyloidosis remains poor. Outlook for reactive (secondary) generalised type is slightly better compared to (primary) systemic and directly depends upon control of the underlying condition. Post treatment resorption of amyloid has been known but rare [3]. Those with immunocyte-derived amyloidosis (AL) excluding cases with multiple myeloma have a median survival of two years following diagnosis.
whereas those with associated myeloma have a poorer prognosis. However, the prognosis of localised primary amyloidosis involving the genitourinary tract, an unusual clinical entity, remains excellent with conservative therapy as long as a definitive histological diagnosis is established and causes of secondary (generalized) amyloidosis are ruled out. Repeated work ups for systemic amyloidosis are not necessary in cases of primary (AL) localised amyloidosis of the lower genitourinary tract because local recurrence is more commonly found than any causes for secondary/systemic amyloidosis [25].

References


CME questions

Please visit www.eu-acme.org/europeanurology to answer these CME questions on-line. The CME credits will then be attributed automatically.

1. Amyloid is stained in the laboratory using
   A. Congo green
   B. Congo blue
   C. Congo red
   D. Congo yellow

2. Ultrastructurally, amyloid is made up of non-branching fibrils of
   A. 7.5–10 cm
   B. 7.5–10 μm
   C. 7.5–10 mm
   D. 7.5–10 nm

3. AA deposits are characteristically laid down in
   A. Chronic inflammatory disorders
   B. Myeloproliferative diseases

4. Deposition of amyloid is
   A. Intracellular
   B. Extracellular
   C. Intranuclear
   D. In basement membranes

5. The core protein in patients on long-term haemodialysis developing amyloid is
   A. Calcitonin
   B. Aβ amyloid
   C. AL
   D. β2-microglobulin

6. The main presenting symptom of amyloidosis of the urinary bladder is
   A. Pain
   B. Urinary tract infection
   C. Haematuria
   D. Acute retention

C. Epithelial malignancies
D. Alzheimer’s disease