Amyloid in prostatic corpora amylacea

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Abstract

Aim: To determine the presence and nature of amyloid in prostatic corpora amylacea using immunohistological studies.

Methods: Prostatic tissue from 18 transurethral and two open resection specimens was studied. Paraffin wax embedded tissue sections were stained with haematoxylin and eosin and the alkaline Congo red method with and without previous treatment with potassium permanganate. Sections were also stained with antibodies to amyloid A, β_2 microglobulin, λ and κ light chains, prealbumin IgA, G, M, S100 protein, prostatic specific antigen, amyloid P component and CAM 5-2 (control and blocking studies were performed).

Results: The prostatic corpora amylacea universally showed the presence of amyloid. In all instances this contained β_2 microglobulin.

Conclusion: Prostatic corpora amylacea represents a localised amyloidosis of β_2 microglobulin origin that is unrelated to chronic renal failure and haemodialysis.

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Prostatic corpora amylacea, also known as prostatic concretions, corpora colloidea, or amyloid bodies, were noted in the earliest studies of the prostate gland. Morgagni (1779), wrote:

"But of what nature are these granules? For I have found them in many bodies, and not then for the first time. In the *Adversaria* I considered them as a humour which is secreted in the prostate, and coagulated into that form: nor do I at present see any reason why I should not consider them in the same point of view also."¹

The few studies on prostatic corpora amylacea have claimed that they contain immunohistochemical cytokeratin positivity,² and electron microscopic studies have suggested a close parallel between the fibrils in the corpora and prostatic epithelial cell intermediate filaments.²⁻⁴ Biochemical studies have suggested a mix of keratin and nucleoprotein within the corpora.⁵ The even more scanty reports specifically on prostatic amyloid, demonstrated by the Congo red method,^{6,7} variously state that "corpora amylacea, which often stain spectacularly, were not considered significant"⁶ or ignored them altogether.

This confusion over their composition and

the incidental finding of β_2 microglobulin (β_2 M) positivity in prostatic corpora amylacea in a study of systemic β_2 M amyloidosis prompted the present study.

Methods

All surgical prostatic resection specimens for 1988 were retrieved. Those specimens which were normal or showed benign prostatic hyperplasia and contained corpora amylacea were studied further. There were 18 transurethral resections and two open prostatectomy specimens. Prostatic tissue from six necropsy cases and material from four cases of systemic amyloidosis of known type with prostatic disease were also used (table 1). Paraffin wax embedded tissue sections (cut at 4 μ m) were stained with haematoxylin and eosin, or by the alkaline Congo red method with and without prior treatment with potassium permanganate (KMnO₄). Sections were also stained with the antibodies listed in table 2, using the avidin-biotin technique with and without digestion with trypsin. A blocking procedure using excess free human β_2 M (Serotec) at a final concentration of 1 mg/ml was applied to tissue sections to assess the specificity of the reaction.

Results

Typical corpora amylacea lay within the prostatic glandular lumina in all the cases studied. Most of the corpora were Congo red positive, and gave apple-green birefringence with crossed polarising filters. The Congo red stain accentuated the lamellar appearance of the corpora, although the degree of staining was variable among corpora. The apple-green birefringence produced a Maltese cross effect (fig 1) in some corpora, the effect being more noticeable at the periphery. The size of the corpora did not seem to affect this reaction, except that the larger corpora were more likely to be either pigmented or calcified (these purely pigmented and calcified corpora were excluded from the immunohistochemical studies). Prior treatment with potassium perman-

Table 1 Amyloid cases

	Amyloid type	Clinical details
1	A K	IgA K myeloma
2	AA, K	Chronic bronchiectasis
3	A λ	Covert myeloma
4	A β_2 M	Chronic renal failure

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Table 2 Antibodies used

	Dilution	Species	Source
Amyloid A	1 in 500	P, Rabbit	Calbiochem
β_2 M	1 in 500		Calbiochem
λ , K	1 in 5000		Dako
Prealbumin	1 in 500		Dako
IgA, G, M	1 in 2500		Dako
S100	1 in 500		Dako
Prostate SAg	1 in 300	M, Mouse	Dako
Amyloid P component	1 in 250		Calbiochem
Cam 5.2	1 in 5		Becton-Dickinson

P = Polyclonal, M = Monoclonal.

ganate either much reduced or totally abolished the Congo red staining of the corpora.

Congo red positive dots were also noted within the prostatic glandular epithelium and were similar to those seen in the seminal vesicle. These were relatively uniform in size (about 1–2 μ m) with some up to 6 μ m, but variable in position within the cytoplasm of the epithelial cells. They did not produce apple-green birefringence, and the staining reaction was abolished by prior potassium permanganate treatment.

The corpora gave consistent immunohistochemical positivity for β_2 M (fig 2) with a patchy, inconsistent and weak positivity for the immunoglobulin heavy and light chains. The interstitial amyloid of the systemic amyloid cases gave results consistent with the vascular and stromal amyloid found in the other body tissues, independent of that of the corpora amylacea. Prostatic epithelial cells (focally) and lymphoid cells were also positive for β_2 M (fig 3). The prostatic epithelial cells were strongly positive for both prostate specific antigen (PSA) and Cam 5.2; the corpora were not. The prostatic epithelial dots did not stain with any of the antibodies used.

Excess free β_2 M blocked the positive anti-

body staining of the corpora amylacea.

Discussion

The Congo red positivity and apple-green birefringence of prostatic corpora amylacea is not a novel finding,^{2 6–8} although it has been dismissed in the past.^{6 8} This combination of congophilia and apple-green birefringence is the most widely used criterion used to identify amyloid in tissue sections and is considered to be given by fibrillar protein depositions which have a β -pleated sheet configuration.⁹ The reduction of the congophilia by prior potassium permanganate treatment, initially thought to be an indicator of AA amyloid¹⁰ is, however, also seen in β_2 M amyloidosis.¹¹

The finding of consistent and specific β_2 M positivity with prostatic corpora amylacea has not been described before. β_2 M is an 11.8 kilodalton molecule that forms the light chain of the HLA class 1 antigen, and as such is found on all nucleated cells. It has strong homology with the other domains of both HLA class I and II antigens, as well as with that of the constant regions of the immunoglobulin heavy chains.¹² The relatively recently described haemodialysis associated amyloid has been found to be due to the deposition of β_2 M.^{11 13 14} This presents clinically as either the carpal tunnel syndrome, a flexor tenosynovitis, or a destructive arthropathy.¹¹ The deposition in chronic renal failure is due to failure of filtration across the renal glomerulus and certain types of dialysis membrane.¹⁵ Systemic, non-articular β_2 M deposition in these cases seems to be relatively minor and restricted to vessel walls.^{16 17} None of the 26 non-systemic amyloid cases studied had evidence of chronic renal failure. Battaglia was able to demonstrate Congo red positivity of prostate corpora, as well as Congo red positive

Figure 1 Corpus amylacea showing birefringence in a Maltese cross pattern. The periglandular and stromal birefringence is white and is due to local collagen (alkaline Congo red).

dots in the prostatic epithelium, and "keratin" positivity (source and reactivity unspecified) of both of these immunohistochemically on frozen sections.² He postulated that the corporal fibrils are formed by the shedding of the epithelial cells, the Congo red dots being groups of keratin fibrils. He therefore coined the term "apoptotic amyloid".

Prostatic epithelium contains four main types of cytokeratin (Moll numbers 5, 8, 18, 19) (Cam 5·2 datasheet; Becton-Dickinson, 1985), of which the monoclonal antibody Cam 5·2 should be able to recognise three (numbers 8, 18, 19).¹⁸ We were able to demonstrate

strong, positive prostatic epithelial positivity of both Cam 5·2 and PSA, but were unable to show the corporal or epithelial dot cytokeratin positivity stated by Battaglia.² This may reflect our use of paraffin wax (and not frozen) prostatic tissue, but digestion with trypsin of the paraffin wax material failed to show any corporal dot immunocytokeratin positivity. This lack of cytokeratin waxed tissue staining means either an alteration of the antigenic sites recognised by Cam 5·2 or absence of Cam 5·2 reactive cytokeratin in corpora amylacea. If corpora are derived (partly or wholly) from prostatic cells this latter possibility seems

Figure 2 Arrowed corpora amylacea give positive staining reactions for β_2 -microglobulin (PAP with haematoxylin).

Figure 3 Focalised positive staining reactions for β_2 -microglobulin in prostatic epithelial cells. Negative control on right (PAP with haematoxylin).

unlikely, especially as there is strong electron microscopic evidence of a close similarity between prostatic epithelia and the corporal filament structure.^{2,4} The failure to demonstrate PSA in corpora suggests that no prostatic epithelial cell surface membrane material is present in corpora, assuming that the antigen is still present in an immunologically recognised form. The β_2 M in corpora can come either from nucleated cells (prostatic epithelial or any other) or from the absorption of free, filtered undergraded urinary β_2 M in cumulative small amounts onto a central nidus. The finding of spermatozoa within corpora¹⁹ shows that reflux into the prostate occurs. It is also known that β_2 M can undergo β -pleating in vitro to form an amyloid.²⁰

We conclude from our studies that the amyloid of prostatic corpora amylacea is derived from β_2 microglobulin. We suggest that the β_2 microglobulin arises from the urine by reflux and that corpora amylacea grow by apposition of the amyloid material on to a central nidus that is probably derived from the prostatic epithelium.

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