Lesions and neoplasms of the penis: a review

Lesions and Neoplasms of the Penis-A Review

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Precis:

Lesions and neoplasms of the penis are reviewed.

Abstract:

In addition to practitioners who care for male patients, with the increased use of high resolution anoscopy, practitioners who care for women are seeing more men in their practices as well. Some diseases affecting the penis can impact on their sexual partners. Many of the lesions and neoplasms of the penis occur on the vulva as well. In addition, there are common and rare lesions unique to the penis. A review of the scope of penile lesions and neoplasms that may present in a primary care setting are presented to assist in developing a differential diagnosis if such a patient is encountered, as well as for practitioners who care for their sexual partners. A familiarity will assist with recognition, as well as when consultation is needed.

Key words: Penile neoplasms, penile diseases.

Introduction:

In addition to urologists and other practitioners who care predominantly for male patients, with the increased use of high resolution anoscopy, practitioners who primarily care for women are seeing more men as well. Some diseases affecting the penis can impact on their sexual partners. A wide variety of conditions can affect the penis, both common, and case-report worthy. Many are identical to lesions affecting the vulva, and there are unique lesions as well. This review is provided to provide familiarity of some of the more commonly encountered as well as significant lesions that may be seen in a primary care setting. This is aimed to assist in developing a differential diagnosis if a patient with such a lesion is encountered, as well as for practitioners who care for their sexual partners. A familiarity will assist with recognition, as well as when consultation is needed.

Anatomy & Histology

The anatomy and histology of the penis are demonstrated in figure 1(fig 1)(1,2).

Pearly Penile Papules

These benign small papules are often found in a ring around the coronal sulcus, and are often multiple(figure 2). They are a normal variant. Histologically they are composed of dense connective tissue(3).

Fordyce Spots

Fordyce spots, prominent sebaceous glands, can be seen along the shaft of the penis(figure 3), and are of no clinical significance. They tend to appear in adolescence(4).

Cysts of the penis

The majority of penile cysts are median raphe cysts, and occur ventrally along the median raphe, anywhere from the urethra to the perineum. They are usually asymptomatic, and may have a variety of linings, including columnar, squamous or mixed. Other less common cysts include epidermal inclusion cysts(also called sebaceous cysts) and dermoid cysts(5).

Priapism

Priapism, a prolonged painful erection lasting generally over four hours can occur spontaneously, or be associated with drugs utilized for erectile dysfunction. Other medications, hematologic disorders, including sickle cell disease, neurologic disorders, and several other uncommon medical conditions may also result in priapism. Most cases are ischemic, due to venous engorgement of the corpora cavernosa, much like compartment syndrome, and requiring emergent treatment. Subsequent erectile dysfunction may occur, even with treatment. The mechanism of ischemic priapism may be intravascular, or due to muscular tissue inadequately augmenting venous outflow. A less common non-emergent, often painless variant is due to increased arterial flow from arteriovenous fistulas. While the treatment of priapism usually

requires a urologic specialist, terbutaline has been used as a first line therapy in the emergency room(6).

Peyronie's disease

Peyronie's disease was first described in 1743 by François Gigot de La Peyronie , who was a surgeon to Louis XV, and known for elevating surgery above the level of barber to the level of physician(7). Peyronie's disease is a chronic incurable condition of unknown etiology. Chronic inflammation of the fibrous septa below the tunica albuginea leads to nodularity, with curvature of the penis, with pain sometimes precluding intercourse. Etiology is unknown, but there may be a hereditary component, as some patients also have Dupuytren's contractures. Clinically, the disease tends to go through an active phase, with painful erections, before entering a quiescent phase with stabilization of the curvature deformity and resolution of the pain. Erectile dysfunction may occur(8). Oral therapies have been used, including vitamin E, but none has been shown to provide definite benefit(8). Therapy has included steroid injections and surgery, but the condition is difficult to treat(3). More recent therapies have included injectables such as verapamil, interferon and collagenase(8) as well as transdermal electromotive administration of verapamil and dexamethasone(9).

Infectious & Inflammatory Lesions

A wide variety of dermatologic conditions that can occur elsewhere on the body may affect the penis. Sexually transmitted diseases, including gonococcal or chlamydial urethritis, as well as herpes, chancroid, or syphilis may also manifest on the penis(6). A few conditions specific to the penis will be considered in the following section.

Molluscum Contagiosum

Molluscum is most often a pediatric disease, but it may affect the penis as it does the vulva, and be sexually transmitted. As such, although lesions can regress, they have been treated with cryotherapy(4) or scraping of the lesions to avoid spread. Grossly they appear as small papules with umbilications. Histologically, these umbilications contain cells with characteristic intracytoplasmic inclusions (figure 4).

Balanitis

Balanitis, inflammation of the glans, or balanoposthitis, which also includes the foreskin, may be due to many causes, including bacteria, fungi, Trichomonas, a variety of dermatologic conditions such as psoriasis, as a manifestation of a systemic disorder, or after exposure to an irritant or trauma(3). Bacterial balanitis is usually a hygiene-related condition of the uncircumcised, easily treated, although it may lead to phimosis. Rarely, in the immunosuppressed, the infection may become life-threatening(3).

Candidal balanitis

Candidal balanitis deserves mention due to its possible association with candidal vaginitis in the female partner, which must also be treated. The differential diagnosis is large, and candidal balanitis must be distinguished from sexually transmitted diseases and other infections and dermatoses of the glans. Diabetes increases the risk of candidal balanitis(10). There is no major risk to a male for developing balanitis if his female partner has vulvovaginal candida(10). Although there may be cases of sexual transmission of candida from men to women(11), evidence does not support this as a significant risk(12). Rarely a male may develop a hypersensitivity reaction rather than candidal infection to a female partner's candida(3).

Plasma Cell Balanitis

Plasma cell(Zoon's) balanitis, a condition of unknown etiology, is seen predominantly in older uncircumcised men(3,13). It can occur on the vulva as well. Clinically it appears as a well-circumscribed shiny bright orange-red lesion involving the inner prepuce or glans(13). Histologically the lesion is composed of abundant plasma cells admixed with other chronic inflammatory cells, hemosiderin, and prominent vessels, with changes in the overlying squamous epithelium(13). Thought to be an inflammatory condition, circumcision has been used as therapy(13), as have topical steroids(14).

Micaceous Balanitis

A rare condition of elderly uncircumcised or late circumcised men, pseudoepitheliomatous keratotic and micaceous balanitis is postulated to be related to either verrucous carcinoma or lichen sclerosus, and is considered a precursor lesion for squamous cell carcinoma. The lesion is hyperkeratotic, and may be asymptomatic, but its periurethral location and thick plaques may lead to multiple urinary streams, termed "watering can penis"(15). Grossly the lesion appears as plaques or excrescences with scaling on the glans, which may ulcerate or crack. Histology is nonspecific, with pseudoepitheliomatous hyperplasia, hyperkeratosis, parakeratosis, acanthosis and nonspecific dermal lymphocytic and eosinophilic inflammation. Mild basal atypia may be seen(16). The differential diagnoses include penile horn(see below), squamous cell carcinoma, verrucous carcinoma, HSIL, psoriasis, and keratoacanthoma(17)

Condyloma accuminata

Condyloma accuminata may occur in both the circumcised and uncircumcised penis, and involve the shaft, the glans, and the urethral meatus and urethra as well. Urethral occult lesions contribute to recurrences. As in women, condyloma acuminata is a sexually transmitted disease associated with HPV types 6 and 11. Female partners of men with condyloma may have vulvovaginal lesions, as well as anal lesions, although anal lesions are greater in men who have sex with men. Immunosuppression is associated with more florid and difficult to eradicate lesions. Oropharyngeal transmission of condyloma can occur, as well as transmission of high risk HPV, and a subset of oropharyngeal cancers are attributable to high risk HPV. Patients and their partners with condyloma should be screened for other HPV-related and other sexually

transmitted diseases. The HPV vaccine is expected to significantly decrease the burden of HPV-related disease in men as well as women, with male vaccination increasing protection, as has herd immunity from vaccinated females(18) .

Bowenoid Papulosis

Bowenoid papulomsis is a clinical diagnosis for a specific presentation of HSIL. Bowenoid papulosis is an HPV-related lesion(usually HPV 16), composed of multiple flat macules or papules of varying color, histologically resembling peIN, however it occurs in younger men less than 40 years old, and tends to regress. It is more common in circumcised men, as opposed to peIN, which is more common in uncircumcised men(3). While bowenoid papulosis is thought to have a low risk of progression, rare cases have developed into squamous cell carcinoma(19). Hence biopsy of suspicious lesions(figure 5) and subsequent excision of the lesions, cryotherapy, or electrocautery are treatment modalities, with some utilization of imiquimod or Moh's surgery, and even 5-FU has been utilized occasionally(20).

Lichen Sclerosus(Balanitis Xerotica Obliterans)

Lichen sclerosus of the penis is sometimes also termed balanitis xerotica obliterans. Analogous lesions of the vulva and penis are shown in table 1. Penile lichen sclerosus can be seen in children as well as adults. Clinically patients may show pain, burning, pruritis, and urinary symptomatology. Lichen sclerosus may lead to phimosis, a known risk factor for squamous cell carcinoma, and perhaps the risk factor for lichen sclerosus-associated squamous cell carcinoma(21). Some authors feel that histologic confirmation by biopsy is mandatory(22). The main therapy is circumcision, with topical and intralesional steroids used as cotherapies(22).

There are no established protocols for follow-up. In a study of boys(mean age 6) who underwent circumcision for medical indications, 15% had lichen sclerosus, of which over half were unsuspected(23).

Penile horn

Cutaneous horns elsewhere are generally benign cosmetic nuisances, however penile cutaneous horns are associated with an approximately 30% risk of developing into low grade squamous cell carcinoma(19). Cutaneous horns are protuberant conical(hence the name) nodules composed of keratin, and may be secondary to a variety of conditions underlying the horn that can cause chronic inflammation. The base of the lesion is composed of a proliferative lesion such as a seborrheic keratosis, actinic keratosis, or squamous cell carcinoma, hence may reflect a benign, premalignant or malignant origin(24).

Premalignant Neoplasms:

Penile Intraepithelial Neoplasia(peIN)

The LAST terminology(25) classifies HSIL of the penis as peIN, however Bowen's Disease and Erythroplasia of Queyrat are clinical descriptive names sometimes used by urologists for the same histopathologic process. Clinically peIN appears in patients over 40 years old(26) as a single scaly red-brown plaque, often on the hair bearing shaft, in distinction to the multiple lesions, glans, preputial or shaft location, and younger age of patients(under 40) (26) with

bowenoid papulosis. Erythroplasia of Queyrat is a bright red well-defined, minimally raised plaque. Histologically, the appearances are identical(see figure 5). Therapeutic options are similar to those in female patients with HSIL of the vulva. peIN is associated in most cases with HPV, often 16(27). It is important to biopsy any suspicious areas, which should be treated. Modalities include simple excision, laser, with some use of 5-FU, and imiquimod(26). peIN has also been separated into HPV-positive and negative lesions (21), analogous to HSIL and differentiated VIN of the vulva.

Paget's Disease

Paget's disease is a form of intraepithelial carcinoma of stem cell origin, although it can become invasive. Penile Paget's disease is similar in appearance and behavior to the more common vulvar Paget's, and is occasionally associated with skin appendage or internal malignancies(20). It can involve the scrotum. Grossly, a mixed red and white lesion is seen. Histologically, the large eosinophilic Paget cells may be seen percolating up the epithelium. Like the vulvar counterpart, the lesion can extend beyond the visible margin, contributing to recurrences.

Malignant Neoplasms of the Penis

Carcinoma of the Penis

Most penile carcinomas occur on the glans, prepuce or coronal sulcus(3). The appearance of these tumors is variable, and it may be endophytic or exophytic, and of varying colors, much like vulvar squamous cell carcinoma, hence any suspicious lesion should be biopsied. The most common histology by far is squamous cell carcinoma(SCC). Under the WHO terminology, there are a variety of histologic subtypes of varying prognostic significance(28). A detailed histologic

review is available for those interested readers(29). Penile squamous cell carcinoma is uncommon in developed nations, but not so rare in developing countries(30). Penile carcinoma represents about 1% of male cancer deaths in the United States, but is significantly greater in countries where circumcision is not routine(31). SCC of the penis can be an HPV 16 and 18-associated lesion(30). In one study, 42% of cases of penile carcinoma had HPV DNA(32). In a literature review, prevalence of HPV in squamous cell carcinoma has ranged from 22-77%, with HPV 16 implicated in 25-94.7% of the cases, and HPV 18 in 10.5-55.4%(33). Penile carcinoma occurs almost exclusively in the uncircumcised penis, and phimosis increases the risk significantly(30). Smoking cigarettes is also a risk factor. Although uncommon, a risk factor of over 58 times is psoralen plus ultraviolet light A (PUVA) therapy for psoriasis(34). Much as in women, there is an association with lichen sclerosus(balanitis xerotica obliterans) in HPV-unrelated carcinomas(20). SCC of the penis is an aggressive disease. It is imperative to detect it early to effect a cure, as the prognosis for advanced disease remains poor. While traditionally partial, and occasionally total penectomies have been employed, less aggressive therapies, including Moh's surgery, and sentinel node sampling, have been integrated into the armamentarium for appropriately selected cases. Prognosis is related to tumor grade, depth of invasion, and lymph node involvement(35). The Lower Anogenital Squamous Terminology(LAST) has supported the AJCC T1a staging as the definition for superficially invasive squamous cell carcinoma(SISSCA) of the penis(25,36). Superficially invasive lesions are amenable to less aggressive therapy. Unlike other lower genital sites, a measured depth of invasion is not part of the criteria, which defines T1a(SISSCA) as a tumor that invades subepithelial connective tissue but has no lymphvascular involvement or high grade differentiation(36). Because of the rarity of penile squamous cell carcinoma, particularly in the

United States, well-controlled clinical trials are lacking. It has been suggested that due to more studies, as well as overlap in anatomy and biology of disease, that aspects of treatment for vulvar cancer can be considered for application to penile carcinoma, including adjuvant radiation after lymph node dissection, and neoadjuvant chemoradiation for advanced vulvar cancer may have a place in the treatment of penile carcinoma(37).

Verrucous carcinoma

Verrucous carcinoma, a subtype of squamous cell carcinoma(28) similar to verrucous carcinoma of the vulva, is a large warty cauliflower-like lesion that may extend deeply, recur locally, but is unlikely to metastasize. Sufficiently deep biopsy is required to provide confirmatory histopathology as there is minimal atypia, and the tumor-native tissue interface needs to be evaluated to confirm this diagnosis. In one study, 3/31 cases of penile verrucous carcinoma showed HPV infection(38), one HPV 11, one HPV 51,52, and one HPV 31,33,44,45. So while HPV may be associated, strong causality has not been established.

Other Primary Malignancies:

Rare penile malignancies include malignant melanoma, which can occur on the glans, prepuce or meatus, as well as in the urethra. It is aggressive and usually advanced at diagnosis.(8,39). Primary malignant lymphoma of the glans has also been reported(40), as has Kaposi's sarcoma(41), and basal cell carcinoma(42). Soft tissue sarcomas are exceptionally rare.

Conclusions:

A review of the scope of penile lesions and neoplasms that may present to non-urologists is presented to aid in recognition, as well as appropriate consultation. As more colposcopists are expanding into high resolution anoscopy, practitioners who are newly seeing men should evaluate the penis and scrotum as well as the anorectum. Suspicious lesions should be biopsied.

Abbreviations and Acronyms:

HPV-Human papillomavirus

HSIL –high grade squamous intraepithelial lesion

5FU-5-fluorouracil

LAST- Lower Anogenital HPV-associated Squamous Terminology

peIN-penile intraepithelial neoplasia

VIN-vulvar intraepithelial neoplasia

SCC-squamous cell carcinoma

Who-World Health Organization

SISSCA-superficially invasive squamous cell carcinoma

AJCC-American Joint Committee on Cancer

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