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Amyloidosis of the Prostate Gland, Seminal Vesicles and Ejaculatory Ducts: Review and Update

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ABSTRACT

It has been iterated that cases of primary amyloidosis of the prostate gland, seminal vesicles as well as ejaculatory ducts are not common and in view of this pathologists, urologists, and oncologists should have a high index of suspicion for the aforementioned three lesions Primary amyloidosis of the prostate gland, seminal vesicles, and ejaculatory ducts had tended to be diagnosed incidentally based upon microscopy histopathology examination of specimens of the prostate gland, seminal vesicle and ejaculatory duct obtained after the undertaking or prostatectomy or during examination of specimens of the prostate gland that had been obtained from prostate biopsies taken during the assessment of the prostate gland to exclude prostate cancer related to raised levels of serum prostate specific antigen (PSA) or abnormal digital rectal examination findings of the prostate gland and or seminal vesicle or at times radiology imaging of the prostate gland and pelvis might reveal features of the prostate gland, seminal vesicle and ejaculatory duct area that look abnormal or irregular which would necessitate the undertaking of radiology image-guided biopsies of the lesion. Majority of cases of primary amyloidosis of the prostate gland, seminal vesicle and ejaculatory duct tend to be asymptomatic but some cases of primary amyloidosis of the seminal vesicle might manifest with blood within the semen of an individual. Some cases of amyloidosis of the prostate gland, seminal vesicles, and ejaculatory ducts had been diagnosed contemporaneously in association with areas of adenocarcinoma of the prostate gland. Pathology examination of areas of the prostate gland, seminal vesicles, and ejaculatory ducts tends to depict or demonstrate amorphous, pale eosinophilic material often associated with cracks from processing of the biopsy or prostatectomy specimen Specimens of amyloid within the prostate gland, seminal vesicle, and ejaculatory duct exhibit immunohistochemical staining features with Congo Red by the demonstration of green birefringence upon polarised microscopy. Amyloidosis of the prostate gland, seminal vesicles, and ejaculatory duct tends to simulate upon radiology imaging undertaken by magnetic resonance imaging (MRI) scan features of prostate cancer invading the seminal vesicle, carcinoma of the urinary bladder invading the seminal vesicle, adenocarcinoma of the rectum invading the seminal vesicle as well as a rare case of primary adenocarcinoma of seminal vesicle. It has been iterated that therapy of primary amyloidosis of the prostate gland, seminal vesicles and ejaculatory does depend upon the underlying condition.

Keywords: Amyloidosis of Prostate Gland; Amyloidosis of Seminal Vesicles; Amyloidosis of Ejaculatory Ducts; Prostate Biopsies; Prostatectomy; Microscopy; Histopathology; Immunohistochemistry; Magnetic Resonance Imaging Scan; Computed Tomography Scan; Ultrasound Scan; Digital Rectal Examination; Abnormal Digital Rectal Examination; Serum Prostate Specific Antigen; Blood in Semen; Carcinoma of Prostate; Asymptomatic; Incidental Finding

Abbreviations: PSA: Prostate Specific Antigen; MRI: Magnetic Resonance Imaging; AL: Amyloid Light-Chain; ATTR: Amyloidosis, Familial Transthyretin-Associated; AA: Amyloid A; SVs: Seminal Vesicles; SSVA: Senile Seminal Vesicle Amyloid; SGI: Semenogelin I; ICC: Immunocytochemistry; LSH: In Situ Hybridization; LAST: Localized Amyloidosis of the Seminal Tract; PB: Prostate Biopsy; CK: Cytokeratin; CRES: Cystatin-Related Epididymal Spermatogenic

Introduction

Some authors had iterated that amyloidosis is a terminology which is utilised to allude to a pathological deposition of extracellular fibrillar proteins within organs and tissues [1,2]. It had been pointed out that the incidence of systemic amyloidosis had tended to be difficult to ascertain or iterate; nevertheless, the incidence of systemic amyloidosis had probably been underestimated, because of the possible fact that amyloidosis could be undiagnosed or misdiagnosed [1]. The commonest types of systemic amyloidosis had been iterated to include amyloid light-chain (AL) amyloidosis, familial transthyretin-associated (ATTR) amyloidosis and amyloid A (AA) amyloidosis, each of which has a different pattern of fibril composition, together with difference in epidemiology, pathogenesis, clinical manifestations, methods of diagnosis and prognosis [1]. It has been iterated that the amyloid A type typically does tend to emanate from an inflammatory stimulus, for example, inflammatory diseases such as rheumatoid arthritis or ankylosing spondylitis. The age-adjusted incidence of AL amyloidosis had been iterated to be nearly 5.1 million to 12.8 per million person-years [1].

It has furthermore, been iterated that amyloidosis could be considered to be a myeloma without osseous deposits and it typically has tended to be associated with abnormal 'free light chains'. The clues to systemic involvement of amyloidosis entail the involvement of more than one organ (for example the heart, the liver/spleen, and the kidney [2]. It has been iterated that localized amyloidosis of the genitourinary tract system had not been reported often [2]. It has been iterated that within the urinary tract, the urinary bladder is the commonest afflicted organ, even though the entire urinary tract could be afflicted by involvement of amyloidosis [2-6]. It has been iterated that the incidental deposition of amyloid within the seminal vesicles (SVs) as well within the ejaculatory system had been reported previously during assessments of diagnostic prostate biopsies.

It had also been iterated that taking into consideration the fact that the seminal vesicles (SVs) usually tend not to be routinely included in the undertaking of diagnostic biopsies of the prostate gland, Urologists and pathologists globally might probably be underestimating the incidence of amyloidosis of the seminal vesicles [2]. Considering also that ejaculatory duct had tended not to constitute the main parts of prostate biopsies in assessments for prostate cancer, it would be envisaged that perhaps ejaculatory duct involvement by amyloidosis would be higher than had been occasionally reported. Based upon immunohistochemistry staining studies, localized urogenital amyloidosis had been iterated to be predominantly Ig light chain about its origin, with primarily Ig kappa or lambda light chains [7,8]. It had been conjectured that whilst the aetiology of localized urogenital amyloidosis is not fully understood, chronic inflammation within the afflicted organ had been postulated to be a causative factor [9].

Considering that only very few sporadic cases of amyloidosis of the prostate gland, seminal vesicles, and ejaculatory ducts had been reported in the global literature, it would be envisaged or contemplated that majority of clinicians globally including Urologists, pathologists, general physicians and radiologists may not have encountered a case of amyloidosis of the genitourinary tract before including amyloidosis of the prostate gland, seminal vesicle and ejaculatory duct and perhaps they would therefore not be familiar with the management of primary amyloidosis of the prostate gland, seminal vesicles and ejaculatory ducts. The ensuing article on primary amyloidosis of the prostate gland, seminal vesicles and ejaculatory ducts had been divided into two parts:

A. Overview which has discussed general overview aspects of amyloidosis and

B. Miscellaneous narrations and discussions from some case reports, case series, and studies related to amyloidosis of the prostate gland, seminal vesicle and ejaculatory ducts with a focus on the seminal vesicle.

Aim

To review and update the literature on amyloidosis of the prostate gland, seminal vesicles and ejaculatory ducts.

Methods

Internet data bases were searched including Google; Google Scholar; Yahoo and PUBMED. The search words that were used included: Amyloidosis of prostate gland; Amyloidosis of Seminal Vesicle; and Amyloidosis of ejaculatory ducts. Fifty-five (55) references were identified which were used to write the article which had been divided into two parts:

A. Overview which has discussed general overview aspects of amyloidosis and

B. Miscellaneous narrations and discussions from some case reports, case series, and studies related to amyloidosis of the prostate gland, seminal vesicle and ejaculatory ducts with a focus on the seminal vesicle.

Results

Overview

Definition / General Statements:

- It has been iterated that primary amyloidosis of the prostate gland is an uncommon disease [10].
- It has been stated that primary amyloidosis of the prostate gland had been reported to have involved seminal vesicles in about 10% of radical prostatectomy specimens examined, and that it usually manifests as a localized form of amyloidosis [10].
- It has been iterated that primary amyloidosis of the prostate gland develops sub-epithelial spreading to include the wall of seminal vesicles and ejaculatory ducts; as well as it had been regarded as being related to advanced age [7].

- It has also been iterated that with regard to primary amyloidosis of the prostate gland, corpora amylacea might stain positive with Congo red during pathology examination of the specimen [2,11].

Essential Features:

The essential features of primary amyloidosis of the prostate gland and seminal vesicles had been summated as follows: [10]

- It had been iterated that pathology examination demonstrate presence of pale amorphous hyaline, eosinophilic substance that accumulates and which could pressure the adjacent epithelium.
- It has been iterated that primary amyloidosis of the prostate gland upon pathology examination may demonstrate the amyloidosis to often display processing cracks.
- It has been iterated that primary amyloidosis is more commonly found afflicting the seminal vesicles and vas deferens more commonly in comparison within the prostate gland.
- It has been iterated that pathology examination of specimens of primary amyloidosis of the prostate gland does demonstrate presence of subepithelial and vascular deposits.

Epidemiology:

The epidemiology of primary amyloidosis of the prostate gland had been summated as follows: [10]

- It has been iterated that primary amyloidosis of the prostate gland had found afflicting 2% to 10% of prostate glands in radical prostatectomy specimens that had been examined [12].
- It has been iterated that incidence of primary amyloidosis of the prostate gland had n=been noted to increase with age, reaching 21% in men who are age 75 years and older, [13,14].
- It has been iterated that: In primary amyloidosis of the prostate gland, vascular amyloid deposits had been visualised in 2% to 10% of prostates that had been diagnosed as benign nodular hyperplasia or adenocarcinoma.
- It had been iterated that with regard to primary amyloidosis of the prostate gland, there tends to be a higher incidence of amyloid deposits in patients who had been afflicted by myeloma, primary amyloidosis of kidney or chronic diseases.
- It has been iterated that in primary amyloidosis of the prostate gland, amyloidosis of the seminal vesicles entails 10% of radical prostatectomy specimens.
- It has been stated that amyloid deposition within the seminal vesicles is apparently commonly visualised in elderly men with a prevalence which has ranged from 16% to 21% and is more commonly visualised in the localized form [14-16].
- It had also been documented that amyloidosis had also been reported in up to 10% of radical prostatectomy specimens that had been examined by pathologists.

Sites:

- It had been iterated that in cases of primary amyloidosis of the prostate gland, amyloidosis had tended to be more commonly found within the seminal vesicles and vas deferens in comparison with the prostate gland [10].
- It has been iterated that in primary amyloidosis of the prostate gland, deposits of amyloid are more commonly found within subepithelial and vascular layers of the organ [10].

Aetiology [10]:

- With regard to the aetiology of amyloidosis, It had been iterated that in primary amyloidosis of the prostate gland, even though immunohistochemistry staining studies often identify lactoferrin, [17] amyloid apparently derives from sarmentogenin I, which is the major secretory product of the seminal vesicles [18].
- It has been iterated that: In primary amyloidosis of the prostate gland, it had been postulated that Sarmentogenin I and II are mainly responsible for immediate gel formation of freshly ejaculated semen and are degraded by the proteolytic action of prostate specific antigen/PSA [19].
- It has been iterated that within the seminal vesicles, amyloid is apparently derived from sarmentogenin 1, which is a secretory product of the seminal vesicles and is postulated to play a pivotal role in the localized form [20].

Pathology [10]:

Some summations that had been documented related to amyloidosis of the prostate gland, seminal vesicles, and ejaculatory duct include the ensuing: [10]

- It had been iterated that amyloid deposits of the seminal vesicles do occur typically, within the sub-epithelium or the lamina propria. In the localized form of amyloidosis, both seminal vesicles are said to be involved.
- Upon the other side, amyloid deposits in vessel walls or within the muscular tissue had been documented to suggest or demonstrate systemic amyloidosis [14,15].

Pathophysiology:

The pathophysiology of primary amyloidosis of the prostate gland, seminal vesicles and ejaculatory ducts had been summarized as follows:[10]

- It had been pointed out that amyloid deposits of the seminal

vesicles do occur typically within the sub-epithelium or the lamina propria.

- It had also been iterated that in the localized form, both seminal vesicles are involved by amyloidosis and that on the other side amyloid deposits within vessel walls or within the muscular tissue does indicate presence of systemic amyloidosis [14,15].

- It has been iterated that in primary amyloidosis of the prostate gland, seminal vesicles and ejaculatory ducts, abnormal folding of proteins that deposit as fibrils within the extracellular tissue and might accumulate as well as prevent normal function.

- It has been iterated that in primary amyloidosis of the prostate gland, amyloidosis does include multiple biochemically distinct proteins but with similar morphology features.

- It has been iterated that in primary amyloidosis of the prostate gland, seminal vesicles, and ejaculatory ducts, different forms of amyloidosis that could be found include: [11]

o Primary systemic amyloidosis (no evidence of preceding or coexisting disease, paraproteinemia or plasma cell neoplasia).

o Amyloidosis associated with multiple myeloma.

o Secondary to coexisting previous chronic inflammatory or infectious conditions, haemodialysis.

o Localized form of amyloidosis

Clinical Manifestations

- It had been iterated that primary amyloidosis of the prostate gland, seminal vesicles, and ejaculatory ducts, most commonly had tended to be asymptomatic [10].

- It had been iterated that primary amyloidosis of the prostate gland, seminal vesicle and ejaculatory duct could mimic prostate or urinary bladder cancer invasion of the seminal vesicles based upon radiology imaging features of magnetic resonance imaging (MRI) scan [10].

- It has been iterated that amyloidosis of seminal vesicles could clinically manifest with blood in the semen [11].

Diagnosis [10]

- It has been pointed out that diagnosis of amyloidosis of seminal vesicle is made by histopathology examination by visualising presence of amyloid deposits within the sub-epithelium or the lamina propria of both seminal vesicles [11,14,15].

- Histology: It had been pointed out that histopathology examination of specimens of amyloidosis of prostate gland, seminal vesicles, and ejaculatory duct, demonstrates amorphous pale eosinophilic material that is often associated with cracks from processing [10].

- It has been pointed out that about cases of amyloidosis of prostate gland, seminal vesicles, and ejaculatory ducts, histochemical stain with Congo red does demonstrate green birefringence on polarized microscopy [10].

Radiology Description:

- It has been iterated that primary amyloidosis of the prostate gland, seminal vesicle and ejaculatory duct, could simulate prostate gland or urinary bladder cancer invasion of seminal vesicles based upon magnetic resonance imaging (MRI) scan radiology imaging features of the lesion that is demonstrated [10].

Radiology Imaging Features

Magnetic Resonance Imaging (MRI) Scan [11]

It had been documented that radiology imaging features of amyloidosis of seminal vesicle upon magnetic resonance imaging demonstrate some similarities with seminal vesicle invasion and these include: [11]

- Wall Thickening
- Luminal Narrowing

It had been documented that apart from seminal vesicle invasion, seminal vesicle amyloidosis does not tend to demonstrate any diffusion restriction or early contrast enhancement [21].

MRI SCAN Signal Characteristics [11]

The MRI scan features of amyloidosis of the prostate gland, seminal vesicles, and ejaculatory duct had been summated to demonstrate the ensuing during the process of the MRI scan procedure: [11]

- T1: hyperintense
- T2: hypointense walls
- DWI: lack of diffusion restriction
- DCE (Gd): lack of normal enhancement

Radiology Image Reporting

It has been recommended that when a radiologist is reporting radiology-images of amyloidosis involving the seminal vesicle, prostate gland and ejaculatory duct the radiology imaging report should include a description of the ensuing: [11]

- Luminal Narrowing
- Associated Findings of the Prostate

History and Etymology

It had been pointed out that diverse descriptions of amyloid within the seminal vesicles had been documented within the 1920s which include for example the documentation of Winkkelman in 1927 [6,11,22].

- Differential Diagnoses of Amyloidosis of Prostate Gland, Amyloidosis of Seminal Vesicle and Amyloidosis of Ejaculatory Ducts

The differential diagnoses of primary amyloidosis of the prostate gland, seminal vesicles, and ejaculatory ducts with a focus on seminal vesicle amyloidosis had been summated to include the ensuing: [10]

- Conditions that may simulate the clinical manifestations or radiology imaging features of the ensuing: [11,15,16,20] .

Seminal vesicle invasion by the following: [11]

- Adenocarcinoma of prostate gland
- Carcinoma of urinary bladder
- Adenocarcinoma of the rectum
- Adenocarcinoma of the seminal vesicles. [11]

Treatment

- It has been iterated that the treatment of primary amyloidosis of the prostate gland, seminal vesicle and ejaculatory duct is based upon the underlying condition [10]

Gross Description [10]

- It had been iterated that macroscopically, primary amyloidosis of the prostate gland, seminal vesicle or ejaculatory duct had tended usually not to be visualised during the gross examination process [10].
- It had been iterated that in primary amyloidosis of the prostate gland, seminal vesicle or ejaculatory duct, when the involvement is massive, the organ could be found on gross pathology examination to be enlarged and firm and the cut section of the amyloidosis lesion could depict a waxy appearance.

Microscopic (Histologic) Description:

The microscopy histopathology examination features of primary amyloidosis of the prostate gland, seminal vesicle and ejaculatory duct had been summated as follows: [10]

- It had been stated that microscopy histopathology examination of the amyloid containing specimen does tend to demonstrate pale amorphous hyaline, eosinophilic substance which does tend to accumulate and which could pressure the adjacent epithelium [10].
- It has been documented that microscopy histopathology examination of the amyloid containing specimen often displays processing cracks [10].
- It had been iterated that microscopy histopathology examination of the amyloid containing specimen does reveal subepithelial location of the amyloidosis [10].
- It had been stated that microscopy histopathology examination of the amyloid containing specimen does show that the amyloid deposit could compress the adjacent epithelium [10].
- It had been iterated that amyloidosis is characterized by the deposition of amyloid fibrils within the extracellular space which does appear as an apple-green birefringence under polarized light and could be positively stained with Congo red [10,11].
- It had furthermore been re-emphasised that amyloid does look like an amorphous pale eosinophilic substance which often features cracks as stated earlier [11].

Positive Stains

It has been iterated that specimens of amyloidosis of prostate gland, seminal vesicles and ejaculatory duct containing amyloid deposits exhibit positive staining to the following stains: [10]

- Trichrome which stains amyloid dusky grey), Congo Red stains positively based upon immunohistochemistry staining for specific amyloid forms [10].
- It had also been stated that immunohistochemistry staining in cases of amyloidosis of prostate, seminal vesicles and ejaculatory ducts usually tend to demonstrate the amyloid tissue exhibiting positive staining for AP protein in localized amyloidosis [10].
- It had also been stated that immunohistochemistry staining studies of specimens of amyloidosis of the prostate gland demonstrate that the amyloid tissue exhibits positive staining with Tryptophan [11].

Electron Microscopy Description [10]

- It has been iterated that electron microscopy examination of specimens of primary amyloidosis of prostate gland, ejaculatory duct and seminal vesicle demonstrated non-branching amyloid fibrils that measure 7.5 nm to 10 nm [23].

Differential Diagnosis [10]

It has been pointed out that it is important to exclude an underlying aetiology of primary amyloidosis of prostate gland, seminal vesicle and ejaculatory duct including plasma cell neoplasia or an inflammatory condition [10].

Miscellasneous Narrations and Discussions from Some Case Reports, Case Series, and Studies Related to Amyloidosis of Prostate Gland, Seminal Vesicles and Ejaculatory Ducts

Kee et al. [7] had studied investigated the incidence of amyloidosis of seminal vesicles and ejaculatory system as well as ejaculatory ducts and vasa deferentia, Kee et al. [7] undertook a review study of whole mounted sections of 447 radical prostatectomy specimens

which had been excised as treatment for adenocarcinoma of prostate gland which had included 273 cases from the United States of America and 174 cases from the Republic of Korea.

Kee et al. [7] Summated the Results as Follows:

- Out of these studied cases, 21 cases which amounted to 4.7% of the cases had contained amyloidosis within the seminal vesicles, vasa deferentia, as well as the ejaculatory ducts.
- Ten (10) of these cases that amounted to 3.7% of the cases were noted to be from the United States of America and 11 cases that amounted to 6.3% had originated from the Republic of Korea.
- The ages of the reported patients had varied between 51 years and 79 years and the mean age of the patients was computed to be 66.1 years based upon the analysis of Kee and associates [7].
- Amyloid deposition was identified in 5 patients who were in their sixth decade of life and these 5 patients had amounted to 3.4% of the cases, 9 patients were noted to be within their seventh decade of life and these 9 patients did amount to 4.7% of the cases, and 7 patients were noted to in their eighth decade of life and these 9 patients had amounted to 9.3% of the cases.
- At the seventh decade of life, the Korean Republic patients were found to have demonstrated a higher incidence which was computed to be 8.3%, in comparison with the American patients who had a computed incidence of 2.5%, nevertheless, the other age groups had shown no difference.
- All of the cases had been noted to be afflicted by bilateral involvement of the seminal vesicles as well as the ejaculatory duct systems.
- The deposits of amyloid had tended to be nodular and had afflicted the subepithelial region of the seminal vesicles, vasa deferens, as well as the ejaculatory ducts.
- There was no evidence of amyloid deposit encompassing the blood vessels or within the parenchyma of the prostate gland.

Kee et al. [7] made the Ensuing Summations:

- Localized amyloidosis of the ejaculatory duct system does tend to entail not only the seminal vesicles but also the vas deferens as well as the ejaculatory ducts system.
- The vessels or stroma of the prostate gland were noted not to be part of this process.
- It has been iterated that amyloidosis does tend to develops subepithelial mode of spreading to include the wall of these organs and does appear to be related to advanced age.
- The incidence of amyloidosis of the ejaculatory system in Republic of Korea patients was higher when compared to the incidence within the United States of America patients.

Argon et al. [12] Iterated the Ensuing:

- Amyloidosis is not a common disease and amyloidosis has been associated with various aetiological entities, which are associated with deposition of extracellular amyloid protein.
- By the year 2012, at least 26 distinctive amyloid forms had been described with different clinical importance and treatment.
- Amyloidosis lesions demonstrate typifying staining features with Congo red.
- It had been iterated that amyloid might be identified in 2% to 10% of prostate glands which had been excised or removed because of benign prostatic hyperplasia or carcinoma of the prostate gland.
- It has been iterated that amyloidosis of the seminal vesicles is understood to be senile amyloidosis and amyloidosis of the seminal vesicles is not accompanied by systemic amyloidosis or clinical manifesting symptoms.
- They had aimed to investigate incidence and histology characteristics of amyloidosis of seminal vesicles within radical prostatectomy materials of patients who had undergone surgical treatment for carcinomas of the prostate gland.

With regard to the material and method of their study, Argon et al. [12] iterated that amyloid depositions within seminal vesicles of 207 radical prostatectomy materials that had been obtained from prostate glands which had been excised or removed as treatment for localized carcinoma of prostate gland were assessed by their team. Argon et al. [12] confirmed amyloid depositions with the use of Congo red staining and polarization microscope. Argon et al. [12] summarised the results as follows:

- Amyloidosis of seminal vesicles was identified in 10 cases which had amounted to 4.8% of the cases.
- The mean age of the patients was 66.2 years.
- Amyloid depositions had tended to be nodular and bilateral in subepithelial region of the afflicted seminal vesicles.
- Amyloid depositions were not identified within the blood vessels in the seminal vesicles or within the parenchyma of the prostate gland.

Argon et al. [12] Made the Ensuing Concluding Iterations:

- The finding of localized amyloidosis of seminal vesicles is not an unusual.
- The incidence of amyloidosis of the seminal vesicles within the Republic of Turkey patients included in their study and his-

topathologic characteristics of these patients were not different from the other reported studies in the literature.

- Systemic AA amyloidosis is the most common type of amyloidosis within their country of Turkey.
- It is important to be aware of the fact that amyloidosis of seminal vesicles is of importance in its differentiation from the other forms of amyloidosis.

Coyne and Kealy, [13] had detected sub-epithelial deposits of amyloid within the seminal vesicles of 13 males from a total of 143 unselected autopsies (9%). Coyne and Kealy reported the ensuing findings:

- The incidence of amyloidosis of the seminal vesicles had increased with increasing age of the men studied.
- The amyloid disease was classified based upon the use of histochemistry, immunohistochemistry and clinical features.
- They had had categorized eight cases as senile vesicle amyloid, two cases as systemic AA amyloid with secondary involvement of the seminal vesicle, and three cases as mixed amyloidosis.
- The morphological characteristic features of the different categories of amyloidosis of seminal vesicles are similar but the finding of a different distribution is common in the different categories of amyloidosis of the seminal vesicles.
- The staining characteristics of senile vesicle amyloid had indicated that this type of amyloidosis contains a different amyloid protein, perhaps locally derived within the seminal vesicle.

Pitkänen P et al. [14] found amyloid deposits within the sub-epithelial region of the seminal vesicles of 34 out of 209 consecutive men they had studied. They reported that the incidence of amyloidosis of seminal vesicles had increased with age and was found in 21% of men who were aged over 75 years. They iterated that senile seminal vesicle amyloidosis (SSVA) is a localized disorder, and the amyloid substance does have unique histochemical and immunochemical properties which are not shared with any other amyloid that had been described until the time of publication of their article in 1983. Harvey and Têtu [17] had iterated that localised amyloidosis of seminal vesicle is relatively infrequent and that they had reported 9 additional cases. Harvey and Têtu [17] retrospectively retrieved the 9 cases from 803 radical prostatectomy cases which had been undertaken between 1995 and 2000 for adenocarcinoma of prostate gland. In each case, the type of amyloidosis was characterised by immunohistochemistry staining studies. Information regarding a possible concurrent contemporaneous disease or previous hormone treatment had been obtained. Harvey and Têtu [17] summarised the results as the ensuing:

- They had found out that the results of their study had shown that the prevalence of amyloidosis of seminal vesicles was lower in their study which represented 1.1%, in comparison with in unselected autopsy cases.
- The prevalence of amyloidosis in patients who had been exposed to previous hormone therapy (LHRH agonist and anti-androgen) was 2% while it had reached only 0.9% in those patients who had received no hormone therapy ($p>0.3$).
- None of the patients been found to have systemic amyloidosis and all of the cases were of non- A-A type.
- Lactoferrin, which is a glycoprotein and produced by normal seminal vesicles, was identified in more than a half of them and this was identified in five out of nine cases (5/9) that amounted to 55.6% of the cases.

Harvey and Têtu [17] made the Ensuing Conclusions:

- No association was identified between the occurrence of amyloidosis of seminal vesicle and the occurrence of adenocarcinoma of the prostate gland, concomitant systemic disease or exposure to previous hormonal treatment.
- Amyloidosis of seminal vesicle is generally a localised condition with no systemic involvement and amyloid deposition is mostly comprised of lactoferrin.

Linke et al. [18] Stated the Following:

- Senile seminal vesicle amyloid (SSVA), which is one of the commonest forms of localized amyloidosis, had tended to be associated with the male aging process.
- Even though it had been documented that the amyloidogenic component had originated from exocrine cells and that, immunohistochemistry staining studies had shown that amyloid is composed of lactoferrin, the nature of SSVA was never established definitively.
- In order to address this issue, they had used their microanalytic techniques to characterize the structure of the congophilic green birefringent protein which was extracted from 5 such amyloid-containing specimens.
- Mass spectrometric analysis had shown that in all cases, the fibrils were composed mainly of polypeptide fragments which were identical in sequence to the N-terminal portion of the major secretory product of seminal vesicles, namely semenogelin I (SgI).
- Even though lactoferrin was identified in 3 instances, the trace amount and seemingly intact form of this molecule, had suggested that it was not the amyloidogenic molecule.
- The SgI nature of the amyloid was confirmed through the demonstration that the deposits were immunostained specifically with Sgl-reactive antibodies.

Linke et al. [18] concluded that the results of their research had provided unequivocal evidence that SSVA is derived from SgI, and they had provisionally designated this form of amyloidosis as ASgI.

Bjartell et al. [19] Stated the Following:

- Semenogelin I and II (Sgl, Sgll) are two separate gene products of chromosome 20 with extensive component constituting 80%, that is identified in the primary structure.
- They are mainly responsible for immediate gel formation of freshly ejaculated semen.
- Degradation of Sgl and Sgll is an emanation of the proteolytic action of prostate-specific antigen (PSA); it results within 5 minutes to 15 minutes in the liquefaction of semen and release of progressively motile spermatozoa.
- By means of cDNA cloning and Northern blots, Sgl and Sgll transcripts had previously been demonstrated to be abundant in human seminal vesicles, but Sgll alone was suggested to be expressed at low levels within the epididymis.
- In order to characterize the expression and tissue distribution of Sgl and Sgll in greater detail, they had produced monoclonal immunoglobulin Gs (lgGs for immunocytochemistry (lCC) and specific [35S]-, digoxigenin-, or alkaline phosphatase-labelled 30-mer antisense probes to Sgl and Sgll for in situ hybridization (lSH).
- Immunocytochemistry staining for both Sgl and Sgll, and lSH detection of both Sgl and Sgll transcripts, were revealed within the cytoplasm of the epithelium of the seminal vesicle.
- In situ hybridization (lSH) test had demonstrated Sgll alone to be expressed within the epithelium of the epididymal cauda.
- Neither lCC nor lSH had demonstrated any evidence of Sgl or Sgll expression in caput or corpus epithelium or in any stromal cells of the epididymis.

Bjartell et al. [19] Made the Ensuing Conclusions:

- Consistent with their previous findings utilising polyclonal lgG, monoclonal anti-Sgll Sgll lgGs had identified epitopes on the posterior head, midpiece, and tail of ejaculated spermatozoa.
- Spermatozoa within the epididymal cauda had also exhibited immunoreactivity, but those within the caput or corpus region of the epididymis as well as those within the testis had exhibited negative reactivity.
- As was demonstrated by lCC, neither Sgl nor Sgll had been expressed within the testis, the prostate gland, the female genital tract, or other normal human tissue specimens.
- Even though the significance of Sg attachment to epididymal and ejaculated spermatozoa had remained to be established, monoclonal anti-Sg lgG might prove to be useful in the establishment of the origin of seminal vesicle tissue components in prostate core biopsy specimens or other biopsy specimens.

Seidman et al. [23] had reported localized amyloidosis of the seminal vesicles (ASV) as an incidental finding in surgical specimens from three elderly men. In two cases, the amyloid deposits were noted to be bilateral, subepithelial, and clinically inapparent, which were reported to be features that were similar to other cases that had been reported in the literature. In one case, the diagnosis was made based upon pathology examination of specimens that had been obtained from a trans-rectal prostatic needle biopsy which included a small portion of seminal vesicle. Seidman et al. [23] stated that to their knowledge, this this type of case, had not been reported previously. Electron microscopy in one case had revealed non-branching fibrils which were characteristic of amyloid, and pre-treatment of tissue sections utilising the permanganate method in two cases shown almost complete ablation of congophilia. Seidmen et al. [23] concluded that:

- Evidence had indicated that ASV is a permanganate-sensitive, non-AA (amyloid, protein A) type of amyloid that might be different from all other types of amyloid-disease, that had been previously characterized.

Singh et al. [24] Stated the Following:

- Primary amyloidosis of the lower urinary tract is a rare clinical entity and it is usually localized to one site.
- The clinical manifestations, and cystoscopy and radiology imaging findings in primary amyloidosis of lower urinary tract are not distinguishable from neoplastic or inflammatory lesions.

Singh et al. [24] reported an unusual case of amyloidosis which had involved many sites including: the stroma of the prostate gland, trigone of the urinary bladder, and lower ureters in the lower urinary tract. Jun et al. [25] reported localized amyloidosis which had involved the seminal vesicles and vasa deferens on both sides, which had been found in two patients who had adenocarcinoma of prostate gland. The first case was a 60-year-old man (case 1) and the second case was a 59-year-old (Case 2) man who had manifested with elevation of serum prostate-specific antigen (PSA) and biopsy proven carcinoma of prostate gland, respectively. Magnetic resonance imaging (MRI) scanning had demonstrated multiple irregular foci of low signal intensity within the prostate glands as well as within both seminal vesicles and vas deferens on both sides upon T2-weighted imaging, indicating adenocarcinoma of prostate gland with extension to both seminal vesicles and vas deferens on both sides in both cases. Under the clinical diagnosis of stage III adenocarcinoma of prostate gland, a radical prostatectomy was undertaken in both patients. Microscopically, Gleason score 7 adenocarcinoma was identified in both patients. In addition, isolated amyloidosis of both seminal vesicles and vasa deferens on both sides was found with no evidence of involvement of carcinoma. Jun et al. [25] made the ensuing iterations:

- Localized amyloidosis within the seminal vesicles, which is considered as senile process, had been occasionally reported in autopsy specimens and in the surgical specimens.
- Amyloid deposition within the vas deferens had also been reported in the literature; nevertheless, the deposition simulating extension of carcinoma had not been reported before.
- In their report, two cases of isolated amyloidosis of the seminal vesicles and vasa deferens bilaterally had been described with electron microscopy study and literature review.

Lawrentschuk et al. [26] Stated the Following:

- Trans-rectal ultrasound scan-guided biopsy of the prostate is an integral step in the investigation of patients who are at risk for the development of adenocarcinoma of prostate gland.
- With an increasing number of prostate biopsies that are being undertaken, uncommon forms of pathology of the prostate gland, would be identified more frequently.
- Amyloidosis of the prostate gland and / or the seminal vesicles might be noted upon transrectal ultrasound-guided biopsy of the prostate gland and the implications of this histological diagnoses do need to be understood.
- They had reported their experience of two such cases of amyloidosis and they had reviewed the literature regarding their management.

Maroun et al. [27] Iterated the Ensuing:

- The finding of amyloid deposits within the seminal vesicles had been known for many years.
- The deposits had usually tended to be localized and asymptomatic.
- Over recent years, amyloidosis of seminal vesicle, had been reported to simulate carcinoma of prostate gland and urinary bladder cancer invasion of the seminal vesicle upon MRI scan.
- They therefore were of the opinion that knowledge of the entity is important and they had therefore reported a typical case which had confirmed the previous findings that amyloidosis of the seminal vesicles is a unique form of amyloidosis, a relatively common incidental finding and one that might be related to prostate cancer.

Caballero et al. [28] reported a clinical and pathology study of eight cases of localized amyloidosis of the seminal vesicles. Caballero et al. [28] undertook an immunohistochemical and histochemical study in the surgical specimens. Caballero et al. [28] summarised the results as follows:

- Two of the eight cases studied for amyloidosis in seminal vesicles, had been obtained from radical prostatectomy specimens; and the patients had prior androgen deprivation therapy for two months.
- Four cases were obtained from radical cystoprostatectomy specimens because of urothelial carcinoma and the last two cases were diagnosed by trans-rectal prostatic needle biopsy which included a portion of seminal vesicle.
- Amyloidosis of seminal the vesicle was found to be permanganate-sensitive; as well as A-Amyloid, laminin, amyloid P protein and collagen IV negative.

Caballero et al. [28] Concluded that:

- Localized amyloidosis of the seminal vesicle is not an unusual finding.
- The incidence of localised amyloidosis of seminal vesicle increases with age.
- The histochemical and immunohistochemistry staining features are different from other amyloid deposits.

Unger et al. [29] Stated the Following:

- Localized amyloidosis seminal vesicle is an unusual finding within surgical pathology material.
- Previous studies had demonstrated that amyloid is directly produced by the seminal vesicle epithelial cells.
- They had investigated the possible association of seminal vesicle amyloid in patients who had been hormonally treated for prostate cancer.

Unger et al. [29] collected cases from over 200 prostate needle biopsies, seminal vesicle biopsies, and prostatectomy specimens from the surgical pathology files at The Mount Sinai Hospital, New York, NY. None of the patients with amyloidosis of seminal vesicle had a chronic inflammatory disorder, serum or urine protein abnormalities, or other identifiable masses. Unger et al. [29] summarised the results as follows:

- Six cases of localized seminal vesicle amyloidosis were found within the surgical pathology material examined.
- Five of the six cases had prostatic carcinoma, and one case was seen in a biopsy for benign prostatic hyperplasia.
- Four of the five carcinoma cases had previous hormonal treatment (luteinizing hormone-releasing hormone agonist with an antiandrogen agent, and one patient, in addition, had received radiotherapy).
- The amyloid deposits were noted to be limited to the seminal vesicle lamina propria without involvement of vascular walls.
- The amyloid had reacted with Congo red staining that was sensitive to potassium permanganate.

- Immunohistochemically, all cases were negative for AA amyloid, beta 2-microglobulin, and kappa and lambda light chains.

Unger et al. [29] concluded that they had raised the possibility that in some instances, prior hormonal treatment may act as a seminal vesicle epithelial stimulant for the elaboration of this protein.

Erbersdobler et al. [30] Stated the Following:

- In order to ascertain whether seminal vesicle amyloidosis (SVA, which is an unusual finding in prostatectomy specimens, with deposits usually localized and asymptomatic) affects the extension of prostate cancer into the seminal vesicles (SVs.)

Erbersdobler et al. [30] identified 73 cases of localized SVA from 6575 prostatectomy specimens, which had been removed because of clinically localized prostate cancer. All of the cases were confirmed by Congo red staining and polarization microscopy. The mean thickness of the amyloid band was measured in each case and correlated with clinicopathological characteristics. The frequency of SV involvement by prostate cancer in the presence of amyloid was compared with the percentage of pT3b classifications in the absence of amyloid. Erbersdobler et al. [30] summarised the results as follows:

- The mean age and age range of the patients who had localized SVAs was 64.4 years and between 52 years and 73 years.

- The mean thickness of the amyloid band did not correlate with the ages of the patients, preoperative serum prostate-specific antigen levels, the weight of the prostate glands, or the Gleason score and T category of the prostate cancers.

- Within the SVA group, seven cancers had invaded the SVs (9.6%), which was not significantly different from the percentage of SV involvement by cancer in the total sample (9.2%, P = 0.932).

Erbersdobler et al. [30] concluded that the pathogenesis of localized SVA had remained poorly understood, but SVA does not seem to provide an absolute or relative protection from SV involvement by prostate cancer.

Yang et al. [2] Iterated the Ensuing:

- Seminal vesicle (SV) amyloidosis is a well-documented histopathology entity, but it has been reported less frequently.

- The incidence of amyloidosis of seminal vesicle is on the rise, which is probably related to the increasing undertaking of prostate biopsies to investigate patients who have raised serum prostate-specific antigen levels.

Yang et al. [2] reported seven cases of incidental SV amyloidosis over a 3-year period and they considered their relationship to the previously suggested aetiological factors. Based upon their series, they had concluded that incidental localized SV amyloidosis observed in diagnostic prostate biopsies does not warrant formal investigations for systemic amyloidosis.

Rath-Wolfson, et al. [20] Stated the Ensuing:

- Senile Seminal Vesicle Amyloidosis (SSVA) increases with age.

- Involvement of the whole seminal tract, for example: the seminal vesicles, ejaculatory ducts and vas deferens ducts was first reported by themselves in an International Symposium on Amyloidosis 1998.

- Since then, they had encountered four more cases of SSVA.

- In all these cases the ejaculatory and vas deferens ducts were also involved by amyloid.

- The amyloid was located mostly within the sub-epithelium and had stained positively with Congo red, as well as had given green birefringence under polarized light and was permanganate sensitive, as well as was slightly positive for lactoferrin immunostaining and negative for all known amyloid types.

- In recent years amyloid had been found to be derived from Semenogelin I, which is a major constituent of the seminal fluid which is found within the epithelial cells of the seminal vesicle and vas deference.

- This would explain the deposition of amyloid not only within the seminal vesicles but also within the deferent ejaculatory ducts which transport the seminal fluid.

- In their review of the literature, they had found three more articles on SSVA in which the amyloid was not limited to the seminal vesicles alone.

- They had proposed to designate this type of amyloid as "Senile seminal Tract Amyloidosis" (SSTA) instead of "Senile Seminal Vesicle Amyloidosis (SSVA)".

Ivan Nemov et al. [31] investigated if localized amyloidosis of the seminal tract (LAST) is associated with subsequent development of systemic amyloidosis. Ivan Nemov iterated that previous-reports had not recorded any systemic amyloidosis at the time of LAST diagnosis. Nevertheless, no follow-up studies existed to confirm that LAST is not a risk factor for the subsequent development of systemic amyloidosis. Ivan Nemov et al. [31] reported that their study cohort included patients whose prostate biopsy (PB) or radical prostatectomy (RP) specimens had demonstrated LAST between 2014–2021. Ivan Nemov et al. [31] analysed the clinical variables including age, race/ethnicity, prostate specific antigen (PSA), and prostate weight. Ivan Nemov et al. [31] assessed the Patients for clinical and laboratory evidence of systemic amyloidosis and lymphoproliferative conditions during the follow-up period. Ivan Nemov et al. [31] summarised the results as follows:

- Thirty-six men (26 RPs, 9 PBs, and 1 cystoprostatectomy) had LAST.

- Their study cohort included 18 white Hispanic, 9 white non-Hispanic, 7 black, and 1 Asian men. Median age was 67 years, mean PSA was 9.8 ng/mL.
- Over a median follow-up period of 20 months (mean, 30) in 27 men, none had developed systemic amyloidosis.
- Frequency of LAST in RP specimens was 1.2% (26/2,135) and had corelated with age (67 vs 63 years, P-value = .004).
- Race/ethnicity, serum PSA, and prostate weight were not associated with the incidence of LAST.

Ivan Nemov et al. [31] Made the Ensuing Conclusions:

- LAST is not a harbinger of systemic disease.
- The incidence of LAST in a contemporary RP cohort was significantly lower than in previously published studies.
- While the ages of the patients had positively corelated with LAST, serum PSA and prostate weight were not associated with the condition.
- There is no difference in the frequency of LAST between white Hispanic, white non-Hispanic, and black men.

Díaz-Flores, et al. [32] Iterated the Ensuing:

- In anatomical regions of the male reproductive system that contribute to the transport, maturation and/or required fluid medium of spermatozoa, localized amyloidosis had been pointed out within the seminal vesicles, vas deferens and ejaculatory ducts [2,7,12-14,23,25,33,34].
- The objective of their work was to report localized amyloidosis within the epididymis for the first time.
- Furthermore, they had studied the ensuing:

(a) Amyloid deposit distribution in the epididymis, to assess where the deposits are formed and

(b) The presence in normal epididymis of the amyloids tested in their cases of epididymal amyloidosis.

- Their observations had demonstrated that epididymal amyloidosis is organ-limited, with a distinctive initial location (intratubular).

Díaz-Flores, et al. [32] stated that after observing two cases (Cases 1 and 2) of pseudo-tumoral epididymal amyloidosis, they examined 120 epididymis for the presence of pathological amyloid deposits and for amyloid detection. A new case (Case 3) of subclinical amyloidosis was obtained in their review. Díaz-Flores, et al. [32] reported that all of the patients were Caucasian. Evidence of systemic amyloidosis, paraproteinemia, or underlying plasma cell dyscrasia was not demonstrated. Finally, the amyloids tested in epididymal amyloidosis were also checked in seven normal epididymis. The study was carried out in accordance with the code of ethics of the World Medical Association.

Díaz-Flores, et al. [32] Summarised the Results as Follows:

General Characteristics of Epididymal Amyloidosis

- In cases 1 and 2 of amyloidosis of epididymis, the surgically removed nodules were firm, yellowish grey in colour, and 1.4 cm and 1.6 cm in size, respectively. Case 3 (obtained after the microscopy review of 120 epididymis) had shown a larger diameter of 0.7 cm.
- In H&E-stained sections, amorphous hyaline eosinophilic deposits were observed (See Figure 1a).
- The deposits had shown Congo red positivity (See Figure 1b), with yellow-green birefringence under polarized light (See Figure 1c), and irregular PAS positivity.
- Immunohistochemistry expression of transthyretin (See Figure 2a), light chains kappa (See Figure 2b) and lambda (See Figure 2c), and amyloid P (See Figure 2d) were identified.
- Pan cytokeratin (CK) AE1 AE3 also exhibited irregular positivity within the amyloid deposits (See Figure 2e).
- There was no immunoreactivity for amyloid A, and no amyloid deposits were visualised within blood vessel walls.
- Spermatozoa were absent.

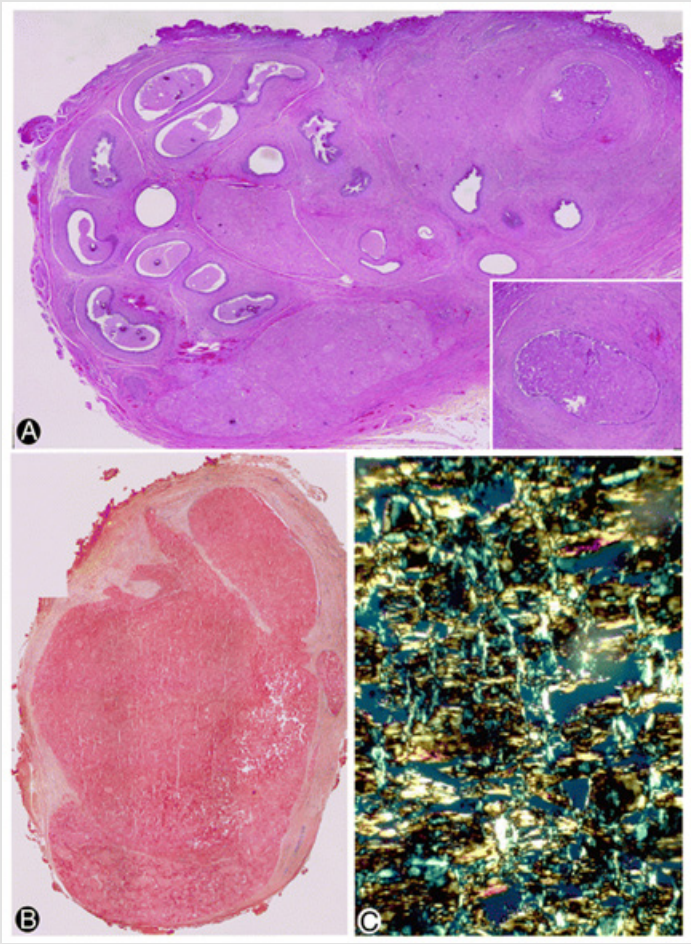

Figure 1: Amyloid deposits in the epididymes. a Eosinophilic amyloid deposits are observed in an H&E stained section. Insert: a zone of deposits in the epididymal lumen. b Congo red positivity. c Yellow-green birefringence under polarized light. a corresponds to case 1, and b and c to case 2. a and b: ×10 (insert in A: ×20). c: ×120 Reproduced from: [32] under the Creative Commons Attribution License which permits reproduction of figures and contents of their journal articles provided the original source is cited.

Distribution of Amyloid Deposits

- Amyloid deposits were visualised within the lumen of the convoluted epididymal tubule and in many lumps within the interstitium (See Figures 1a,2a-2c), exhibiting similar immunohistochemistry staining expression within both locations.

- On rare occasions, many separate aggregates of amyloid deposits were noted to be organized in a similar convoluted path that simulated that of the epididymis (See Figure 2c).

- The distribution and quantity of intratubular amyloid bodies were noted to have varied depending upon the section of the tubule. In view of this, they were noted to be scarce and free within the lumen of some tubular sections of the epididymis; however, numerous within others, where they were noted to be densely grouped, occluding as well as widening the lumen of the epididymis (See Figures 1a,2a-2c).

- The free bodies within the lumen had exhibited Congo red positivity (See Figure 2f), with immunofluorescence which was undertaken under polarized light (See Figure 2g) and amyloid P expression (see Figure 2h), and they were also found to be associated with other materials, including vesicles, particles, filaments and small dense bodies.

- Intraluminal CD68+ macrophages (See Figure 2i) were also visualised with intracytoplasmic PAS+ granules (See Figure 2j), which had exhibited immunohistochemistry expression for transthyretin and amyloid P (See Figure 2k, corresponding to amyloid P).

- The interstitial amyloid deposits had formed aggregates, which had ranged from small to large interstitial masses (See Figures 1a,1b,2a-2c).

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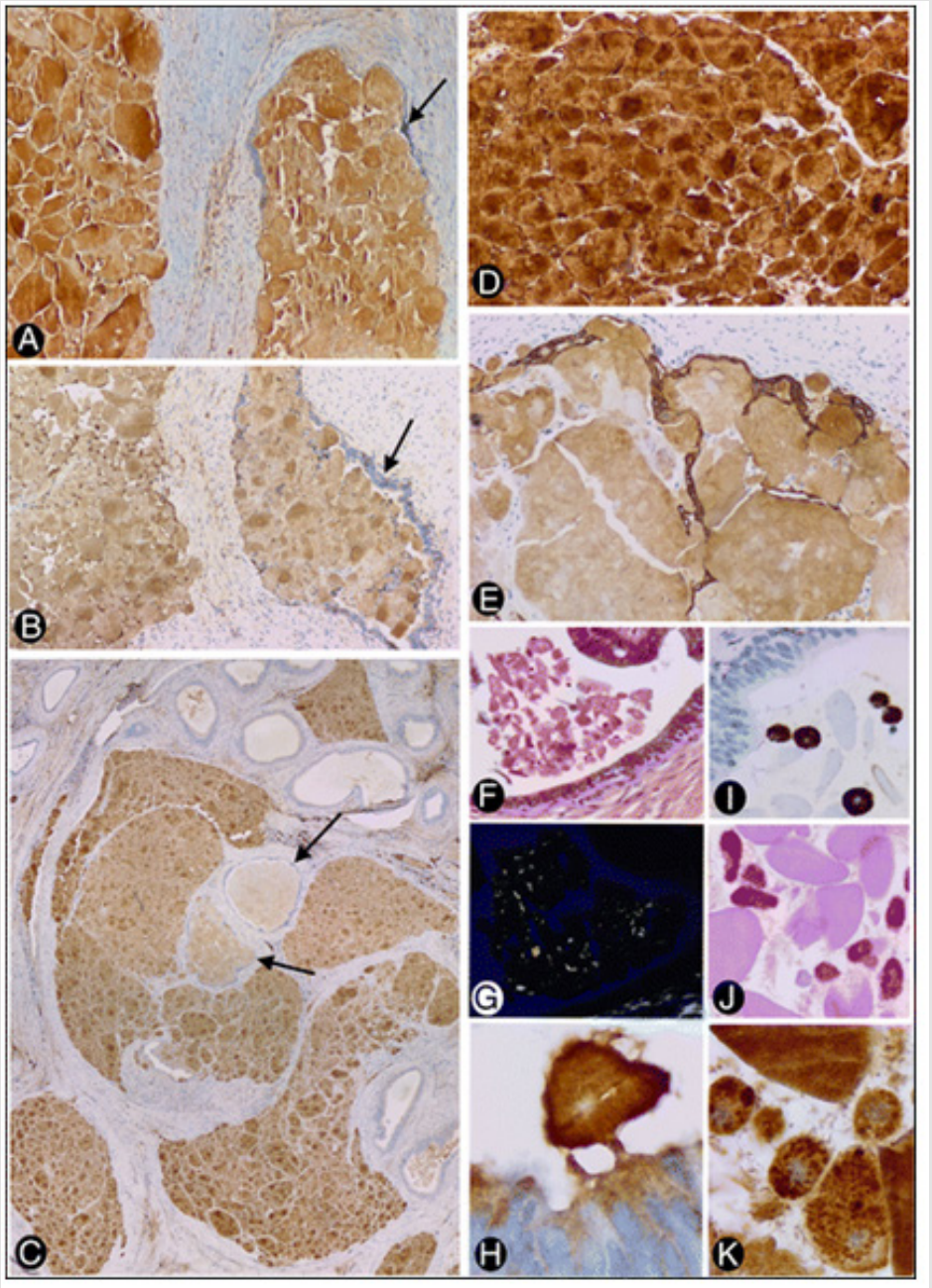

Figure 2: Immunohistochemical expression and distribution of amyloid deposits (a to e), and characteristics of free bodies and macrophages in other regions of the epididymal lumen (f to k). Expression in the amyloid deposits of transthyretin (a), light chain kappa (b) and lambda (c), amyloid P (d) and pan CK AE1 AE3 (e) is observed. Note the presence of epithelium-lined (arrows) (intraluminal) and non-epithelium-lined (interstitial) amyloid deposits. In C, the intraluminal and interstitial deposits are organized in a similar convoluted path to that of the epididymal tubule. In E, residual pan CK AE1 AE3+ epithelial cell bands persist in the periphery of the interstitial deposits. In other regions of the epididymal lumen, free amyloid bodies in the lumen associated with vesicles, particles and filaments are present (f to h). Note Congo red positivity (f) with yellow-green birefringence (g) and immunohistochemical expression of amyloid P (h). Intraluminal CD68 positive macrophages (i) showing PAS positive intracytoplasmic granules (j), which express amyloid P (k), are also observed. a, b, d and e correspond to case 2. c and f to k correspond to case 3. a, b, d and e: ×120, c: ×10, f, g, I and j: ×320, h and k: ×480. Reproduced from: [32] under the Creative Commons Attribution License which permits reproduction of figures and contents of their journal articles provided the original source is cited.

Relationship between Intratubular and Interstitial Amyloid Deposits

- Frequently, the luminal and interstitial deposits were in contiguity and were therefore partially lined by epithelium (See Figure 3a), which had exhibited pan CK AE1 AE3 and epithelial membrane antigen (EMA) expression.
- Residual epithelial bands were even visualised upon the surface of larger interstitial deposits (See Figure 2e).
- The intratubular and interstitial zones within these confluent deposits were not only identified by the presence or absence of epithelial coating, the existence of other components within the deposits.
- A reticulin network, and immunohistochemistry staining positivity CD4 (CD34+) and/or αSMA (αSMA+) stromal cells were visualised within interstitial but not within luminal zones of the deposits (see Figure 3b, corresponding to the reticulin network).
- Furthermore, epithelial folds which had exhibited degenerative phenomena encompassed occasionally portions of intraluminal amyloid deposits, which were which were noted to be partially incorporated within the interstitium (See Figures 3c-3e).

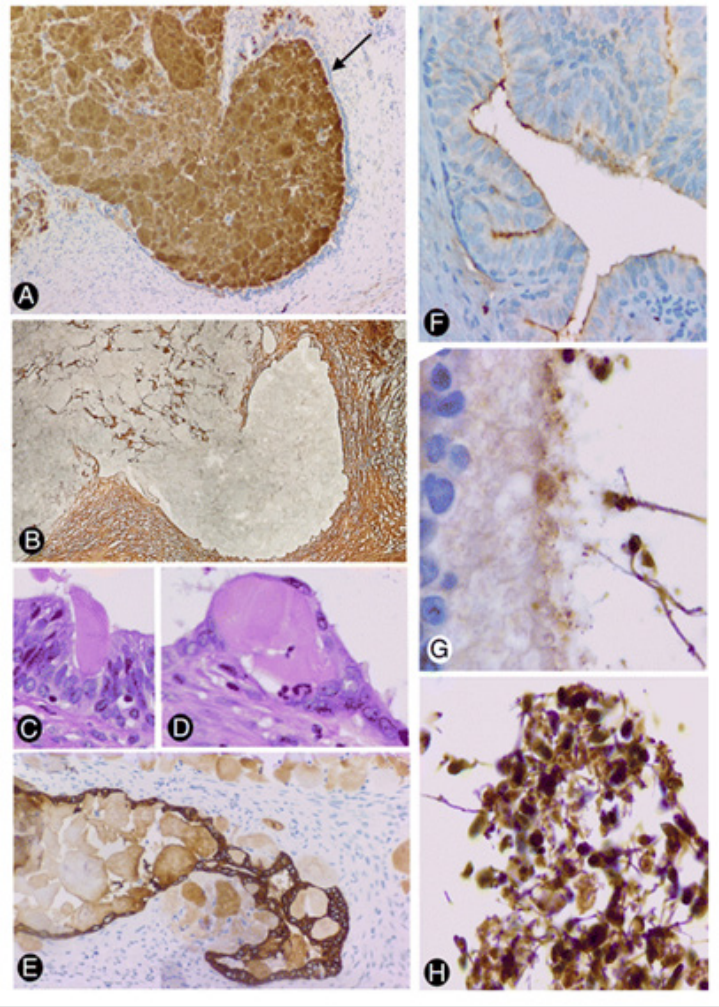

Figure 3: Relationship between intratubular and interstitial amyloid deposits (a to d), and detection of amyloids in normal epididymis (e to g). a: Epithelium-lined (arrow) (intraluminal) and non-epithelium-lined (interstitial) zones of an amyloid deposit are observed in continuity. b: A reticulin network in the interstitial zone but not in the luminal zone of the amyloid deposit is observed. c to e: Epithelial folds with degenerative phenomena are observed surrounding small portions of intraluminal amyloid deposits, which are partially incorporated in the interstitium. In normal epididymis, expression of transthyretin (f) and amyloid P (g) is observed in the apical surface of the epididymal epithelium. Strong expression of amyloid P is also shown in spermatozoa (g and h). a: transthyretin immunostaining. c and d: H&E staining. e: pan CK AE1 AE immunostaining. a, b, e and f: ×120; c and d: ×320; g and h: ×340. Reproduced from: [32] under the Creative Commons Attribution License which permits reproduction of figures and contents of their journal articles provided the original source is cited.

Detection of Amyloids (With Tested Expression in Epididymal Amyloidosis) in Normal Epididymides

- Within the epididymis that were surgically obtained from neighbouring pathological processes, the cells upon immunohistochemistry staining exhibited positive staining for transthyretin (See Figure 3f) and amyloid P (See Figure 3g) were also expressed within the apical surface of the epithelium.
- It was found that amyloid P also had exhibited strong expression in spermatozoa (See Figures 3g & 3h).
- Occasional macrophages that contained PAS and amyloid P positive bodies were visualised.

Díaz-Flores, et al. [32] Made the Ensuing Educative Discussions:

They had reported three cases of localized amyloidosis within the epididymis, two were clinically identified as a nodular mass and the other was obtained along with a neighbouring pathological process which was a contemporaneous para-testicular liposarcoma.

- Even though localized amyloidosis had been described within many locations of the male reproductive system, which contribute to the transport, maturation as well as/or required fluid medium of spermatozoa [2,7,12-14,23,25,33,34], to the best of their knowledge, their reported cases had represented the first description of localized epididymal amyloidosis in the global literature.
- Awareness of the existence of amyloidosis of the epididymis as well as awareness of its clinical manifestation as small nodules within the epididymis, as well as knowledge of its histopathology examination features, is of interest for the clinical and pathological differential diagnoses, including tumours.
- In addition, the characteristics of the lesion had supported the initial development of amyloid deposits within the epididymal lumen, where a specific proteome had been stated to occur [35-37], and non-pathological functional amyloids and mechanisms of protein aggregation control do take place [38-40].
- As summated in the ensuing documentations, they had examined these issues.
- Their cases were identified in patients who were aged 67 years and older than 67 years.
- Even though this type of amyloidosis could be regarded as a senile form of amyloidosis, larger series are necessitated so as to confirm this possibility.
- Their observations had indicated an initial deposition of amyloid within the epididymal lumen, with subsequent passage to the interstitium.
- The findings which had supported this sequence are as follows:

(a) Densely grouped deposits within some sections of the epididymis occupy both the lumen and the interstitium, ensuing distention of the epididymal lumen and partial epithelial disruption,

(b) Presence of epithelial folds with degenerative phenomena, encompassing portions of intraluminal amyloid deposits, which are partially incorporated in the interstitium,

(c) Epithelial strips remained upon the surface of some large interstitial amyloid masses,

(d) Many distinct aggregates of amyloid deposits were organized in a similar convoluted path to that of the epididymis, and

(e) The deposits occupying both the interstitium and the lumen appear with and without reticulin networks and/or stromal cells, respectively.

- Both intraluminal and interstitial deposits within the epididymis were identified as having exhibited amyloid features, including positivity for Congo red with yellow-green birefringence under polarized light. In our observations, apparent negativity for amyloid A, any evidence of systemic amyloidosis, paraproteinemia or underlying plasma cell dyscrasia, and the absence of amyloid deposits involving vascular walls support an organ-limited deposition of heterogeneous amyloids, including light chains κ and λ, and transthyretin. Amyloid P was also noted to be present.
- Nevertheless, their immunohistochemistry staining results were obtained based upon examination of the specimens that had been obtained from paraffin-embedded tissue blocks, and amyloid deposits could contain many misfolded proteins. In view of this, a more specific characterization of the proteome and misfolded proteins requires further study (see below).
- It had been postulated or understood that the commencement of amyloid deposits within the epididymal lumen might be related to their results demonstrating amyloid P (involved in the deposition, stabilization and persistence of amyloid) and transthyretin (which is a transport protein that is found in the serum and cerebrospinal fluid) expression within the apical surface of the normal epithelial cells of the epididymis.
- Furthermore, amyloid P had exhibited strong immunohistochemistry staining within the spermatozoa, which had concurred with the observations of others authors [41].
- Similarly, immunohistochemistry staining for pan CK AE1 AE3 also had also been demonstrated with the presence of keratins within the sperm proteome [42].
- The comparison with amyloidosis which had been described within other locations of the male reproductive system that con-

tribute to the transport, maturation and/or required fluid medium of spermatozoa, mainly seminal vesicles, had illustrated that the deposits have a different location: initially intraluminal with subsequent passage to the interstitium in the epididymis, and predominantly sub-epithelial within the seminal vesicles [2,7,12-14,23,25,33,34] as is found within choroid plexus amyloidogenic papillomas [43].

- The mechanisms that need to be utilised to explain these differences within the polarization of the deposits do need to be studied further. Similarly, the positive immunohistochemistry staining reaction for light-chain antibodies had been documented or described for many cases of localized amyloidosis within the urogenital tract [44,45], and the immunohistochemistry staining expression of light chains κ and/or λ within localized amyloidosis within other regions had been stated not to be exceptionally un-common [46].

- It had been iterated that the unique and distinctive location of amyloid deposits within the epididymal lumen, with subsequent passage to the interstitium, could depend upon the peculiar functions of this anatomical region, in which proteomic studies had demonstrated the more sequentially modified milieu of the body [35-37].

- It had been pointed out that indeed, the epididymis does actively participate in the maturation, protection and acquisition of motility and fertility of spermatozoa by synthesis, secretion and post-transitional modifications of important molecules, including a high concentration of several hundred proteins, majority of which are actively secreted by the epididymal epithelium (for review, see [37].

- A number of authors had explained that spermatozoa are dependent upon this extracellular environment, in view of the fact that their DNA is highly compacted, this makes the processes of transcription and translation impossible [47-49].

- It had been iterated that epididymosomes (which is the finding of vesicles present within the epididymis) are involved in the acquisition of new sperm proteins during epididymal transit [47-49].

- It had also been stated that some of these proteins might form functional amyloids, and in vitro studies had revealed amyloid formation in this unique milieu. Hence, this milieu comprises cystatin-related epididymal spermatogenic members (CRES), that pass from monomeric forms in the proximal caput region to an aggregated amyloid state in the distal caput region [43,50], and amyloidogenic prion protein is found within epididymosomes and associated with hydrophobic proteins in lipophilic complex [51-53].

- It had been iterated that similarly, concentration of luminal content occurs within the epididymis (more than 90% of the fluid is removed from the epididymis) [54], which facilitates macromolecular crowding, and protein misfolding as well as aggregation.

- Nevertheless, it had been iterated that within the epididymis, amyloids do act without causing any pathology, in view of the mechanisms of extracellular quality control [38,39,49]. This control had been documented to include the ensuing:

(a) Ubiquitin-dependent proteolysis (classically considered as an intracellular quality control system and currently as also having extracellular functionality in sperm quality control) [55],

(b) Chaperones (involved in the prevention of protein aggregation), since chaperone clustering is found within soluble high molecular mass lipophilic complex present in the lumen of the epididymis during sperm maturation (around 30% of total epididymal secretion [36]), and

(c) Transglutaminase, that prevents the formation of amyloid-type aggregates of CRES in the epididymis by post-translational modifications (transglutaminase cross-linking of cystatin CRES – [50]).

- In view of this, the onset of amyloidosis deposits within the lumen of the epididymis, with subsequent passage to the interstitium, does suggest a disturbance of the mechanisms mentioned above, mainly of extracellular (intraluminal) functional amyloid control.

- It has been iterated that whilst intracellular, post-translational quality control systems to repair or remove misfolded proteins had been well studied, extracellular mechanisms of folding control of secreted proteins had not been well described, except within the lumen of the epididymis [38,39].

- It had been iterated that these mechanisms within the epididymis had been considered highly significant for understanding the misfolded protein formation involved in some pathology processes, including Alzheimer's disease, cerebral angiopathies, and type II diabetes mellitus [38,39].

- In this way, amyloid deposits within the epididymis might provide a substrate to explore not only the alteration of the reproductive function, but also the mechanism of extracellular protein misfolding control in several diseases.

- In view of this, new studies related to amyloidosis of epididymis are necessary in order to ascertain the functional amyloids which had been outlined above and the molecules that act in their extracellular quality control.

Díaz-Flores, et al. [32] Made the Ensuing Conclusions:

- They had described the presence of localized amyloidosis within the epididymis for the first time.

- The initial intraluminal formation is particularly interesting

in view of the fact that it may also be the pathological expression of amyloid in an anatomical region with critical functions during sperm maturation, including the uniqueness of the human epididymal proteome and several molecular pathways, such as those involved in specific intraluminal functional amyloids and their quality control.

Conclusion

- Cases of amyloidosis of the seminal vesicle, prostate gland and ejaculatory ducts are being reported sporadically and hence all clinicians need to be aware of this.
- Seminal vesicle (SV) amyloidosis is a well-documented histological entity, but it is observed infrequently.
- The incidence of amyloidosis of the seminal vesicle is rising and that has been explained to be probably related to the increasing use of prostate biopsies to investigate patients with elevated serum prostate-specific antigen levels.
- There are no specific diagnostic symptoms associated with primary amyloidosis of the prostate gland, seminal vesicles or ejaculatory ducts.
- Treatment of amyloidosis is based upon the treatment of the underlying associated pathology in that if there is an associated primary carcinoma of the prostate gland then the treatment would be based upon the pathology grade and stage of the prostate cancer.

Conflict of Interest

Nil.

Acknowledgement

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