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Review Article

Ossification in Human Penis: Review and Update

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Abstract

Human penile ossification is a rare urological condition with about 40 cases reported in the literature. While bone is essential for penetrative intercourse in many non-human mammals, human penile ossification appears to be part of a metaplastic process occurring after injury or trauma. Conditions such as Peyronie's disease, diabetes mellitus, local trauma, and end-stage renal disease have been associated with this entity Human penile ossification may be asymptomatic or may be associated with previous trauma to the penis, or could on rare occasions be congenital. Ossification of the penis may be asymptomatic or may present with a lump in the penis, pain in the penis, or pain and curvature of penis in association with erection. Radiology imaging does demonstrate the ossification within the penis and complete excision of the ossification area of the penis tends to be associated with resolution of the symptoms. In the rare situation of osteosarcoma of the penis, surgical excision of the entire lesion does constitute an appropriate treatment.

Key words: ossification in penis; bone in penis; congenital; peyronies disease; curvature of penis; diabetes mellitus; trauma; gout; pathology; excision

Introduction

Belshoff et al. [1] stated the ensuing:

- Human penile ossification is a rare urological condition with about 40 pathologically confirmed cases reported in the medical literature up to the time of publication of their article in 2021. [2] [3] [4] [5] [6] [7] [8] [9].
- While this is typically an acquired condition, there had been one documented congenital case, which had involved a five-year-old boy who had other genitourinary defects [2].
- Pathological calcification occurs through heterotopic mineralization of the penile soft tissues and had been associated with end-stage renal disease, diabetes mellitus, trauma, malignancy, and calcium dysregulation [3] [4] [5]
- Nevertheless, the triggering mechanism was not entirely understood.
- Historically, ossification of the penis had been presumed to be of vestigial origin due to the presence of penile bone in other animals, which facilitates reproduction [6]
- Other people had challenged this postulate, favouring instead a primarily metaplastic process sustained by fibrosis [7] [8].
- The condition that had been most commonly associated with penile ossification is Peyronie's disease.
- This condition is typified by the development of fibrous penile scar tissue, resulting in curvature and painful intercourse, which might preclude sexual function.
- Surgical reconstruction is often necessary in order to restore sexual function.
- These surgical procedures include penile straightening through the use of tunica albuginea plication sutures, or partial excision of the scar with grafting into the tunica defect, among others [10].
- Significant penile ossification in this setting does represent a unique challenge for the reconstructive urologist [9].

Considering the rarity of penile ossification, it would be envisaged that majority of clinicians globally and well as most patients globally would not be familiar with the fact that bone or ossification could on rare occasions be found within the penis and they would tend not to be familiar with the manifestation, diagnosis, management and outcome of penile ossification. The ensuing article on penile ossification or bone tissue within the penis is divided into two parts: (A) Overview which has discussed general overview aspects of penile ossification, and (B) Miscellaneous narrations and discussions from some case reports, case series and studies related to penile ossification.

Aim

To review and update the literature on bone or ossification within the human penis.

Methods

Internet data bases were searched including Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: Bone in penis; penile ossification; OS Penis; and Penile OS. Fifty-seven (57) references were identified which were used to write the article which has been divided into two parts:

Results

[A] OVERVIEW

Definition and General Statements [11]

- Heterotopic bone within the penis is stated to be most commonly found in the elderly and in children. [12] [13] The presence of os penis in man is very rare Up the time of publication of their article, only 11 cases had been published. A close study of these cases shows their extreme heterogeneity. We think that the os penis should be considered as a heterotopic bone structure similar to that found in the animal world. To confirm this, they had presented their personal case study.
- It had been pointed out that male mammals with the exception of Chimpanzees and human beings have intra-penile bone which is referred to as bacula.
- It has also been iterated that, human beings, do have an equivalent of strong distal ligament within the glans penis. [14]

Terminology

- It has been iterated that heterotopic bone within the penis is also referred to as baculum penis and also penile bone.[11]

Aetiology

The ensuing summations had been made regarding the aetiology of bone in the penis: [11]

- Ossification of the penis could occur pursuant to trauma or injury to the penis. [15]
- Ossification of penis had also been noted to be associated with diabetes mellitus, gout, venereal diseases, Peyronie's disease, as well as neoplasia.
- It has also been iterated that ossification of the penis had on rare occasions been congenital developments of penile ossification [2]

Presentation

- Some of the possible presentations of ossification within the penis include: incidental finding upon radiology imaging for something else; curvature of penis upon erection; painful penis upon coital activity; and the finding of a lump within the penis with or without a history of trauma to the penis in the past, diabetes mellitus, and gout.

Clinical Assessment Findings

- Clinical examination of the penis may demonstrate normal findings, tender spot in the penis, curvature of penis upon erection, a lump palpable within the penis and on rare occasions a possible ulcer on the penis in association with a lump or tenderness in the penis.

Miscellaneous Laboratory Investigations

Urine

- Generally, in majority of cases of either heterotopic ossification of penis and osteosarcoma of the penis, the results of urinalysis, urine microscopy and urine culture would tend to be normal; nevertheless, urine examination tends to be part of general assessments of patients and if the scenario of a rare case of urinary tract infection, the infection would be appropriately treated to improve the general condition of the patient.

Blood tests

Haematology blood tests

- Full blood count tends to be part of the general assessment of patients who have ossification of the penis and usually the results would tend to be normal.

Biochemistry blood tests

- Some of the blood tests that tend to be undertaken in the assessment of patients who have ossification of the penis include: CRP, Bone profile, serum urea and electrolytes, eGFR, liver function, parathyroid function tests, and serum urate and usually in majority of cases the results would tend to be normal.

Plain X-ray

- Plain x-ray of the penis could demonstrate opacification within the penis, the site and size as well as number of the opacifications.

Ultrasound Scan

- Ultrasound scan of penis would demonstrate opacification within the penis, the site and size as well as number of the opacifications.

Computed Tomography (CT) scan

- CT scan of penis would demonstrate opacification within the penis, the site and size as well as number of the opacifications.

Magnetic Resonance Imaging (MRI) scan

- MRI scan of penis would demonstrate opacification within the penis, the site and size as well as number of the opacifications.

Treatment

- Small opacifications could be left alone or treated conservatively or expectantly.
- Complete excision of the site of ossification and surgery to correct the curvature of the penis tends to provide effective treatment

Pathology Examinations

- Pathology examination of the specimen of the excised ossification lump from the penis does demonstrate features of the bony ossification with no evidence of inflammation; nevertheless, in cases of osteosarcoma of the penis features that demonstrate the tumour would be demonstrated as well as if the edges of the excised lesion are free of tumour.

Differential Diagnosis

- Ossification within the Corpora Cavernosa. [16] is a differential diagnosis of heterotopic ossification of the penis.

Outcome

- Generally, the outcome of excision of penile ossification has been good.

[B] Miscellaneous Narrations And Discussions From Some Case Reports, Case Series, And Studies Related To Bone Within The Penis

Belshoff et al [1] reported a 65-year-old man who was referred to their urology department for an eight-year history of dorsal curvature of his penis with erections. He had described a near 90-degree curvature, which had been stable for several years and was refractory to in-office verapamil injections. He did not have any difficulty obtaining erections; nevertheless, they were painful and bothersome. He found sexual intercourse to be also difficult and painful for both him and his partner due to the curvature. His medical and surgical history was otherwise unremarkable. Upon his examination, his penis was uncircumcised with a palpable, firm plaque along the dorsal aspect of his midshaft of penis measuring about 2.5 cm by 1.5 cm. A penile Doppler ultrasound was undertaken, which demonstrated a broad, linear, sheet-like densification of the dorsal tunica albuginea extending from the base of the penis along most of the shaft, predominantly along the right side (see figure 1).

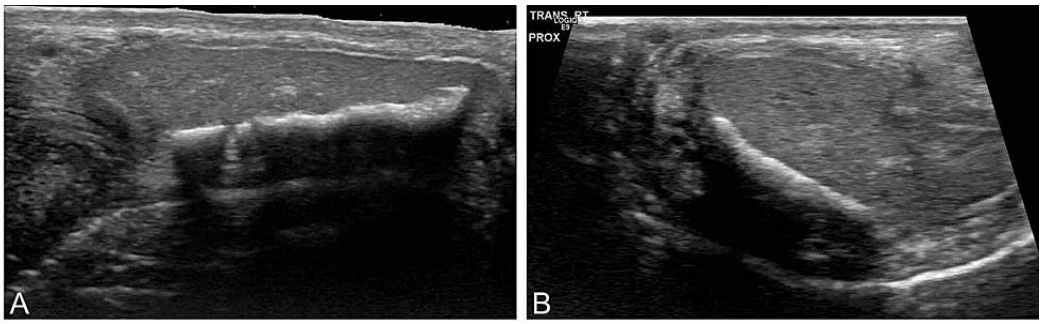

Figure 1: Penile Doppler ultrasound imaging demonstrating a 2.5-cm dorsal density with acoustic shadowing
A) Longitudinal view of the right corpora. **B)** Transverse view primarily of the right corpora Reproduced from [1] under the Creative Commons Attribution License

In view of the extensive degree of plaque and the impact upon his quality of life, he was taken to the operating theatre for partial excision and grafting. Intraoperatively, the large, firm ossified plaque was immediately visualised, and care was taken to excise this while preserving the neurovascular bundles. The corporal defect was closed utilising a bovine pericardial graft (Coloplast, Minneapolis, MN). Upon intraoperative induction of an artificial erection, the partial curvature was still apparent, which necessitated placement of two tunica albuginea plication sutures along the ventral shaft. The penile curvature was corrected to 10 degrees dorsally at the end of the procedure. The remainder of his hospital course was unremarkable, and he was discharged home the same day.

His postoperative course was documented to be also uneventful, with minimal residual curvature noted during his two-month follow-up assessment. He denied any erectile dysfunction and was then able to obtain satisfactory erections without medications. He was sexually active with his partner and he denied pain or difficulty with intercourse.

Macroscopy pathology examination of the excised tissue had demonstrated multiple tan-white, elongated segments of glistening tissue with central areas of calcification that measured in aggregate 3.2 cm by 1.6 cm by 1.1 cm. The tissue was examined after decalcification. The hematoxylin and eosin histology sections revealed a centrally located bony tissue encompassed by penile fibrous tissue (see figure 2A). The bony tissue exhibited features of lamellar bone under polarized light (see figure 2B). No inflammation was found present within the lamellar bone and adjacent fibrous tissue.

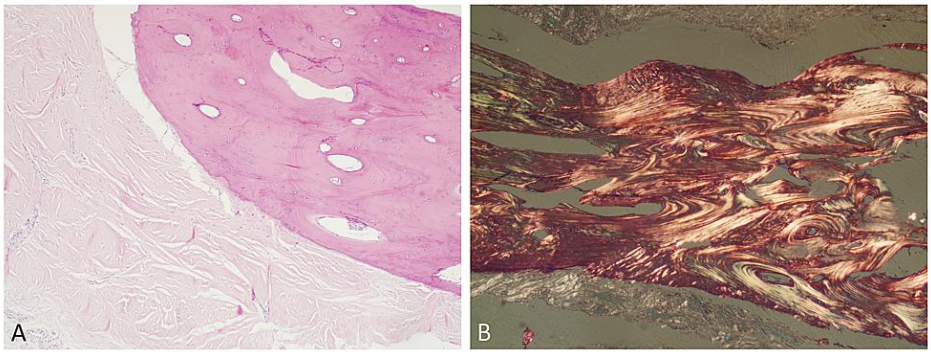

Figure 2: Microscopic examination
A) H&E section showing bone surrounded by unremarkable stroma. B) The same section examined under polarized light showing lamellar bone. Original magnification: 300x H&E: hematoxylin and eosin. Reproduced from [1] under the Creative Commons Attribution License.

Belshoff et al.]1] made the ensuing educative discussions

- Since the earliest case of penile ossification, was reported by McClellan in 1827, only about 40 cases have been described in the literature up to the time of the report of their article.

- In view of the limited case count available for study, their understanding of this condition and its aetiology was limited [2] [3] [4] [5] [6] [7] [8] [9].
- The presence of penile ossification often emanates in sexual dysfunction, which necessitates referral to a urologist.
- This rare condition presents a unique challenge for the reconstructive surgeon as the dense, bony tissue might require excision and grafting for correction of the penile curvature.
- Referral to a reconstructive urologist with experience in the surgical treatment of Peyronie's disease should be considered in order to optimize functional outcomes and patient satisfaction.

Belshoff et al. [1] made the ensuing conclusions:

- Penile ossification is a condition which often is ensued by the development of sexual dysfunction, necessitating referral to a urologist.
- Referral to a reconstructive urologist with experience in the surgical treatment of Peyronie's disease should be taken into consideration in order to optimize functional outcomes and patient satisfaction.

In 2007, de Arruda et al. [17] stated the ensuing:

- Ossification in the human penis was such a rare condition that only 34 histologically evident cases had previously been reported.
- Among many conditions that had been correlated with this problem the most frequent is Peyronie disease.
- In all these conditions, human penile ossification appeared to be a metaplastic bone formation process.

de Arruda et al. [17] reported a 59-year-old white man who had manifested with a one-year history of slight pain upon erection and during intercourse. He also did complain of hard plaque near the base of his penis. One year preceding his manifestation, he had sustained blunt trauma during intercourse. Examination of his penis demonstrated a fixed firm mass which had extended over the proximal third of his penile shaft, that measured 3.0 x 3.0 x 2.0 cm and which had involved his corporal sponge, without surface extension. He did not have any impotence or other relevant clinical finding. Radiography on the penis had demonstrated irregular calcification in the same position as the palpable mass and in the septum of the proximal inner third of his penis. de Arruda et al. [17] stated that:

- The importance of this report lied in the extent of the human penile ossification, as demonstrated by the radiological and histopathology examination confirmation.

Frank et al. [18] stated the following:

- Human penile ossification is a rare event and only a limited number of cases had appeared in the literature.
- Many reported cases had been related to local trauma and plastic induration of the penis.

Frank et al. [18] reported an additional case of ossification of the penis in 1989.

Yilmaz et al. [6] stated the following:

- Pathological calcification or ossification refers to the process by which calcium salts build up within soft tissue, causing it to harden and form extra-skeletal bone.
- This might result from a malignant infiltrative process, hypercalcemia secondary to a paraneoplastic syndrome, end stage renal disease, calcium-phosphate abnormalities caused by hyperparathyroidism or other metabolic derangements, or from a local metaplastic process resulting from repeated trauma or a chronic inflammatory state.
- Ossification which occurs within the human penis is very rare, with less than 40 cases reported in the literature by the time of publication of their article in 2013.
- Another related condition, "congenital human os penis," is also very rare, with only 1 documented reported case in a 5-year-old boy. [2]
- Ossification of the penis is most commonly due to Francois de la Peyronie's disease, which a chronic inflammation of tunica albuginea that leads to penile fibrosis.
- The hardened plaque within the penis reduces flexibility and does lead to a penile bend or curvature during erection.
- Less common aetiologies of penile ossification had been reported, including local trauma to the penis, chronic haemodialysis in patients with end-stage renal disease, chronic inflammatory states as in syphilis and gonorrhoea, and with general metabolic disorders such as gout and diabetes mellitus.
- They had reported a unique case of penile ossification of the corporal bodies with histological confirmation.

Yilmaz et al. [6] reported a 54-year-old man, who had presented to the urology office with a 1-year history of a painless hard proximal penile masses which had involved one-third of the length of his corporal bodies bilaterally. He was neither sexually active nor bothered by symptoms from this penile lesion; he manifested; nevertheless, for workup concerning the possibility of malignancy. He denied having any history of trauma or family history of genitourinary malignancy. He also denied having penile pain, dysuria, irritative voiding symptoms or any other subjective complaints. To the patient's knowledge, the hard mass had been present for many years and had gradually increased in size over time. His clinical examination demonstrated a mobile, rock-hard, calcified mass that was palpable within the base of his penis circumferentially which had involved both proximal corpora. The result of his digital rectal examination was normal and no inguinal nodes were palpable on examination. The results from his routine laboratory assessments were normal. He had a magnetic resonance imaging scan of his pelvis with gadolinium which failed to demonstrate any corporal abnormalities, and no pelvic lymphadenopathy was seen upon the imaging. At that point, the decision was taken to undertake a cystoscopy and excisional biopsy of the calcified mass at the base of his penis. His cystoscopy demonstrated a normal urethra, urinary bladder mucosa, and prostate, which had confirmed that the plaque was external to the urethra. After degloving the phallus, the hard calcified proximal corpora were easily palpated and felt to be entirely replaced by a calcific process. An excisional biopsy was undertaken of the right corpora, with minimal bleeding noted from the calcified corporal body. Histopathology examination of this specimen demonstrated metaplastic ossification to lamellar bone with eosinophilic ossified matrix, lacunar spaces and haversian vascular canals characteristic of bone (see figure 3).

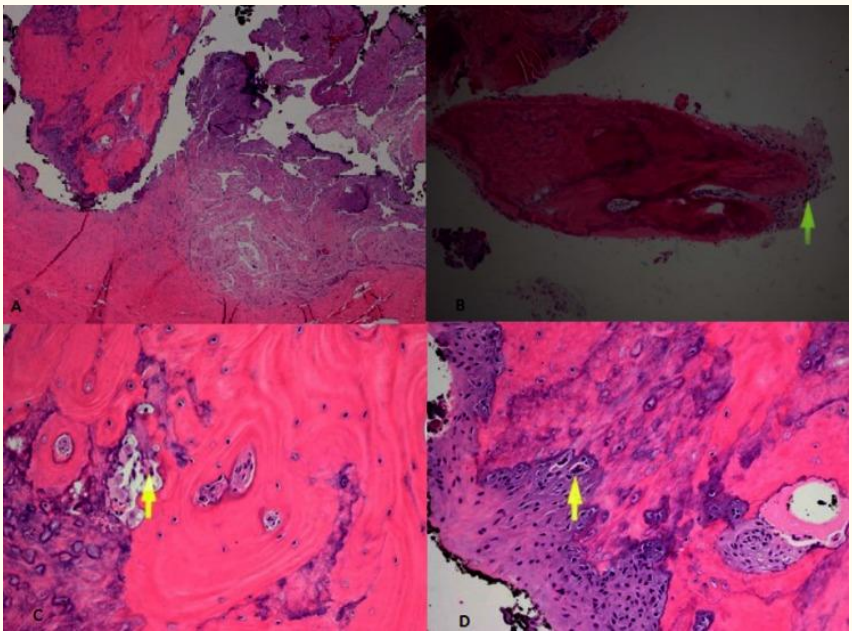

Figure 3 A: Photomicrograph of histological section from the lesion, showing metaplasia of bone tissue in the corpus cavernosum. **B:** Osteoblastic rimming around bone tissue C: Osteoblasts. D: Multinucleated osteoclasts.

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Yilmaz et al. [6] made the ensuing educative discussions:

- The earliest case of penile ossification in the literature was reported by McClellan in 1827, [19] who had reported a case of ossification along the full length of penis.
- In 1899 Chetwood had reported a second case of ossification of corpora cavernosa in a postmortem specimen of a 55-year-old diabetic man.[20]
- In 1933, Vermooten had reported a 19-year-old male in whom a bony mass had developed in his glans penis.[4] The patient also had a gunshot wound at that site 3 months earlier. Presumably his ossification had taken place within fibrosis emanating from this injury.
- A fourth case of penile ossification was reported by Eglitis in 1953. [21] In this case, microscopic examination of sections taken from a grossly normal penis at autopsy had demonstrated bony plaques within the subcutaneous tissue, with no clues as to the aetiology of this ossification.
- In 1962, Elliot and Fischerman had reported a case of a 68-year-old man who had manifested with a 5-cm bone within his corpus spongiosum that required surgical excision.[21] The man had previously been diagnosed with gout; nevertheless, the bone formation was considered to be unrelated.
- Pursuant to these rare cases of penile ossification reported in the early literature, other cases of localized penile ossification secondary to Francois de la Peyronie's disease had been reported.[22]
- In view of the fact that the condition is so rare, controversy had remained as to the aetiology of penile ossification. Some had alluded to a possible connection between human penile ossification and the normally occurring os penis in animals.
- It had been known from the literature that many species of mammals have a bone within their penis, that is located within the septum or within the glans penis itself. [21] These are called or referred to as baculum or os priapi, and their presence enables a male of the species to mate for an extended period of time with a female in the absence of well-developed erectile tissue.
- Baculum vary in size, shape, and function from one species to the next. For example, in whales it measures up to 2 meters in length.
- In wolves and bears this structure is needed to achieve a rapid erectile state of the penis for copulation strategy, while in the dog it serves as a channel for the urethra. According to evolutionists, the os penis has progressively diminished in size over the years. For example, in apes it is insignificantly small in size, measuring only 10 to 20 mm, and in chimpanzees, our closest ancestors, all that remains are small pieces of bone in the glans penis.
- In human beings, the os penis seemed to have been acquired during the aging process because almost all of the cases were observed in 50 years to 80-year-old men. But the atavistic theories concerning the human os penis in evolutionary terms were further supported by the aforementioned case described by Vermooten. [4] Because the patient was young and the bony fragments were present within the glans penis, Vermooten believed that there could be a relation to the os penis seen in animals despite the fact that the ossification site had a history of a bullet wound. His conclusion had bolstered the earlier view which was postulated by Chetwood in 1899, who found fibrous hardenings in his patient's glans penis and had concluded this to be the result of an evolutionary process. [20]
- Finally, Champion and Wegrzyn had reported a case of congenital os penis in 1964 in a 5-year-old boy who had bone within his penis making its curvature fixed from the birth. [2] As with the earlier cases, this observation was considered to strengthen the atavistic viewpoint.
- Despite the early postulates of an evolutionary explanation for the few cases of human penile ossification, more contemporary authors had theorized that there is no relationship between the rare ossification that is seen within certain parts of the fibrous structures of the human penis and the os penis seen in animals.

- In 1924, Furuta had rejected the atavistic postulates because the bone tissue does not fit organically to the form of the penis, instead manifesting as inhibitory factor for copulation especially during erection.[23]
- Similarly, Bett had argued that the os penis in man was unlikely to be a phylogenetic structure in view of its associated barrier to copulation.[23]
- At the time of publication of their article, more recent explanations for the origin of the bone tissue had attributed the ossification to a metaplastic process.
- As reported throughout the literature, the human body is able to form bone tissue or cartilage in places that are affected by pathological conditions when connective tissue is present.
- Bone tissue is understood to originate even in places that have nothing in common with the skeleton, including the mammary gland, salivary gland and the testes.
- Many pathologists accept that fibrous tissue has the ability to transform into a new tissue, including bone, in the unique cases of human penile ossification.[15]

Yilmaz et al. [6] made the following conclusions:

- The aetiology of ossification of penis had remained controversial.
- In majority of cases the ossification process in the penis appears to be a metaplastic process as a result of local trauma or a late manifestation of Francois de la Peyronie's disease.
- In their patient's case, the ossification was not attributable to any previous trauma or medical condition (systemic or local) and its cause therefore had remained a mystery.

Villani et al. [13] stated the following:

- The presence of os penis in man is very rare.
- Up to 1984, only 11 cases had been published.
- A close study of these cases had shown their extreme heterogeneity.
- They thought that the os penis should be considered as a heterotopic bone structure similar to that found in the animal world.
- They had reported their personal case study.

Homero Oliveira de Arruda et al. [24] reported a 59-year-old white man, who was referred with a one-year history of slight pain upon erection and during sexual intercourse. He also had complained of hard plaque near the base of his penis. One year earlier, he had sustained blunt trauma during sexual intercourse, after which he began to experience pain when the penis became turgid. He did not have any history of metabolic disorder or erectile impotency. Examination of his penis demonstrated the presence of a firm fixed mass, which had extended over the proximal third of the shaft of his penis. It was irregular, mass that measured 3.0 cm x 3.0 cm x 2.0 cm, and which had involved the corporal sponge without surface extension. There were no other relevant clinical findings. The results from his routine laboratory evaluations were normal. Radiography on his penis demonstrated irregular calcification within the same position as the palpable mass and in the septum of the proximal inner third of the penis (see figures 4 and 5). The calcified mass was excised surgically via a dorsal midline incision of the tunica albuginea, which had extended across the corpus cavernosum on both sides. The defect of the corporotomy was closed utilising a watertight running 4-0 vicryl suture, without grafting. A quick examination of the specimen demonstrated an irregular mass of greyish brown tissue with hard white calcified foci. His postoperative course was uneventful and the patient reported a full straight erection without pain. Histopathology examination of the specimen demonstrated cancellous bone encompassed by dense collagen tissue. Homero Oliveira de Arruda et al. [24] made the ensuing educative discussions:

- Several conditions had been correlated with penile ossification.
- The most frequent of these is Francois de la Peyronie disease, but correlations with penile trauma, other diseases like metabolic disorders (for example gout and diabetes mellitus), intra-cavernous self-injection of vasoactive agents and chronic haemodialysis had also been reported. [22] [25] [26]
- One extremely rare case of a congenital condition had been reported. [2]
- McClellan was probably the first to report human penile ossification, in 1827, and Gerster and Mandelbaum were the first to undertake a histopathology examination study on the specimen. They concluded that the problem had developed within the connective tissue, from the dorsal side of the septum between the corpora cavernosa, as a result of a metaplastic process.
- In 1933, Vermootenapud [2] described a case of ossification in a man who had suffered a gunshot injury to his penis. Histopathology analysis on the mass demonstrated metaplastic bone marrow and cartilage formation at the fibrosis site.
- Many other cases of small calcifications in the penis had been found by macroscopic observation or X-ray.
- The single case of congenital ossification of the penis was reported by Champion and Wegrzyn in 1964. That child also had a cleft scrotum. [2]
- More recently, Vapnek had reported a case of heterotopic bone formation within the corpora cavernosa of a patient with papaverine-induced priapism. [22]
- It is well known that many animals present a penile bone called "os penis", "os priapi" or "baculum". It is usually located within the glans penis and aids copulation.
- In whales it might measure about two hundred centimetres in length and forty centimetres in circumference.
- In dogs it serves as a channel for the urethra, while in bears and wolves, it is essential for producing a rapid erectile state for copulation. [15]
- It seemed that, during later stages of evolution, the penile bone diminished in size and, in some species, appears as an insignificant structure of 10 mm to 20 mm in length.
- In chimpanzees, man's nearest kin, there is no "os penis", but only a virtual fragment of bone in the glans. [15]
- Ossification of the cavernous tissue in human beings is unrelated to phylogenetic structure. Instead of aiding copulation, as observed in the animals that have such ossification, in men it is sometimes uncomfortable and possibly painful. It is often multiple and found in the shaft as well as in the septum and tunica albuginea, while in animals it is single and situated in the glans. In most of the cases in which human penile ossification was reported, it

appeared to have been acquired during adult life and was related to trauma and Peyronie's disease. [15] [26]

- According to Devine, 6 the fibrous tissue of the plaque could reach maturity without calcification, but calcification is a sign of the end of the healing process and might be present in 25% of the patients.
- It is most likely that ossification, like the plaque in Peyronie's disease, is a scar and not the result of an inflammatory or autoimmune process.
- In all these conditions, human penile ossification appeared to be a metaplastic process.
- Somers and Dawson3 had demonstrated that the disease most likely commences with buckling trauma which causes injury to the septal insertion of the tunica albuginea.
- The fibroblastic tissue thus formed might provide good conditions for metaplastic bone formation. [22] [26]
- There is no good medication for treating Francois de la Peyronie's disease, because few medical management methods had been subjected to double-blind drug testing.
- For surgery to be considered, candidates must present mature and stable disease. It is only recommended when the curvature is enough to impair coital activity.

Homero Oliveira de Arruda [24] concluded that:

Their understanding of this case was that the ossification in their patient probably had developed as a consequence of unusual repair of the tunica albuginea, following some blunt trauma sustained during sexual intercourse.

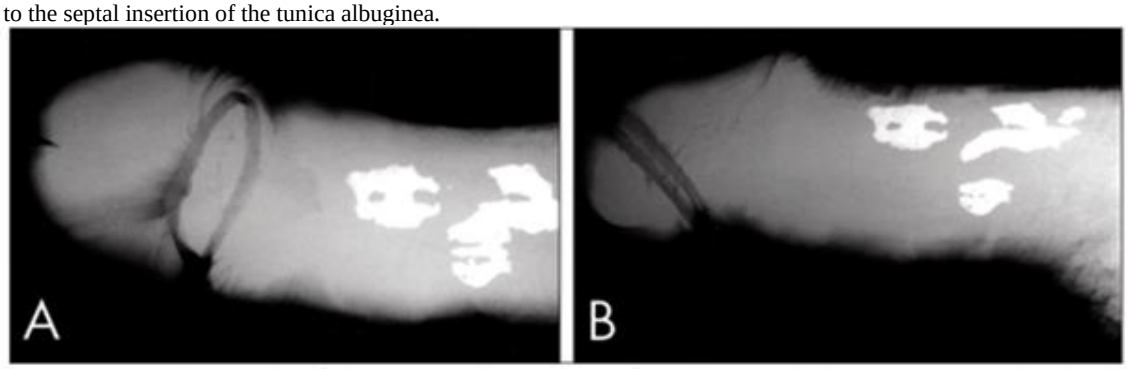

Figure 4. Radiograph of the penis showing ossification inside the septum and in both corpora cavernosa. A: Frontal view; B: Sagittal View. Reproduced from [24] under the Creative Commons Attribution License.

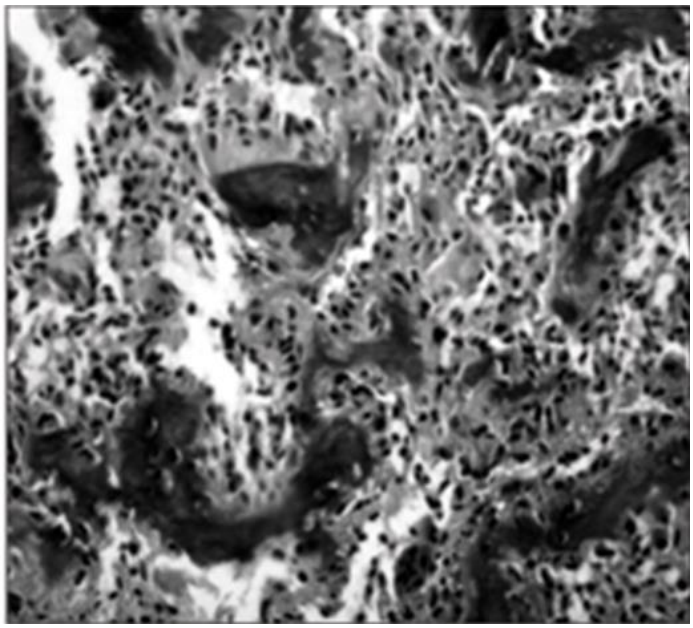

Figure 5. Photomicrograph of histological section from the lesion, showing metaplasia of bone tissue in the corpus spongiosum. Reproduced from [24] under the Creative Commons Attribution License.

Ustriyana et al. [28] stated the following:

- Mineralized Francois de la Peyronie's plaque (MPP) impairs penile function.
- The association, colocalization, and dynamic interplay between organic and inorganic constituents could provide insights into biomineralization of Peyronie's plaque.

Ustriyana et al. [28] reported that human MPPs ($n = 11$) were surgically excised, and the organic and inorganic constituents were spatially mapped utilising multiple high-resolution imaging techniques. Multiscale image analyses resulted in spatial colocalization of elements within a highly porous material with heterogenous composition, lamellae, and osteocytic lacuna-like features with a morphological resemblance to bone. The lower (520 ± 179 mg/cc) and higher (1024 ± 155 mg/cc) mineral density

regions were associated with higher (11%) and lower (7%) porosities in MPP. Energy dispersive X-ray and micro-X-ray fluorescent spectroscopic maps in the higher mineral density regions of MPP had revealed higher counts of calcium (Ca) and phosphorus (P), and a Ca/P ratio of 1.48 ± 0.06 similar to bone. More importantly, higher counts of zinc (Zn) were localized at the interface between softer (more organic to inorganic ratio) and harder (less organic to inorganic ratio) tissue regions of MPP and adjacent softer matrix, indicating the involvement of Zn-related proteins and/or pathways in the formation of MPP. In particular, dentin matrix protein-1 (DMP-1) was colocalized in a matrix rich in proteoglycans and collagen that contained osteocytic lacuna-like features. Ustriyana et al. [28] made the ensuing conclusion and statement of significance:

- This combined materials science and biochemical with correlative micro-spectroscopic approach had provided insights into the plausible cellular and biochemical pathways that incite mineralization of an existing fibrous Peyronie's plaque.
- Aberrant human penile mineralization is known as mineralized Peyronie's plaque (MPP) and often emanates in a loss of form and function.
- This study had focussed on investigating the spatial association of matrix proteins and elemental composition of MPP by colocalizing calcium, phosphorus, and trace metal zinc with dentin matrix protein 1 (DMP-1), acidic proteoglycans, and fibrillar collagen along with the cellular components using high resolution correlative micro-spectroscopy techniques.
- Spatial maps provided insights into cellular and biochemical pathways which incite mineralization of fibrous Peyronie's plaque in humans.

Hsu et al. [14] stated that in order to elucidate the anatomic distal ligament of the human glans penis and associated clinical implications, they compared the structures of the glans penis and corpora cavernosa in dogs, rats, and humans. From May 2001 to March 2003, gross dissection, microscopic examinations, and stains for elastic fibres and collagen subtypes were made in the penises of 11 adult human male cadavers, 7 dogs, and 5 rats. A distal ligament in the human glans penis replaced the os penis which is present in dogs or rats, also termed the baculum, but retained collagen types I and III as common structural and interlocking components, respectively. The intercavernosal septum was complete, and intracavernosal pillars (ICPs) were abundant in dogs, absent in rats, and moderately developed in humans. A tunica with numerous elastic fibres existed to fulfil the requirements of erectile function in humans but not in dogs or rats, since it was essential for establishing tissue strength to serve as a buttress. They would conclude as follows:

- In dogs and rats, the strong os penis is designed for ready intromission and is associated with a pair of well-developed nonelastic corpora to serve as a buttress for the os penis.
- These structures are necessary for the rigorous coitus observed in dogs.
- The less compliant corpus cavernosum is suitable for the flipping action observed in a mating male rat.
- These specific anatomical designs may provide explanations for the individual requirements for the specific physiologic functions that differ from species to species.
- Even though there is no os in the human glans, a strong equivalent distal ligament is arranged centrally and acts as a supporting trunk for the glans penis.
- Without this important structure, the glans could be too weak to bear the buckling pressure generated during coitus and too limber to serve as a patent passage for ejaculation, and it could be too difficult to transmit the intracavernosal pressure surge along the entire penis during ejaculation.
- Given the common histological nature of the distal ligament, which is associated with the tunica albuginea and serves a similar function as the os penis observed in the dog and the rat, one may ask whether the healing process of a tunica may take as long as that required in a bony structure.
- Further research is necessitated to answer this question.

Athanazio et al. [12] reported a 19-year-old patient, who had noticed a deep nodule within the dorsal side of his penis 2 years preceding his presentation. The nodule had been assessed clinically in other service. During this period, no skin lesions were noted. Over the preceding last months, the lesion had rapidly grown causing ulceration in his dorsal skin and invaded corpora cavernosa and corpus spongiosum (as evaluated by imaging studies). An incisional biopsy was undertaken showing a high-grade neoplasm with many non-neoplastic osteoclast-type multinucleated giant cells. An immunohistochemical panel study including SATB2 positivity in mononuclear cells had favoured sarcoma over sarcomatoid carcinoma. A partial penectomy without lymphadenectomy was undertaken (see figure 6) demonstrating a large tumour with pushing borders and 5-cm maximum diameter.

Figure 6: Gross appearance of penile osteosarcoma. Clinical appearance before surgery (**A**) and after resection and formalin fixation (**B**). Cut surface of the specimen. Fleshy tumour involving corpora cavernosa and corpus spongiosum. Upper left section shows uninvolved margin and bottom right shows the uninvolved distal glans (**C**). Reproduced from: [12] under the Creative Commons Attribution License.

The microscopy pathology examination findings of the penectomy specimen mirrored those of the incisional biopsy. The entire tumour was submitted for microscopic evaluation. The tumour had demonstrated highly pleomorphic sarcoma with epithelioid and fusiform cells intermixed with numerous non neoplastic osteoclast-type multinucleated giant cells (see figure 7). Necrosis was identified within < 10% of the whole tumour volume. There was brisk mitotic activity with 30 mitoses per 2 mm^2. Angiolymphatic invasion was also identified. There was no clearcut foci of osteoid matrix; nevertheless, some foci of tumour cells demonstrated lace-like or trabecular deposition of matrix which was difficult to discern from collagenous stroma (see figure 8).

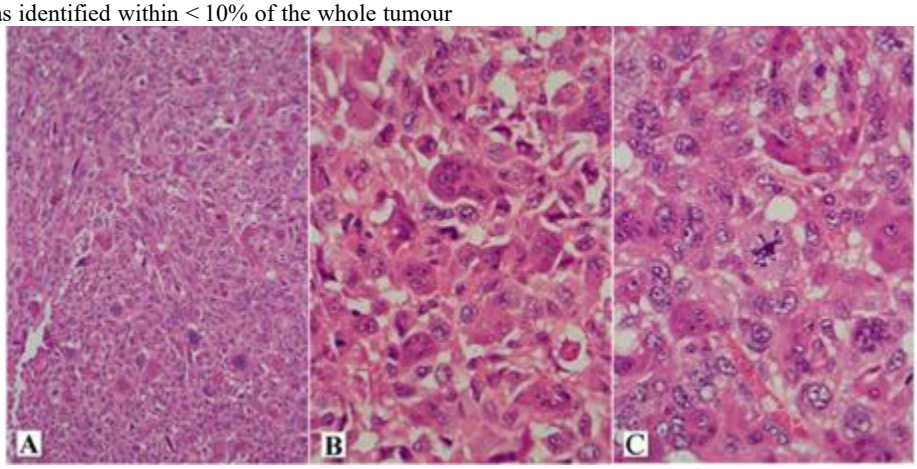

Figure 7: High-grade sarcoma with numerous non neoplastic osteoclast-type multinucleated giant cells (**A**: HE, 10x). It shows brisk mitotic activity (**B**: HE, 100x) and frequent atypical mitoses (**C**: HE, 400x). The whole tumour was submitted for histological analysis and few areas of equivocal osteoid matrix production were observed (**C**: 400x, HE stain). Atypical mononuclear cells show diffuse nuclear staining for SATB2 (**E**: 100x and **F**:400x) while only osteoclast-type multinucleated giant cells stained for marker of histiocytic differentiation, CD68 (**G**: 400x) Reproduced from [12] under the Creative Commons Attribution License

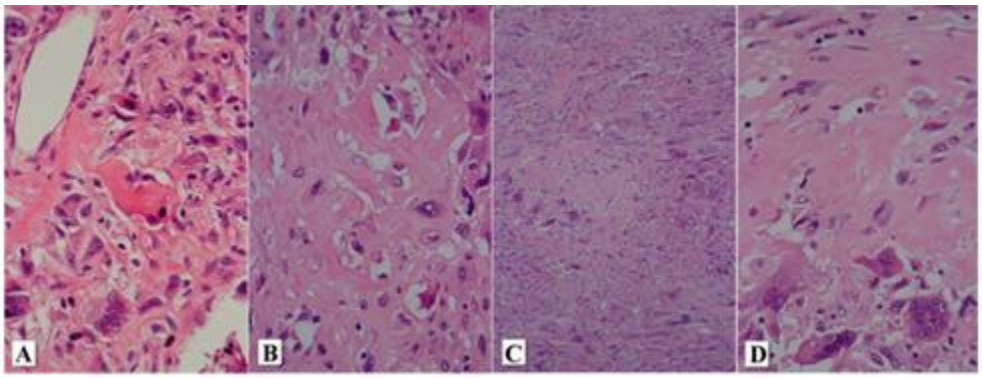

Figure 8: Equivocal areas of osteoid formation that may yield differential diagnosis with collagenous stroma (HE – **A**, 400x; **B**, 400x, **C**, 40x; **D**, 400x). Reproduced from [12] under the Creative Commons Attribution License

In both biopsy and penectomy specimen, atypical mononuclear cells were found to be diffusely positive for SATB2 (a marker of osteoblastic differentiation), CD99 and vimentin. These cells were negative for pan-keratin, GATA3, EMA, SOX10, S100 and ERG. Desmin was focally expressed. CD68 was expressed only in multinucleated giant (osteoclast-like) cells. The tumour cells had exhibited preserved INI1/SMARCB1 expression. See immunohistochemical photomicrographs in Figure 9.

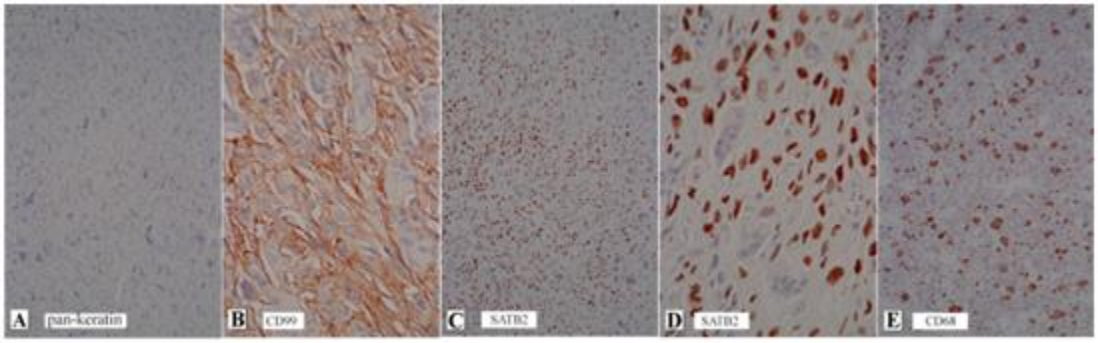

Figure 9: Immunophenotype of a giant-cell rich penile osteosarcoma: no pan-keratin expression (**A**, 40x), CD99 expression restricted to neoplastic cells (**B**, 40x), SATB2 expression in tumour cells (**C**, 40x; **D**, 400x), and CD68 positivity in giant osteoclast-type cells (**E**, 40x) Reproduced from [12] under the Creative Commons Attribution License

The radiology imaging studies had excluded any bone primary tumour. The patient had developed lung metastases after ten months of his follow up.

Athanazio et al. [12] made the ensuing educative discussions:

- Special AT-rich sequence-binding protein 2 (SATB2) is a product of gene implicated in cleft palate defects (Berg & Schaeffer, 2017) [29].
- It is utilised in Diagnostic Pathology as a immunohistochemical marker that, among carcinomas, is sensitive and specific for colorectal and appendiceal primary sites.
- It is also expressed in benign and malignant neoplasm with bone differentiation and, among neuroendocrine carcinoma, it is expressed in most Merkel cell carcinomas.
- It is also usually expressed by epithelium of the lower gastrointestinal tract, brain, nongerminal centre lymphoid cells, ductal epithelium of the testis and epididymis.
- Among high-grade soft tissue sarcomas, SATB2 expression could be utilised as an indicative of extra-skeletal osteosarcomas with poor matrix production (Yamashita & Hameed, 2020) [30]
- The recent new WHO Classification had stated that "SATB2 immunoreactivity could be useful for the detection of osteoblastic differentiation when immature osteoid is difficult to distinguish from collagenous stroma" (Yamashita & Hameed, 2020 [30].
- This tumour also exhibited focal areas of p63 expression. Staining was always weak.
- Rather than evidence of squamous differentiation in this case, they had interpreted this feature as expected in giant cell tumours (both bone and soft tissue primaries) and osteoclast-rich osteosarcomas (Shooshtarizadeh et al., (2016) [31]; Jo & Fletcher, 2011) [32].
- Primary penile extra-skeletal osteosarcomas are exceedingly rare.
- A recent report had also shown the feature of osteoclast-rich areas (Wu et al., 2012). [33]
- The same is true for extra-skeletal osteosarcomas of other sites (Oh & Chang, (2017) [34].
- Penile primary extra-skeletal osteosarcoma is very rare and that would be the eighth described in English literature (Wu et al., 2012) [33]; (Bastian et al., 2003) [35]; (Fraser et al., 2000) [36].
- The first in which recently available SATB2 immunohistochemistry was helpful to identify osteoblastic differentiation. The 2-year evolution is a more protracted course than expected from osteosarcomas of the bone. Interestingly,

other case of giant cell rich- extra-skeletal osteosarcoma of the penis was diagnosed as a small nodule (1.2 cm) with 1 year period of slow growth (Wu et al., 2012) [33].

- The main differential diagnosis in this case would be melanoma with osteosarcomatous differentiation and sarcomatoid carcinoma.
- Melanoma was excluded by absent expression of S100 and SOX10.
- Sarcomatoid carcinoma was considered in the differential diagnosis, but the patient had experienced a two-year growth of a deep palpable nodule with no relationship with penile skin or urethra.
- The dorsal skin was ulcerated after rapid and recent growth. The urethra was uninvolved in the resection specimen, even though the erectile tissue of corpus spongiosum was infiltrated. The uninvolved urethra and lack of GATA3 expression argue against a sarcomatoid urothelial carcinoma. Pan-keratin was negative. P63 expression - as discussed above - cannot be used in the differential between squamous carcinoma and giant cell rich tumours of soft tissue. In addition, sarcomatoid squamous cell carcinoma is typically an HPV-independent neoplasm that are much more common in older patients.
- Preserved INI1/SMARCB1 expression had argued against the diagnosis of epithelioid sarcoma.
- They had also considered the possibility of metastatic osteosarcoma. Radiology imaging of the skeleton, nevertheless, demonstrated no suspicious bone lesions.
- Soft tissue neoplasms of the penis are rare, and the incidence is difficult to estimate in view of the fact that these cases are mostly documented as case reports.
- The most common benign soft tissue tumours of the penis are those with vascular differentiation including haemangioma (including epithelioid haemangioma), angiokeratomas an lymphangiomas.
- The most common malignant sarcomas of the penis are leiomyosarcoma and vascular neoplasms (such as angiosarcoma, Kaposi sarcoma and epithelioid haemangioendothelioma) (Amin et al., 2014). [37]
- Some recent examples of soft tissue malignancies reported as primary of the penis include Kaposi sarcoma in the set of HIV infection / transplant patients (Tammam et al., 2022) [38]; Anderson et al., (2021) [39], post-radiation sarcomas (Rodriguez-Perez et al., 2021) [40]; Hoyos et al., 2922) [41] and primitive neuroectodermal tumor (PNET)/Ewing's sarcoma (Asari et al., 2021) [42]; (Krakorova et al., 2021) [43]; Estaphanous et al., (2022) [44].
- Differentiating true penile sarcomas from sarcomatoid carcinoma is crucial for prognosis and treatment, and this including even the proposed surgery since lymphadenectomy may considered for sarcomas but is obligatory for sarcomatoid carcinoma since 75–89%% of sarcomatoid squamous cell carcinomas of the penis show nodal metastasis at the time of diagnosis (Alvarado-Cabrero et al., 2022) [45].

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

- In high-grade sarcomas, including in the penis, SATB2 staining might be useful to identify extra-skeletal osteosarcoma.

Wu et al. [33] stated the following:

- Extra-skeletal osteosarcoma (EOS) is a malignant mesenchymal neoplasm which is located within soft tissues.
- It is a very rare disease, and accounts for only 4% of osteosarcoma and 1% of soft tissue sarcomas [46].
- Clinical diagnosis of EOS is difficult, X-ray, CT and magnetic resonance imaging (MRI) techniques might be helpful for the detection of the primary site, volume and relationship with the encompassing tissue of the tumour [47], and significant to the choice of operation.
- Careful histopathology analysis is necessary to establish the final diagnosis.

Wu et al. [33] reported a 68-year-old man, who had manifested with a tender subcutaneous nodule of his penis. The nodule had localized pain and grown from about 0.3 cm × 0.3 cm × 0.3 cm to 1.2 cm × 0.8 cm × 0.5 cm in a year. Upon clinical examination, a 1.2 cm × 0.8 cm × 0.5 cm mass was palpated that measured 0.8 cm to the right to coronary sulcus. There was no red swelling of the skin and abnormal temperature. The edge of the mass was clear. The mobility of the mass was poor. The scrotum and testis of the patient were normal, and there was no touched intumescent lymph node in his inguinal region. The operation was undertaken in May, 2009. Wu et al. [33] stated that the patient received 1% Lidocaine injection at the root of his penis and the surgery was undertaken. The skin and subcutaneous tissue were dissected to segregate the mass. The tumour was noted to have slightly adhered to the encompassing tissue but did not invade to tunica albuginea. Finally, the mass was excised and a histological diagnosis was made. The patient was followed up for 10 months, and then lost to follow-up. Macroscopy examination of the specimen demonstrated that the neoplasm without envelope was greyish-white, greyish-pink and 1.5 cm×1 cm × 1 cm. The cut surface of the mass was greyish-white and rigid, and had sense of grit and no weaving shapes.

Microscopy examination of the specimen demonstrated that the cells within the tumour were widespread and irregular, mainly spindle and ovoid. The cytoplasm of the cells is basophilic. The nuclei were obviously atypical, mostly clostridial form and polygons. Massive bone matrix which coexisted with multinucleated giant cells could be found everywhere within the tumour. The tumour cells were noted to be in palisade arrangement and most commonly seen in and around the bone matrix. In some instances, 3.5 to dozen nuclei could be visualised in a single multinucleated giant cell.

Wu et al. [33] made the ensuing discussions:

- EOS is a malignant mesenchymal neoplasm which is located in soft tissues without direct attachment to skeletal system.
- EOS was first reported by Wilson in 1941[48].
- It is extremely rare, and accounts for only 1% of soft tissue sarcomas.
- Distinct to osteosarcoma usually afflicting young people, EOS mainly afflict people who are older than 50 years, and the mean age was 54.6 years and the ages of the patients had ranged between 16 years and 87 years) [49] [50].
- Trauma and radiotherapy are well- documented predisposing factors [51].
- Majority of people consider that multi-potential-mesenchymal cells develop to allotypic osteoblasts, that lead to the growth of EOS.
- The precise origin was not clear.

- EOS most commonly arises in the retroperitoneum and the muscles of thighs and limb girdles, rarely in lung, prostate gland, scalp, mammary gland, spermatic cord, pelvis and orbit.
- EOS of the penis is very rare; only six other well-documented cases had been reported in the literature in English [52] [53] and none in Chinese. The main types are osteoblastoma, chondroblastoma and fibro- blastoma.
- The tumour which is full of giant cells is extremely rare. There was no significant difference in clinical manifestation between EOS and other soft tissue sarcomas.
- Localized swelling and pain are commonly encountered.
- X-ray examination demonstrates scattered floccules or patchy high-density opacities in parenchyma, and the tumour has no connection with the adjacent bone tissue which is the characteristics of EOS. But the iconographic characteristic has no specificity. It is hard to be differentiated from with other malignant tumours, the final diagnosis must depend upon histopathologic examination.
- The volume of EOS has ranged from 2.5 to 20 cm^3 and mostly lobulated, and 20% of the tumours were described as pseudo-encapsulated masses and with satellite nodules surrounded. The cut surface ranged from grey-white to tan-yellow to dark-red, depending upon the degree of mucification, haemorrhage, and necrosis. Some tumours demonstrated focal to cystic change. Except for the above-mentioned, there are some other subtypes such as: epithelioid osteosarcoma, clear-cell variant osteosarcoma, malignant fibrous histiocytoma and giant cells-rich osteosarcoma [54] [55] [56] [57]. They are all short of unique bio- characteristics, and have no significance to therapy and prognosis. The distribution mode, volume and number of nuclei of the giant cells they had reported were similar to those of giant cell tumours, and the number of osteoclast- like multinucleated giant cells increased obviously. But massive bone trabecula and allotypic tumour cells had more density and uniformity than the giant cells. According to the result of immunohistochemistry, they had concluded thar the tumour was the giant cell-rich type of EOS.
- Lee, et al. [46] introduced the diagnostic criteria of EOS as follows: (I) in soft tissue and not attached to bone or periosteum; (II) osteosarcoma with the same image; and (III) produce osteoid or cartilaginoid matrix. The case of giant cell-rich EOS should be distinguished from the following diseases in pathology: (I) Myositis ossificans: Patients usually have a history of trauma. Patients often have masses with the construction of active proliferation fibrous tissue, irregular osteoid tissue and mature trabecular bone. (II) Malignant mesenchymal tumours: In addition to components of osteosarcoma, it should also find other malignant mesenchymal elements, such as rhabdomyosarcoma, and liposarcoma. (III) Giant cell tumour: They both have affluent multinucleated giant cells, but giant cell tumour has no formation of tumorous bone trabeculae in spindle cells. (IV) Periosteal osteo- sarcoma: The mass is often located in the cortical bone surface, and closely integration and the formation of radial bone can be seen.
- EOS was reported to portend an exceptionally poor prognosis.
- EOS is generally involved in invasion and metastasis.
- The recurrence, transfer and 5-year survival rates were 45%, 65% and 25% to 37%, respectively.
- In view of the fact that the exact preoperative clinical diagnosis is difficult, so patients with newly diagnosed EOS usually underwent local mass excision, and often died of metastasis of lung, liver, lymph nodes, bone or soft tissue in 2 to 3 years.

Conclusions

- Rare cases of ossification of penis tend to be reported sporadically and clinicians need to have a high index of suspicion for ossification within the penis in order to establish the diagnosis and to provide appropriate treatment for their patients.

Conflict of Interest – None

Acknowledgements

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