Clinical considerations of penile cutaneous lesions

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It is not uncommon for family physicians, dermatologists, and urologists to encounter patients in their practices with penile cutaneous lesions. The differentiation of premalignant lesions from benign dermatosis can be a challenging task due to the rarity of some of these conditions, as well as the overall low incidence of penile neoplasms in industrialized nations.[1] A retrospective British study found that one-fifth of patients with penile carcinoma are first referred to specialists other than urology.[2] Thus, early investigation is fundamental for the treatment of these lesions, which may have already suffered significant diagnostic delays due to either lack of knowledge for these conditions or patient-related stress/embarrassment from genital malady.

The etiology for these cutaneous lesions can range from benign causes, which can be classified as infectious vs. non-infectious, to neoplastic conditions, along with associated risks of morbidity and psychosocial distress. Clinical presentation of these lesions can guide diagnosis and treatment in the majority of cases. A biopsy is indicated whenever diagnosis is in doubt. Irregular erythematous patches or keratotic plaques should have prompt evaluation due to the possibility of carcinoma in situ. Most benign lesions can be managed with observation or corticosteroids, while neoplastic lesions typically will require more extensive excision, along with a thorough workup.

This review aims to provide a practical approach to the various aspects of diagnosis and management of penile cutaneous lesions. It is not a complete list of diagnoses, but rather a compilation of some of the most encountered ailments in a community practice. In some cases, a multidisciplinary approach in formulating treatment recommendations for those with suspected or confirmed cancer is also recommended. It is hoped that this primer will provide clinicians with a basic understanding of the different diagnostic and therapeutic approaches in the management of penile lesions.

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Patient presentation, differential diagnosis, and management of penile lesions

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Introduction

Penile lesions may arise from the squamous epithelium of the glans, prepuce, or shaft. Due to often delayed medical presentation after initial onset, it is necessary for the urologist to appropriately and effectively diagnose and manage these lesions in order to optimize outcomes and minimize morbidity. Herein, we review the differential diagnosis and basic diagnostic approaches of penile lesions. We emphasize the need for awareness of premalignant and malignant tumours. We also review common office-based treatment modalities for benign and malignant lesions.

Diagnostic evaluation of a penile lesion

A thorough history and physical examination is required, with attention to previous sexual history, including contraceptive use and any previous sexually transmitted infections. Other useful information includes previous tobacco and drug use, circumcision status, and associated sexual and urinary symptomatology. A thorough genital examination with a complete skin survey should be enough to characterize most cutaneous anomalies. Assessment of the inguinal nodes for nodularity or fixation can also be noted at this time. For indeterminate lesions, workup can involve different diagnostic considerations, especially when systemic findings are present. Biopsy is reserved for an unclear diagnosis, and should be promptly performed if neoplasm is high in the differential diagnosis. If a malignant tumour is found, consideration for magnetic resonance imaging (MRI), with possibly induced erection, may be performed to rule out corporal invasion and improved clinical staging. A tertiary referral centre should also be considered for larger size lesions requiring further evaluation.

Classification of penile conditions

Benign conditions

The most relevant benign penile growths include cysts, syringomas, seborrheic dermatitis, pearly papules, and Fordyce spots.[1] Penile cysts are rare lesions, typically asymptomatic, and usually do not interfere with sexual or urinary function. Most of them are present since birth and are classified as acquired or pseudocyst and true cysts, which are mostly congenital.[2] The most common cystic lesion of the penis and prepuce is the smegma cyst, sometimes called "smegmoma." These cysts are usually found under the unretractable foreskin and they appear as small, yellowish lumps due to smegma content. Preputial cysts are generally classified as median raphe or urethroid cysts and epidermoid or follicular cysts.[3] Most penile cysts are harmless and do not require any treatment.

Penile syringomas are benign, small, soft, flesh-to-yellow-coloured, dermal papules that are derived from the intraepidermal portion of eccrine sweat ducts. They are extremely rare and are typically asymptomatic. Syringomas of the penis usually present as multiple lesions (Fig. 1) on the dorsal and lateral aspect of the penile shaft in about 91% of patients. Treatment of penile syringomas is elective and similarly to penile cysts, is performed based on the patient's preferences.[4]

Penile Fordyce spots are heterotopic sebaceous glands that can occur on the penile shaft, usually the ventral surface. They were named after an American dermatologist, John Addison Fordyce, who first described them in 1896. Typically presenting after puberty, they become a concern to adolescent and adult men given the occasional resemblance to genital warts. Treatment is not necessary other than for cosmetic reasons, since it is an anatomical variation and a benign condition.[5]

Hirsuties coronae glandis, also known as pearly penile papules, are benign lesions of the penis. They are considered a normal anatomical variant. The prevalence of penile pearly papules is diversely appreciated and ranges from

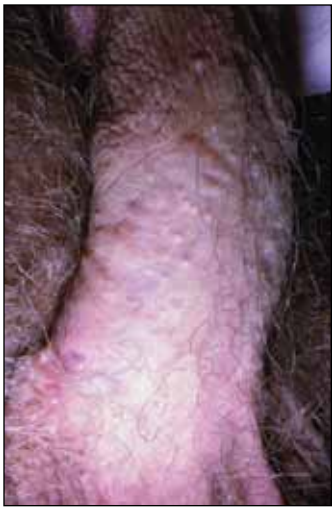

Fig. 1. Penile syringomas present as multiple flesh-coloured papules. Adapted from: Cohen PR, et al. Penile syringoma: Reports and review of patients with syringoma located on the penis. *J Clin Aesthet Dermatol* 2013;6:38-42.

14–48% of males.[6] The papules are flesh-coloured or white, dome-shaped or filiform (Fig. 2). Because of the benign nature of pearly penile papules, as well as their possible resolution with age, treatment is not indicated unless for cosmetic reasons. Healthcare providers may use ablative lasers for removal or liquid nitrogen as cryotherapy.

Seborrheic dermatitis is a papulo-squamous disorder of the skin, which usually affects the oily areas where sebum production is high. It may be caused by the proliferation of a skin pathogen known as *Malassezia* in its yeast form, although this is controversial.[7] Seborrheic dermatitis of the penis appears as red plaques that are scaly in nature and run along the glans of the penis and its shaft. Treatment mainly consists of keratolytic agents, topical or oral antifungals, or topical steroids. Ketoconazole can be as effective as steroids, but with much fewer side effects.[8]

Infectious conditions

A wide range of infectious dermatoses can affect the male genitalia. These include viral, mycotic, parasitic, and bacterial infections, with the most prevalent causative agents being human papilloma virus (HPV), herpes simplex virus (HSV), candidiasis, sarcoptes, chlamydia, and neisseria. Treatment is directed.

Fig. 2. Pearly penile papules. Adapted from: Badri T, et al. Papue, pearly penile. In StatPearls. 2018, StatPearls Publishing LLC.

HPV

The prevalence of virologically detectable subclinical or latent HPV infection may be as high as 30–50%.[9] Currently, there are over 60 different HPV types, with genital types characterized as either low- or high-risk.[10] Genital warts are commonly produced by HPV serotypes 6 and 11, which have a strong tendency to induce condyloma (Fig. 3). Condylomata acuminata refers to soft, papillomatous growths considered to be benign. In males, it occurs most commonly on the glans, penile shaft, and the prepuce. About 5% of patients can have urethral involvement. HPV 16 and 18 are more likely to be present in subclinical infection and are the types most commonly associated with genital cancer.[11] Risk factors that may increase rates of infection with HPV include presence of foreskin, increasing numbers of sexual partners, lack of condom use, and smoking.

Several treatment modalities exist for the treatment of genital warts. These include topical agents, such as imiquimod cream, podofilox, and sinecatechins ointment, as well as photodynamic therapy with 5-aminolevulinic acid (ALA/PDT) and energy-based treatments, such cryotherapy, laser ablation, and electro-fulguration. Table 1 lists commonly used treatments and other relevant information.

HSV

HSV is the most common cause of genital ulceration.[17] Genital HSV infection is predominantly caused by HSV type 2, although type 1 is responsible for about 5–30% of first episodes of genital herpes.[18] Clinically, true primary genital herpes appears as macules and papules, followed by vesicles, pustules, and ulcers. Treatment depends on patient's status (immunocompromised vs. immunocompetent) and whether it is a first episode or a recurrent infection. It includes oral acyclovir, valacyclovir, famciclovir, or acydovir.

Candidal infections

The most common clinical syndromes caused by *Candida albicans* include genital mild burning and pruritus with erythema of the glans and/or the prepuce, and subpreputial discharge. Diabetes mellitus, HIV infection, iatrogenic immunosuppression, presence of prepuce, and widespread use of antibiotics are often found to be underlying medical conditions in patients with fungal balanitis, especially Candida balanitis.[19] The guidelines for the treatment of Candida balanitis have not yet been standardized. Treatment options usually involve topical antifungal therapy, either associated or not with systemic antifungal treatment. Azole agents, such as clotrimazole, miconazole, econazole, fluconazole, and itraconazole, are the usually recommended antifungal agents. Sometimes, other antifungal agents, such as terbinafine, are used with favourable outcomes.[20]

Table 1. Selected treatment options for genital warts

	Mechanism of action	Dosing	Effectiveness
Imiquimod, 3.75 or 5%	Immune response modifier	Should be applied for 8 hrs daily for 2 weeks Maximum of 8 weeks for 3.75% vs. 16 weeks every other day for 5% imiquimod	Two phase 3 double-blind controlled trials have shown imiquimod 3.75% to be more effective than placebo with a 33% clearance rate Primary cure rates for the 3.75% imiquimod are not as high as the 5% imquimod[12]
Podofilox 0.5%	Stops division of infected cells and causes tissue necrosis	Applied twice daily for 3 consecutive days each week Can repeat up to 4 weeks with at least 4 days in between	Clearance rates range from 45–77%[13]
Sinecatechins 15% ointment	Botanical treatment using epigallcatechin gallate, which is active against virally infected cells	Applied 3 times daily for up to 16 weeks	Approximately 53% complete clearance rate in one U.S. trial[12]
Trichloroacetic acid	Causes protein denaturation and cell death	Applied 1–3 times weekly and repeat as needed	Clearance is estimated to be 70–80%, with recurrence of 36%[14]
Cryotherapy	Uses liquid nitrogen or cryoprobe to freeze lesions	Can be used in 2 or 3 cycles with thawing in between	Clearance rates range from 71–79%, with recurrence rates of 38–73% at 6 months[15]
Laser therapy	Most commonly with CO_2, which causes tissue coagulation	Continuous or pulsed mode can be used as monotherapy or in combination with other modalities	Clearance rates range from 23–52% ,with recurrence rates as high as 77%[16]
ALA/PDT	Uses photosensitization to create free radicals	Apply ALA to affected area with photoxicity occuring at certain wavelengths	Not as effective as primary treatment, but can be used as adjuvant treatment after CO_2 laser ablation or cryotherapy[12]

ALA/PDT: photodynamic therapy with 5-aminolevulinic acid; CO_2: carbon dioxide.

Scabies

Scabies is an infestation caused by a mite, *Sarcoptes scabiei*. The mites burrow tunnels into the horny layer of the epidermis. Multiple typical burrows and papules are often present on the glans penis, scrotum, and penis shaft. The chief clinical symptom is pruritus that is usually worse at night or after hot baths. The preferred treatment for scabies is permethrin 5% cream applied from neck to the feet, with special attention given to the perianal and genital areas, as well as to the free nail edge and folds, and then rinsed off after 8–14 hours.[21]

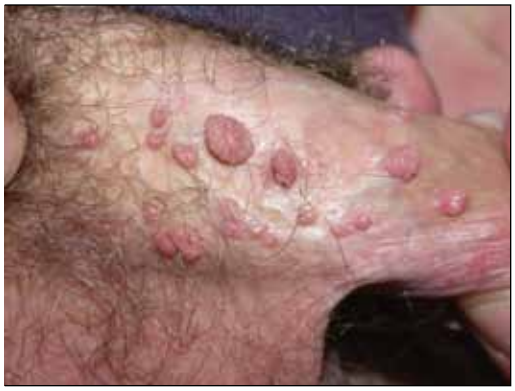

Fig. 3. Condyloma acuminatum. Adapted from: Wart, genital. Contributed by DermNetNZ, in StatPearls. 2018, StatPearls Publishing LLC.

Chlamydia and gonorrhea

Chlamydia is caused by the bacteria *Chlamydia trachomatis*. Symptoms in men include dysuria, urethral discharge, and epididymitis. In men, diagnosis is most often made with nucleic acid amplification test on urogenital or rectal samples. Treatment for uncomplicated urogenital infections include azithromycin 1 g orally once or doxycycline 100 mg orally twice daily (for seven days), and all sexual partners should be treated to prevent re-infection.[22] Gonorrhea is caused by the bacteria *Neisseria gonorrhoeae*. In men, it is most often asymptomatic, but symptoms can include dysuria or mucopurulent discharge. Disseminated gonococcal infection presents as few skin lesions limited to the extremities, which progress to bulla, petechiae, and necrotic lesions. Due to increasing resistance to ciprofloxacin, treatment for gonorrhea is ceftriaxone 250 mg intramuscularly once and one dose of oral azithromycin 1 g, which also serves as dual therapy to treat the common coinfection with *Chlamydia trachomatis*.[23]

Premalignant conditions

Premalignant genital lesions represent an area of great diagnostic challenge, even for an experienced urologist. It is paramount to take a detailed history regarding risk factors, such as circumcision history, phimosis, hygiene, smoking, sexual history, and HPV infection. Several premalignant lesions of the penis have been described, although the risk of progression to invasive penile cancer depends on the site

and type of lesion. Previous nomenclature for premalignant lesions, such as carcinoma in situ (CIS), Bowen's disease, and erythroplasia of Queyrat, have been more recently termed penile intraepithelial neoplasia (PeIN). These lesions are further subdivided into differentiated and undifferentiated subtypes. Differentiated PeIN is associated with chronic inflammatory conditions, and is typically not associated with HPV positivity, whereas undifferentiated type is generally associated with HPV positivity.[24]

Penile cutaneous horn

This is a rare lesion that usually develops over a preexisting skin lesion (wart, nevus, traumatic abrasion, or malignant neoplasm) and is characterized by overgrowth and cornification of the epithelium, which forms a solid protuberance (Fig. 4). These lesions may recur and may demonstrate malignant change on subsequent biopsy, even when initial histological appearance is benign.[25] As a result, careful histological evaluation of the base and close followup of the excision site are essential.

Pseudoepitheliomatous micaceous and keratotic balanitis

This is an unusual lesion that manifests as hyperkeratotic, micaceous growths on the glans that tend to recur (Fig. 5). Treatment includes excision, laser ablation, or cryotherapy. These lesions require aggressive treatment and close followup.[26]

Male lichen sclerosus (balanitis xerotica obliterans)

Lichen sclerosus, also known as balanitis xerotic obliterans (BXO) is associated with 4–6% of patients with penile squamous cell carcinoma (SCC). Many times patients present with obstructing voiding symptoms due to severe phimosis (Fig. 6). It manifests as a whitish patch on the prepuce or glans, often involving the meatus and sometimes extending into the fossa navicularis. It presents mainly in uncircumcised men and affects most commonly middle-aged men, but it does occur in boys, too.[27] Other symptoms include pain, dyspareunia, pruritus, and painful erections. The etiology of male lichen sclerosus is unknown; however, a recent study identified *Borrelia burgdorferi* infection in affected tissues in the early course of the disease.[28] Treatment involves clobetasol propionate cream for 2–3 months.

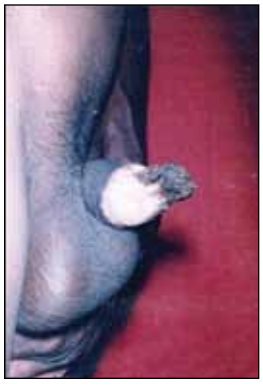

Fig. 4. Cutaneous horn projecting from glans penis. From the National Library of Medicine (https://openi.nlm.nih.gov/).

Bowenoid papulosis

Bowenoid papulosis was described by Kopf and Bart in 1977 as a condition having a histological appearance like that of CIS, but with a benign course. It manifests as multiple papules on the penile skin, usually during the second or third decade of life (Fig. 7). A causative role of HPV has been suspected since DNA sequences of HPV 16 have been identified in specimens of bowenoid papulosis. Biopsy is the gold standard for diagnosis. Whereas histologically this condition is a CIS, the clinical course is invariably benign.[29] Treatment consists of destruction, such as excision, electrocautery, cryotherapy, laser, or 5-fluorouracil [5-FU] topical therapy.

Malignant conditions

Squamous cell CIS

Squamous cell CIS manifests as a full-thickness alteration in the epithelium, with incidence increasing in recent decades.[30] It can manifest as well-demarcated erythematous plaques either on the penile shaft (Bowen's disease) or on the glans or prepuce (erythoplasia of Queyrat). Unlike invasive disease, CIS can be managed by various innovative organ-sparing methods, including topical chemotherapy, laser ablation, and local excisional treatments (such as Moh's micrographic surgery, total or partial glansectomy, glans resurfacing, or wide local excision with or without circumcision).[31] These options, in general, can achieve good local control with adequate functional and cosmetic outcomes.

Penile carcinoma

Invasive penile cancer is a rare malignancy that carries significant morbidity and mortality. It typically presents after the fifth decade of life, with the highest incidence being observed between the ages of 50–70. The most important predictor of survival is lymphatic invasion. Reports have suggested that tumour virus-transforming proteins from HPV types 16 and 18, particularly the E6 and E7 proteins, may target tumour-suppressor gene products pRB and TP53 and may be the causative agents in a subset of penile SCC.[32] It can present as a non-healing penile lesion,

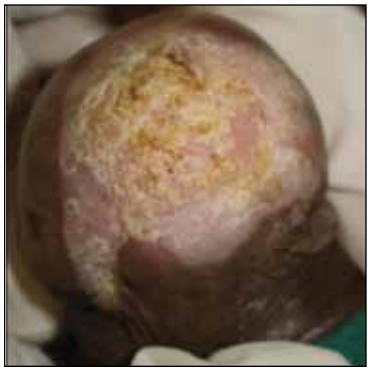

Fig. 5. Pseudoepitheliomatous keratotic and micaceous balanitis. Adapted from: Adya KA, et al. Pseudoepitheliomatous keratotic and micaceous balanitis. *Indian J Sex Transm Dis AIDS* 2013;34:123-5.

induration, ulceration, or fungating lesion (Fig. 8).The most important pathological predictors for metastatic spread are tumour grade, depth of invasion, and the presence of perineural invasion.[33] Because a delayed diagnosis can have devastating consequences, physicians should maintain a high index of suspicion for penile SCC in patients presenting with a lesion that is persistent and irregular in appearance. Adequate biopsies of sufficient depth are essential during initial evaluation and for selection of appropriate treatment strategies. Treatment generally involves excision and is discussed in the next section.

Kaposi sarcoma

Kaposi sarcoma is a tumour of the reticuloendothelial system. It appears as a raised, painful, bleeding papule or ulcer with bluish discolouration. There are currently four categories of Kaposi sarcoma, including classic, which occurs in patients without known immunodeficiency and has typically an indolent course; immunosuppressive treatment-related, which occurs in patients undergoing immunosuppression for organ transplantation or other reasons; African Kaposi sarcoma, which occurs in young men and can be indolent or aggressive; and epidemic or HIV-related, which occurs in patients with AIDS. The classic and immunosuppressive forms of the disease are considered non-epidemic. Non-epidemic Kaposi sarcoma limited to penile involvement should be aggressively treated because it is rarely associated with diffuse organ involvement.[34]

Management options

Topical therapy

Topical therapies are attractive options due to relatively simple ease and ability to administer in the outpatient setting. For most benign conditions, topical corticosteroids are the first-line treatment for inflammatory and immune-related lesions such as lichen sclerosus. Once-daily application of corticosteroids is sufficient because genital skin is permeable, and corticosteroid receptors remain saturated for almost 24 hours.[35] Potent corticosteroids should not be used for more than two weeks due to skin atrophy, and if long-term therapy is required, dermatological consultation should be considered. In cases of pre-malignant lesions and low-risk SCC, topical chemotherapy with 5-FU at 5% concentration can be used twice a day for six weeks. One study of 44 patients showed a complete response rate of 57%.[36] Due to severe irritation, circumcision is mandatory in order to limit the major side effects of this medication. In addition, imiquimod can be used as second-line therapy. It is typically applied for longer and less frequent applications than 5-FU. One meta-analysis found it to be more effective for lesions of the shaft than those of the glans and prepuce.[37] In all cases where initial topical therapy is chosen, patient adherence and strict followup is a must, and prompt re-biopsy is necessary for lesions that fail to respond.

Fig. 6. Balanitis xerotica obliterans. Adapted from: Nemota K, et al. Balanitis xerotica obliterans with phimosis in elderly patients presenting with difficulty in urination. *Hinyokika Kiyo* 2013;59:341-6.

Surgical excision-based treatments

Circumcision for isolated preputial lesions can be an effective procedure for most low-risk neoplastic lesions. Those with lichen sclerosus should go undergo circumcision to relieve obstructive symptoms and decrease the pro-carcinogenic environment that may promote invasive SCC. At a minimum, all patients with suspicion of penile cancer should undergo circumcision to decrease potential complications from treatment. For patients with CIS, Ta, and T1 tumours, a myriad of organ-sparing surgeries (OSS) are available and should be offered as a first option. Regardless of surgical approach, achieving a negative margin is necessary. Use of intraoperative frozen section is encouraged. Of the OSSs, Moh's micrographic surgery is the least invasive with favourable functional outcomes, although high recurrence rates have been reported during long-term followup.[38] Due to the low radicality of the procedure, Moh's surgery has greater benefit for small superficial shaft lesions, but should not be used for large or high-risk tumours.

For small- to medium-sized lesions, a wide local excision may be necessary to achieve a negative margin. The literature has shown surgical margins of a few millimeters are as safe as the traditional 2 cm surgical margin.[39] Depending on the size, defects may be closed primarily or with use of skin grafting. The key remains appropriate patient selection and strict followup. For glans lesions, options are glans resurfacing and glansectomy. Resurfacing involves removal of the epithelium and subepithelium of the glans penis, which can be covered with skin grafting. Total or partial glans resurfacing may be performed with high graft take and excellent cosmesis. The procedure is ideal for lichen sclerosus, as well as in situ tumours. Deep spongiosal biopsies should be performed to

Fig. 7. Bowenoid papulosis. Adapted from: Sudhir UK, et al. Bowenoid papulosis. *Indian J Sex Transm Dis AIDS* 2015;36:223-5.

Fig. 8. Penile carcinoma of distal shaft and glans. Reprinted with permission from patient.

rule out invasive disease. The procedure inherently carries a high risk for positive margins and re-operation is not uncommon. At experienced centres, minimal to no local recurrences have been reported.[40,41]

Glansectomy is the most radical of the OSS procedures and has the highest local control rate. The glans is separated from the corporal heads and urethra transected with a distal urethrostomy constructed. The shaft skin can be advanced or split, or a full-thickness skin graft used.[42] For large, invasive SCC tumours, amputation with either partial or total penectomy should be performed. Since these patients will also require lymphatic staging, upfront referral to a centre with experience in penile cancer is encouraged.

Other thermal modalities

Cryoablation, electrocautery, and laser ablation are good treatment modalities for non-cancerous lesions for which pathological evaluation is not necessary. Cosmesis may be a concern for those with more extensive lesions. Laser treatments offer promising results because they are associated with minimal morbidity and cosmetically acceptable outcomes. Two commonly used laser mediums are carbon dioxide (CO_2) and neodymium:yttrium-aluminum-garnet (Nd:YAG). The literature is conflicting in regards to their effectiveness for cancerous lesions. The CO_2 laser can be advantageous due to its precise thermal damage and better preservation of tissue for pathological examination. CO_2 allows effective vapourization of affected areas, followed by the removal of the heat-separated tissue.[42] The Nd:YAG laser is another option that can penetrate the skin to cause coagulation at a depth of 3–10 mm.[43] Studies evaluating laser therapies vs. conventional OSS are scarce. One study of 205 CIS patients found those treated with laser therapy had a significantly higher recurrence rate (48%) when compared to excisional procedures.[31] Although laser technologies are attractive options due to ease of use, their low depth of destruction may not provide adequate treatment for malignant tumours. Radiation is another option for those with invasive SCC refusing surgical treatment. It may be delivered as brachytherapy with interstitial implant or external beam radiation. Consideration should be deferred to centres of experience and is outside the scope of this review.

Conclusion

Many penile cutaneous lesions are first seen by community practitioners and general urologists. Most lesions are benign or infectious in origin, and diagnosis and management are guided by clinical appearance and symptoms (Fig. 9). Irregular erythematous patches, ulcers, horns, or fungating masses should undergo prompt evaluation. Biopsy is indicated when diagnosis is in doubt or if suspicion for neoplasm is present. Benign lesions can be treated with topical creams, limited excision, or observation. Malignant lesions may require more extirpation, and due to their rarity and aggressive nature, referral to tertiary centre is a good option for these patients.

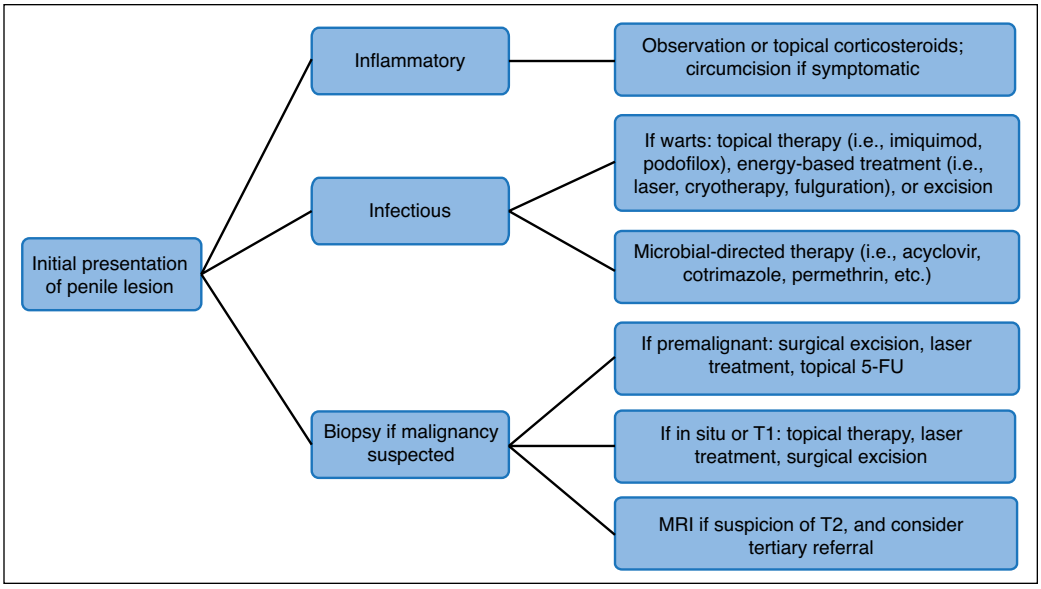

Fig. 9. Flowchart for patients presenting with a new penile lesion. 5-FU: 5-fluorouracil; MRI: magnetic resonance imaging.

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This paper has been peer reviewed.

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