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Research Article

Amyloidosis of the Seminal Vesicle, Ejaculatory Duct, vas Deferens and Epididymis an Update

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Abstract:

It has been iterated that cases of primary amyloidosis of the prostate gland, seminal vesicles, vas deferens, epididymis as well as ejaculatory ducts are not common and in view of this pathologists, urologists, and oncologists should have high index of suspicion for the aforementioned four lesions Primary amyloidosis of the prostate gland, seminal vesicles, epididymis 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 and epididymis obtained pursuant to 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 demonstrate features of the prostate gland, seminal vesicle and ejaculatory duct or epididymis 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 and epididymis tend to be asymptomatic but some cases of primary amyloidosis of the seminal vesicle vas deferens, ejaculatory duct might manifest with blood within the semen of an individual. Some cases of amyloidosis of the prostate gland, seminal vesicles, vas deferens epididymis 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 vas deferens and epididymis tends to depict or demonstrate amorphous, pale eosinophilic material which is often associated with cracks from processing of the biopsy or prostatectomy specimen Specimens of amyloid within the prostate gland, seminal vesicle, vas deferens, epididymis 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, vas deferens epididymis and ejaculatory duct tends to simulate upon radiology imaging undertaken by magnetic resonance imaging (MRI) scan features of prostate cancer invading the seminal vesicle, vas deferens, epididymis or ejaculatory duct, carcinoma of the urinary bladder invading the seminal vesicle, vas deference, epididymis as well as ejaculatory duct, and adenocarcinoma of the rectum invading the seminal vesicle, epididymis, vas deference and ejaculatory duct 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; incidental finding; asymptomatic

Introduction

Amyloidosis of the seminal vesicle of Seminal vesicle (SV) amyloidosis is a well-documented histology examination entity; however, amyloidosis of the seminal vesicle is observed infrequently. It has been pointed out that the incidence of amyloidosis of seminal vesicle is rising which is perhaps related to the increasing undertaking of prostate biopsies to investigate patients with raised serum prostate-specific antigen levels. [1] Diagnostic prostate biopsies are commonly undertaken in men who are suspected of having prostate cancer and are typically prompted by raised serum prostate-specific antigen (PSA) levels. The protocol for trans-rectal ultrasonography (TRUS)-guided prostate biopsies has been well developed, and 10 to 12 cores are

typically undertaken [1] [2] For patients who have initially negative biopsies, the ensuing options often tend to be considered: (i) a period of serum PSA monitoring; (ii) early repeat prostate biopsies (10 to 12 cores); (iii) saturation prostate biopsies under TRUS guidance; and (iv) trans-perineal (template) mapping of prostate biopsies. With an increasing trend for serum PSA testing in the asymptomatic male population over 50 years of age, urologists are undertaking prostate biopsies on an increasing number of patients, and an increasing number of needle cores are being collected at each setting, including that of the template approach for prostate biopsies. [1] [3] [4] [5]

Incidental pathology examination findings in the prostate and the seminal vesicles (SVs) are well described, including SV amyloidosis, a well-documented histological entity. [1] [6] SV amyloidosis is reported to be associated with haematospermia [7] and prostatitis, especially in ageing men. [6] [8]

It has been iterated that within anatomical regions of the male reproductive system which contribute to the transport, maturation and/or required fluid medium of spermatozoa, localized amyloidosis had been reported within the seminal vesicles, vasa deferentia and ejaculatory ducts [1] [6] [7] [8] [9] [10] [11] [12] [13] [14].

Diaz-Floez et al. [9] reported the first three cases of amyloidosis of the epididymis in 2017. Considering that amyloidosis of the seminal vesicles, vas deferens, ejaculatory duct and seminal vesicles are rare and they generally tend to simulate carcinoma of the prostate gland as well as carcinoma of the urinary bladder, it is important for every urologist to have a high index of suspicion for amyloidosis in order not to treat amyloidosis of the seminal vesicle, ejaculatory duct, vas deferens or epididymis under a mis-diagnosis of cancer. The ensuing article on amyloidosis of the seminal vesicle, ejaculatory duct, vas deferens or epididymis is divided into two parts: (A) Overview and (B) Miscellaneous narrations and discussions on case reports, case series, and studies related to amyloidosis of the seminal vesicle, ejaculatory duct, vas deferens amyloidosis and epididymis.

Aim

To provide an update on amyloidosis of seminal vesicle, vas deferens, ejaculatory duct and epididymis which tend to be diagnosed upon prostate biopsy and prostatectomy specimens.

Methods

Internet databases were searched including: Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: amyloidosis of seminal vesicle, amyloidosis of vas deferens, amyloidosis of ejaculatory duct amyloidosis of vas deferens, and amyloidosis of epididymis. Twenty-four (24) references were identified which were used to write the article which has been divided into two parts: (A) Overview and (B) Miscellaneous narrations and discussions on case reports, case series, and studies related to amyloidosis of the seminal vesicle, ejaculatory duct, vas deferens amyloidosis and epididymis.

Results

[A] Overview

Definition / general statements [15]

- Primary amyloidosis of the prostate gland, or seminal vesicle or epididymis or vas deferens is an uncommon disease.
- Primary amyloidosis involves seminal vesicles in about 10% of radical prostatectomies, usually represents a localized form and it also involves the epididymis, ejaculatory duct and epididymis less often.
- Amyloidosis develops subepithelially spreading to include the wall of seminal vesicles and ejaculatory ducts; appears to be related to advanced age [12]
- **C**orpora amylacea may stain positive with Congo red. [15]

Essential features

- Amyloid is pale amorphous hyaline, eosinophilic substance that accumulates and can pressure the adjacent epithelium. [15]
- Amyloid often displays processing cracks. [15]
- Amyloid is more common in seminal vesicles and vas deferens. [15]
- Subepithelial and vascular deposits of amyloid tend to be seen. [15]

Epidemiology

- Amyloidosis is stated to occurs in 2% to 10% of radical prostatectomy specimens. [10]
- The incidence of amyloidosis is documented to increase with age, reaching 21% in men age 75 years and older. [6] [8]
- Vascular amyloid deposits are stated to be present in 2% to 10% of prostates with nodular hyperplasia or adenocarcinoma. [15]
- It has been pointed out that there is a higher incidence of amyloid deposits in patients with myeloma, primary amyloidosis of kidney or chronic diseases. [15]
- It has been iterated that amyloidosis of the seminal vesicles involves 10% of radical prostatectomy specimens. [15]

Sites

- It has been pointed out that amyloidosis is more common in seminal vesicles and vas deferens. [15]
- It has been iterated that amyloid deposits are more commonly subepithelial and vascular. [15]

Aetiology

- It has been explained that even though immunohistochemistry often detects lactoferrin [16] amyloid apparently derives from semenogelin I, the major secretory product of the seminal vesicles. [17]
- It has been pointed out that Semenogelin 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 [18]

Pathophysiology

The pathophysiology of amyloidosis has been summated as follows: [15]

- Amyloidosis develops from abnormal folding of proteins that deposit as fibrils within the extracellular tissue and may accumulate preventing normal function
- Amyloidosis includes multiple biochemically distinct proteins but with similar morphologic appearance. [15]
- Different forms of amyloidosis include: [15]
    - Primary systemic amyloidosis (no evidence of preceding or coexisting disease, paraproteinemia or plasma cell neoplasia). [15]

- Amyloidosis tends to be associated with multiple myeloma. [15]
- Amyloidosis tends to be secondary to coexisting previous chronic inflammatory or infectious conditions, haemodialysis. [15]
- Localized form of amyloidosis also exists. [15]

Clinical features

The manifesting features of amyloidosis of the prostate gland, seminal vesicle, ejaculatory duct and epididymis had been summated as follows: [15]

- Amyloidosis of the prostate gland, seminal vesicle, ejaculatory duct and epididymis is most commonly asymptomatic. [15]
- Amyloidosis of the prostate gland, seminal vesicle, ejaculatory duct and epididymis Can simulate prostate or bladder cancer invasion of seminal vesicles upon MRI scan. [15]

Diagnosis

The diagnosis of amyloidosis has been summated as follows: [15]

- **Histology**: Histopathology microscopy examination of specimens of amyloid or amyloidosis demonstrates amorphous pale eosinophilic material often with cracks from processing. [15]
- **Histochemical stain with Congo red shows** green birefringence on polarized microscopy in the scenario of amyloidosis. [15]

Radiology description

- It has been pointed out that radiology-image features of amyloidosis can simulate the features of prostate gland or urinary bladder cancer invasion of seminal vesicles on MRI scan. [15]

Treatment

- It has been explained that the treatment of amyloidosis of the prostate gland, seminal vesicle, ejaculatory duct, vas deferens, and epididymis is based upon the underlying condition. [15]

Gross description

The macroscopy pathology examination features of amyloidosis of the prostate gland, seminal vesicle, ejaculatory duct and epididymis had been summated as follows: [15]

- Amyloidosis or amyloid is usually not visualised grossly. [15]
- When involvement of amyloidosis is massive, the organ can be enlarged and firm and cut section could demonstrate a waxy appearance. [15]

Microscopic (histologic) description

The microscopy pathology examination features of amyloidosis of the prostate gland, seminal vesicle, ejaculatory duct and epididymis had been summated as follows: [15]

- The macroscopy pathology examination features of amyloidosis of the prostate gland, seminal vesicle, ejaculatory duct and epididymis demonstrate: pale amorphous hyaline, eosinophilic substance that accumulates and can pressure the adjacent epithelium. [15]
- Microscopy examination of amyloidosis specimen of the prostate, seminal vesicle, ejaculatory duct and epididymis often displays processing cracks. [15]
- Microscopy examination of amyloidosis specimen of the prostate, seminal vesicle, ejaculatory duct and epididymis demonstrate the subepithelial location of the amyloid specimen. [15].
- The amyloid specimen upon microscopy examination could be seen as compressing the adjacent epithelium. [15]

Positive stains

The staining features of amyloidosis specimens include the ensuing: [15]

- **Trichrome** (stains amyloid dusky grey), **Congo**, immunohistochemistry for specific amyloid forms

Electron microscopy description

Electron microscopy examination features of amyloidosis specimens had been summated as follows: [15]

- Electron microscopy examination demonstrates non-branching amyloid fibrils which measure 7.5 nm to 10 nm [13]

Differential diagnosis

- It has been pointed out that it is important to exclude an underlying aetiology in including plasma cell neoplasia or an inflammatory condition. [15]

[B] Miscellanous Narrations and Discussions from Some Case Reports, Case Series and Studies Related to Amyloidosis of The Seminal Vesicle

Yang et al. [1] made the ensuing iterations:

- Seminal vesicle (SV) amyloidosis is a well-documented histopathology entity; nevertheless, it is observed infrequently.
- The incidence of SV amyloidosis is on the rise, which is probably related to the increasing undertaking of prostate biopsies to investigate patients with raised serum prostate-specific antigen levels.

Yang et al. [1] reported seven cases of incidental SV amyloidosis over a 3-year period and considered their relationship to the previously suggested aetiological factors. Based on their series, they concluded that incidental localized SV amyloidosis observed in diagnostic prostate biopsies does not warrant formal investigations for systemic amyloidosis.

Kee et al. [12] investigated the incidence of amyloidosis of seminal vesicles and ejaculatory system including ejaculatory ducts and vasa deferentia. Kee et al. [12] reviewed the whole mount sections of 447 radical prostatectomy specimens removed for prostatic cancer, including 273 cases from the United States of America and 174 cases from Korea. Kee et al. [12] summated the results as follows:

- Out of these, 21 cases (4.7%) had demonstrated amyloidosis within seminal vesicles, vasa deferentia, and in ejaculatory ducts.
- Ten of these (3.7%) cases were from the United States and 11 cases (6.3%) from Korea.
- The patients' age had ranged from 51 years to 79 years (mean, 66.1 years).

- Amyloid deposition was found in 5 patients within the sixth decade (3.4%), 9 patients in the seventh decade (4.7%), and 7 patients in the eighth decade (9.3%).
- At the seventh decade of life, the Korean patients had shown a higher incidence (8.3%) than American patients (2.5%), but other age groups showed no difference.
- All cases demonstrated bilateral involvement of the seminal vesicles and ejaculatory systems.
- The deposits of amyloid tended to be nodular and affected the subepithelial region of seminal vesicles, vasa deferentia, and ejaculatory ducts.
- There were no amyloid deposits surrounding blood vessels or within the prostatic parenchyma.
- Localized amyloidosis of the ejaculatory system involved not only the seminal vesicles but also the vasa deferentia and the ejaculatory ducts.
- The vessels or prostatic stroma were not part of this process.

Kee et al. [12] made the ensuing conclusions:

- Amyloidosis develops sub-epithelially spreading to include the wall of these organs and appears to be related to advanced age.
- The incidence of amyloidosis of the ejaculatory system in Korean patients was higher than in USA patients.

Argon et al. [10] made the ensuing iterations:

- Amyloidosis is a rare disease with various aetiologies with extracellular amyloid protein depositions.
- By 2012, at least 26 distinctive amyloid forms had been detected with different clinical importance and treatment.
- They have characteristic staining features with Congo red.
- Amyloid may be detected in 2% to10% of prostates that have been removed because of hyperplasia or carcinoma.
- Amyloidosis of seminal vesicles is accepted as senile amyloidosis and it is not accompanied by systemic amyloidosis or clinical symptoms.
- This condition is the most common form of localized amyloidosis.
- They had investigated incidence and histopathology characteristics of amyloidosis of seminal vesicles within radical prostatectomy materials of the patients whose prostate carcinomas were treated surgically.

Argon et al. [10] reported amyloid depositions in seminal vesicles of 207 radical prostatectomy materials of prostates had been removed due to localized prostate carcinoma. Amyloid depositions were confirmed with Congo red staining and polarization microscope. Argon et al. [10] summated the results as follows:

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

Argon et al. [10] made the ensuing conclusions:

- Localized amyloidosis of seminal vesicles is not an unusual finding. amyloidosis of seminal vesicles incidence in Turkish patients included in this study and histopathologic characteristics of these patients are not different from the other studies.
- Systemic AA amyloidosis is the most common form of amyloidosis in their country.
- To be aware of amyloidosis of seminal vesicles is of importance in discrimination from the other forms of amyloidosis.

Coyne and Kealy [8] reported the following:

- Subepithelial deposits of amyloid were detected within the seminal vesicles of 13 males from a total of 143 unselected autopsies (9%).
- The incidence increased with increasing age.
- The amyloid was classified using histochemistry, immunohistochemistry and clinical features.
- Eight cases were categorized as senile vesicle amyloid, two as systemic AA amyloid with secondary involvement of the seminal vesicle, and three as mixed amyloidosis.
- The morphology appearances of the different categories of seminal vesicle amyloidosis were similar but a different distribution was common.

Coyne and Kealy [8] concluded that:

- The staining characteristics of senile vesicle amyloid had indicated that this is a different amyloid protein, perhaps locally derived within the seminal vesicle.

Pitkänen et al. [6] reported the ensuing findings in their study:

- Amyloid deposits were found sub-epithelially within the seminal vesicles of 34 of 209 consecutively men they had studied.
- The incidence had increased with age and was found in 21% of men over 75 years.
- This senile seminal vesicle amyloidosis (SSVA) was a localized disorder, and the amyloid substance had unique histochemical and immunochemical properties not shared with any other amyloid described until 1983.

Harvey and Têtu [16] stated localised seminal vesicle amyloidosis, is relatively infrequent. Harvey and Têtu [16] reported 9 additional cases. Harvey and Têtu [16] retrospectively retrieved the 9 cases from 803 radical prostatectomies which were undertaken between 1995 and 2000 for prostatic adenocarcinoma. In each case, the type of amyloidosis was characterised by immunohistochemistry staining features. Information regarding a possible concurrent disease or prior hormone therapy had been obtained. Harvey and Têtu [16] summated the results of their study as follows:

- The prevalence of amyloidosis of seminal vesicles was lower in their study (1.1%) than in unselected autopsy cases.
- The prevalence of amyloidosis in patients exposed to prior hormone therapy (LHRH agonist and anti-androgen) was 2%

while it reached only 0.9% in those who received no hormone therapy ($p>0.3$).

- None of the patients had systemic amyloidosis and all cases were of non-A-A type.
- Lactoferrin, a glycoprotein produced by normal seminal vesicles, was detected in more than a half of them (5/9).

Harvey and Têtu [16] made the ensuing conclusions:

- No association was found between the occurrence of seminal vesicle amyloidosis and occurrence of a prostatic adenocarcinoma, concomitant systemic disease or exposure to prior hormone therapy.
- Seminal vesicle amyloidosis is a localised condition without systemic involvement and amyloid deposition is composed mostly of lactoferrin.

Linke et al. [17] made the ensuing iterations:

- Senile seminal vesicle amyloid (SSVA), one of the most common forms of localized amyloidosis, is associated with the male aging process.
- Even though it had been postulated that the amyloidogenic component originated from exocrine cells and that, upon the basis of immunohistochemistry, that the amyloid was composed of lactoferrin, the nature of SSVA was never established definitively.

In order to address this issue, Linke et al. [17] used their microanalytic techniques to characterize the structure of the congophilic green birefringent protein extracted from 5 such amyloid-containing specimens. Linke et al. [17] summated the results as follows:

- Mass spectrometric analysis had shown that in all cases, the fibrils were composed mainly of polypeptide fragments identical in sequence to the N-terminal portion of the major secretory product of seminal vesicles, namely semenogelin I (SgI).
- Even though lactoferrin was detected in 3 instances, the trace amount and seemingly intact form of this molecule indicated that it was not the amyloidogenic molecule.
- The SgI nature of the amyloid was confirmed through demonstration that the deposits were immunostained specifically with Sgl-reactive antibodies.

Linke et al. [17] 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. [18] made the ensuing iterations:

- Semenogelin I and II (Sgl, Sgll) are two separate gene products of chromosome 20 with extensive (80%) identity in primary structure.
- They are mainly responsible for immediate gel formation of freshly ejaculated semen.
- Degradation of Sgl and Sgll is due to the proteolytic action of prostate-specific antigen (PSA); it results within 5-15 minutes in 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 is suggested to be expressed at low levels in the epididymis.

In order to characterize the expression and tissue distribution of Sgl and Sgll in greater detail, Bjartell et al. [18] produced monoclonal immunoglobulin Gs (lgGs for immunocytochemistry (lCC) and specific [35S]-, digoxigenin-, or alkaline phosphatase-labeled 30-mer antisense probes to Sgl and Sgll for in situ hybridization (lSH). Bjartell et al. [18] summated the results as follows:

- Immunocytochemical staining for both Sgl and Sgll, and lSH detection of both Sgl and Sgll transcripts, were demonstrated in the cytoplasm of seminal vesicle epithelium. lSH showed Sgll alone to be expressed in the epithelium of the epididymal cauda.
- Neither lCC nor lSH yielded any evidence of Sgl or Sgll expression in caput or corpus epithelium or in any stromal cells of the epididymis. Consistent with their previous findings using polyclonal lgG, monoclonal anti-Sgll Sgll lgGs identified epitopes on the posterior head, midpiece, and tail of ejaculated spermatozoa.
- Spermatozoa in the epididymal cauda were also immunoreactive, but those within the caput or corpus region of the epididymis as well as those in the testis were negative.
- As demonstrated by lCC, neither Sgl nor Sgll were expressed within the testis, the prostate, the female genital tract, or other normal human tissue specimens.

Bjartell et al. [18] made the ensuing conclusions:

- Even though the significance of Sg attachment to epididymal and ejaculated spermatozoa had remained to be established, monoclonal anti-Sg lgG might prove useful in establishing the origin of seminal vesicle tissue components in prostate core biopsies or other biopsy specimens.

Seidman et al. [13] 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 bilateral, subepithelial, and clinically inapparent, features similar to other cases in the literature. In one case, the diagnosis was made based upon a trans-rectal prostatic needle biopsy which included a small portion of seminal vesicle; and to their knowledge, this had not been previously reported. Electron microscopy in one case had shown non-branching fibrils characteristic of amyloid, and pretreatment of tissue sections using the permanganate method in two cases showed almost complete ablation of congophilia. Seidman et al. [13] concluded that:

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

Caballero Martínez et al. [19] undertook a clinical and pathological study of eight cases of localized amyloidosis of the seminal vesicles with a review of the literature. Caballero Martínez et al. [19] undertook an immunohistochemical and histochemical study in surgical specimens of the eight patients. Caballero Martínez et al. [19] summated the results as follows:

- Two of the eight cases studied for amyloidosis in seminal vesicles, were 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 transrectal prostatic needle biopsy which including a portion of seminal vesicle.
- Amyloidosis of seminal the vesicle was permanganate-sensitive; A-Amyloid, laminin, amyloid P protein and collagen IV negative.

Caballero Martínez et al. [19] made the ensuing conclusions:

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

Singh et al. [20] made the ensuing iterations:

- Primary amyloidosis of lower urinary tract is an uncommon entity and it is usually localized to a single site.
- Its clinical features, and cystoscopy and radiology-image findings are indistinguishable from neoplastic or inflammatory lesions.

Singh et al. [20] reported an unusual case of amyloidosis involving multiple sites (prostatic stroma, trigone and lower ureters) in the lower urinary tract. MRI scan findings of bladder amyloid, which could be used to suspect this condition, were also described.

Jun et al. [21] reported localized amyloidosis involving seminal vesicles and vasa deferentia, which was found in two patients with prostatic adenocarcinoma. A 60-yr-old (Case 1) and a 59-yr-old (Case 2) man presented to their hospital with elevation of serum prostate-specific antigen (PSA) and biopsy proven carcinoma, respectively. MRI scan had demonstrated multiple irregular foci of low signal intensity within the prostates as well as within both seminal vesicles and vasa deferentia on T2-weighted imaging, indicating prostatic carcinoma with extension to both seminal vesicles and vasa deferentia in both cases. Under the clinical diagnosis of stage III prostatic adenocarcinoma, a radical prostatectomy was undertaken in both patients. Microscopy pathology examination of the specimens demonstrated Gleason score 7 adenocarcinoma in both patients. In addition, isolated amyloidosis of both seminal vesicles and vasa deferentia was found without carcinoma involvement. Jun et al. [21] made the ensuing discussions:

- Localized amyloidosis in the seminal vesicles, which is regarded as senile process, had been occasionally reported in the autopsy 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.
- In their report, two cases of isolated amyloidosis of the seminal vesicles and vasa deferentia were described with electron microscopy study and literature review.

Lawrentschuk et al. [3] made the ensuing iterations:

- Trans-rectal ultrasound-guided biopsy of the prostate is an integral step in the investigation of patients at risk of prostate adenocarcinoma.
- With an increasing number of biopsies being undertaken, uncommon forms of prostatic pathology would be identified more frequently.
- Amyloidosis of the prostate and/or the seminal vesicles might be noted upon transrectal ultrasound-guided biopsy of the prostate and the implications of this histological diagnosis should be understood.

Lawrentschuk et al. [3] reported their experience of two such cases of amyloidosis.

Maroun et al. [22] made the ensuing iterations:

- The finding of amyloid deposits within the seminal vesicles had been known for many years.
- The deposits are usually localized and asymptomatic.
- Over recent years seminal vesicle amyloidosis had been reported to simulate prostate and bladder cancer invasion upon MRI scan.

Maroun et al. [22] stated that they therefore felt that knowledge of the entity is important and hence they had reported a typical case confirming 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.

Rath-Wolfson et al. [23] made the ensuing iterations:

- Senile Seminal Vesicle Amyloidosis (SSVA) increases with age.
- Involvement of the whole seminal tract, for example, the seminal vesicles, ejaculatory and deferent ducts was first reported by them in the International Symposium on Amyloidosis 1998.
- Since then, they had encountered four more cases of SSVA.
- In all these cases the ejaculatory and deferent ducts were also involved by amyloid.
- The amyloid was located mostly sub-epithelially, stained positively with Congo red, gave green birefringence under polarized light and was permanganate sensitive, slightly positive for lactoferrin immunostaining and negative for all known amyloid types.
- Over recent years the amyloid was found to be derived from Semenogelin I, a major constituent of the seminal fluid which is present in 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 an ejaculatory-ducts, which transport the seminal fluid.
- In a 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)”.

Diaz-Florez et al. [9] stated that after observing two cases (Cases 1 and 2) of pseudo-tumoral epididymal amyloidosis, epididymides (n: 120) were examined for the presence of pathological amyloid deposits and for amyloid detection. A new case (Case 3) of subclinical amyloidosis was obtained in their review. All patients were Caucasian, and the relevant findings of the

cases had been illustrated in Table 1. Evidence of systemic amyloidosis, paraproteinemia, or underlying plasma cell dyscrasia was not identified. Finally, the amyloids tested in epididymal amyloidosis were also checked in seven normal epididymides. The study was undertaken in accordance with the code of ethics of the World Medical Association.

Case	Age (years)	Presentation and resulting diagnosis	Larger diameter (cm)	Contralateral epididymal exploration	Operation	Follow-up (months)	IHC Primary antibodies used
1	77	Nodule in the left epididymis Result: Epididymal amyloidosis	1.4	Thickened	Nodule removal	48 (Free of disease)	Light chain λ Dako [D: 1:50] Light chain κ Dako [D: 1:50] Transthyretin Dako [D: 1:600] Amyloid P Abcam [D: 1:50] Amyloid A Dako [D: 1:50] CK AE1 AE3 Dako [D: 1:100] EMA Dako [D: 1:100] CD68 Dako [D: 1:100] CD34 Dako [D: 1:50] αSMA Dako [D: 1:50]
2	72	Nodule in the right epididymis Result: Epididymal amyloidosis	1.6	NED	Nodule removal	9 (Free of disease)	
3	67	Left scrotal swelling for 4 years. Physical examination: a firm, non-reducible mass. Result: Para-testicular liposarcoma and Epididymal amyloidosis without tumour involvement	0.7 (size refers only to epididymal amyloidosis)	NA	Radical Orchiectomy	NA	

Table 1: Characteristics of reported cases and antibodies used for immunohistochemistry

From: Localised amyloidosis of the epididymis: a previously unreported phenomenon

IHC Immunohistochemistry, *NED* No evidence of disease, *NA* Not available, *CK* Cytokeratin, *EMA* Epithelial membrane antigen

Reproduced from [9] under the Creative Commons Attribution License. They summated the results as follows:

General characteristics of epididymal amyloidosis

In cases 1 and 2 of epididymal amyloidosis, the surgically removed nodules were noted to be firm, yellowish grey in colour, and 1.4 and 1.6 cm in size, respectively. Case 3 which was obtained pursuant to the microscopic review of 120 epididymides, demonstrated a larger diameter of 0.7 cm (see Table 1). In H&E-stained sections, amorphous hyaline eosinophilic deposits were identified (see figure 1a). The deposits demonstrated Congo red positivity (see figure 1b), with yellow-green birefringence under polarized light (see figure 1c), and irregular PAS positivity. Immunohistochemical expression of transthyretin (see figure 2a), light chains kappa (see figure 2b) and lambda (see figure 2c), and amyloid P (see figure 2d) was identified. Pan cytokeratin (CK) AE1 AE3 also demonstrated irregular positivity in the amyloid deposits (see figure 2e). There was no immunoreactivity for amyloid A, and no amyloid deposits were identified within blood vessel walls. Spermatozoa were absent.

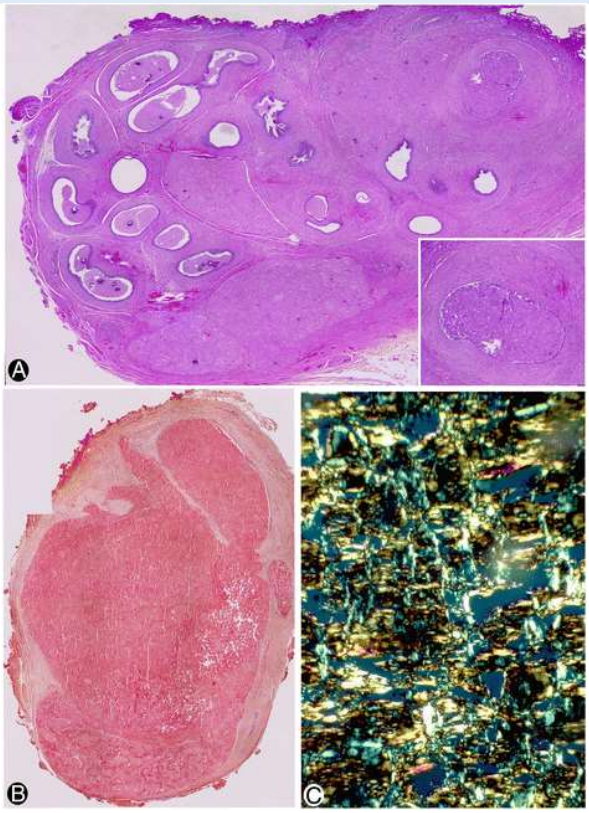

Figure 1

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 [9] under the Creative Commons Attribution License.

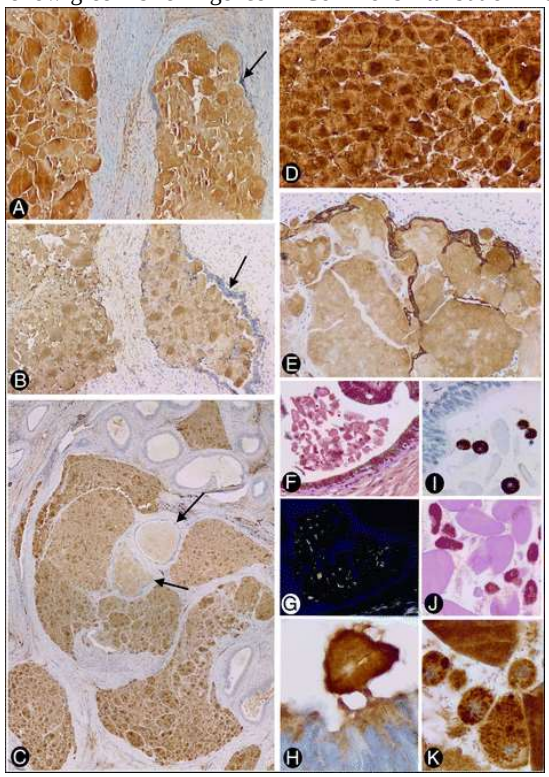

Figure 2

Immunohistochemical expression and distribution of amyloid deposits (**a, b, c, d, and 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 [9] under the Creative Commons Attribution License.

Distribution of amyloid deposits

Amyloid deposits were identified within the lumen of the convoluted epididymal tubule and in several lumps in the interstitium (see figures 1a and 2a to c, demonstrating similar immunohistochemical expression in both locations. On occasion, many separate aggregates of amyloid deposits were found to be organized in a similar convoluted path to that of the epididymis (see figure 2c).

The distribution and quantity of intratubular amyloid bodies had varied depending upon the section of the tubule. Hence, they were scarce and free within the lumen of some tubular sections of the epididymis, but many within others, where they were densely grouped, obliterating and distending the epididymal lumen (figures 1a and 2a to c). The free bodies within the lumen demonstrated Congo red positivity (see figures 2f), with immunofluorescence under polarized light (see figure 2g) and amyloid P expression (see figure 2h), and were associated with other materials, including vesicles, particles, filaments and small dense bodies. Intraluminal CD68+ macrophages (see figure 2i) were also identified with intracytoplasmic PAS+ granules (see figure 2j), which expressed transthyretin and amyloid P (see figure 2k, corresponding to amyloid P). The interstitial amyloid deposits formed aggregates, ranging from small to large interstitial masses (see figures 1a, b and 2a to c).

Relationship between intratubular and interstitial amyloid deposits

Frequently, the luminal and interstitial deposits were noted to be in continuity and they were therefore partially lined by epithelium (see figure 3a), which demonstrated pan CK AE1 AE3 and epithelial membrane antigen (EMA) expression. Residual epithelial bands were even identified upon the surface of larger interstitial deposits (see figure 2e). The intratubular and interstitial zones in these confluent deposits were not only differentiated by the presence or absence of epithelial coating; but, also by the existence of other components within the deposits. A reticulin network, and CD34+ and/or αSMA+ stromal cells were identified in interstitial but not within luminal zones of the deposits (see figure 3b, corresponding to the reticulin network). Moreover, epithelial folds with degenerative phenomena surrounded occasionally portions of intraluminal amyloid deposits, which were partially incorporated in the interstitium (see figures 3c to e).

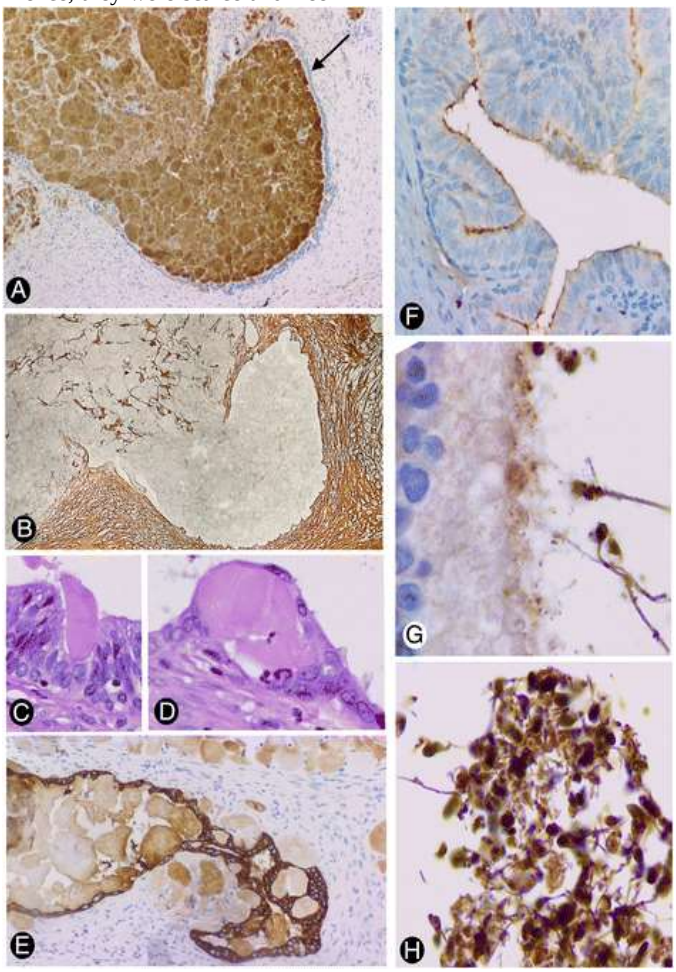

Figure 3

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 [9] under the Creative Commons Attribution License.

Detection of amyloids (with tested expression in epididymal amyloidosis) in normal epididymides

Within the epididymides surgically obtained from neighbouring pathological processes, transthyretin (see figure 3f) and amyloid P (see figure 3g) were expressed in the apical surface of the epithelium. Amyloid P also demonstrated strong expression within spermatozoa (see figures 3g and h). Occasional macrophages with PAS and amyloid P positive bodies were demonstrated.

Diaz-Florez et al. [9] made the ensuing discussions and conclusion:

- They had reported three cases of localized amyloidosis in the epididymis, two clinically detected as a nodular mass and the other obtained together with a neighbouring pathologic process (para-testicular liposarcoma).
- Even though localized amyloidosis had been described in many locations of the male reproductive system, which contribute to the transport, maturation and/or required fluid medium of spermatozoa, [1] [6] [7] [8] [9] [10] [11] [12] [13] [14] to the best of their knowledge, this was the first description of localized epididymal amyloidosis.
- Awareness of the existence of epididymal amyloidosis and of its manifestation as small nodules within the epididymis, as well as knowledge of its histopathology, is of interest in clinical and pathological differential diagnoses, including tumours.

Nemov et al. [24] investigated if localized amyloidosis of the seminal tract (LAST) is associated with subsequent development of systemic amyloidosis. They stated that previous reports had recorded no systemic amyloidosis at the time of LAST diagnosis. Nevertheless, no follow-up studies exist to confirm that LAST is not a risk factor for subsequent development of systemic amyloidosis. Nemov et al. [24] reported their study cohort, which included patients whose prostate biopsy (PB) or radical prostatectomy (RP) specimen demonstrated LAST between 2014-2021. Clinical variables including age, race/ethnicity, prostate specific antigen (PSA), and prostate weight of they were analysed by Nemov et al. [24] Nemov et al. [26] assessed the patients for clinical and laboratory evidence of systemic amyloidosis and lymphoproliferative conditions during the follow-up period. Nemov et al. [24] summated 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.
- The 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 corelated with age (67 vs 63 years, P-value = .004).
- Race/ethnicity, PSA, and prostate weight were found not to be associated with the incidence of LAST.

Nemov et al. [24] made the ensuing conclusions:

- LAST is not a harbinger of systemic disease.
- The incidence of LAST in a contemporary RP cohort is significantly lower than in previously published studies.
- Whilst patient age positively corelates with LAST, PSA and prostate weight are not associated with the condition.
- There is no difference in the frequency of LAST between white Hispanic, white non-Hispanic, and black men.

Conclusions

- Cases of amyloidosis of the seminal vesicle, prostate gland and ejaculatory ducts, seminal vesicle and vas deferens are being reported sporadically and therefore 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, vas deferens and epididymis which are diagnostic of amyloidosis.
- 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

Acknowledgements

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