Review Article

Premalignant male genital dermatoses

Rochit Rajesh Singhal, Trusha Manoj Patel, Kira Antony Pariath, Rita Vipul Vora
Department of Skin and VD, Shree Krishna Hospital, Karamsad, Gujarat, India

Address for correspondence:
Dr. Rita Vipul Vora, Opd 111, Shree Krishna Hospital, Anand, Karamsad - 388 325, Gujarat, India. E-mail: ritavv@charutarhealth.org

Abstract

The spectrum of conditions affecting the penile skin is varied and ranges from simple, benign dermatoses to premalignant and malignant conditions. Anogenital malignancies and premalignancies are an important personal/public health problem due to their effects on individuals' physical, mental, and sexual health. Furthermore, due to their etiological association with human papillomavirus infection, anogenital malignancies, and premalignancies constitute an immense public health burden. Bowen's disease, Bowenoid papulosis, and erythroplasia of Queyrat are the most widely seen premalignancies of anogenital region and are all forms of squamous intraepithelial neoplasia. Histopathologically, these conditions share identical histologic features of squamous cell carcinoma *in situ*, but their clinical features differ. In this article, we explore the common precancerous states that can lead to penile carcinoma.

Key words: Human papillomavirus, premalignant, squamous cell carcinoma

INTRODUCTION

Premalignant male genital dermatoses are frequently encountered in routine dermatology practice. Many a times, it is difficult to distinguish these premalignant lesions from other benign genital dermatoses. A tendency for delayed presentation, often with a history of long-term self-management, or unsuccessful treatment, can result in progression to an invasive carcinoma, requiring more extensive surgery.[1] It not only affects a person's physical well-being but also his or her psychological health and quality of life. Therefore, early diagnosis and treatment before the invasion is very essential for conservative treatment, thus avoiding the need for partial or complete penile amputation. The rarity of these conditions has resulted our knowledge to be based on small, nonrandomized, retrospective studies. This review outlines the common features of premalignant penile lesions.

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ETIOLOGY AND CLASSIFICATION

Several risk factors have been associated with the development of malignant genital lesions. These include the presence of a foreskin, phimosis, poor hygiene, smoking, chronic inflammation, and having multiple sexual partners. Infection with human papillomavirus (HPV) is one of the most important risks factors in penile cancer development.

Premalignant penile lesions can be broadly divided into:

1. Those related to HPV infection
2. Those which are not HPV related but caused by chronic inflammation.

HPV-related lesions include Bowen's disease (BD), erythroplasia of queyrat (EQ) and Bowenoid papulosis (BP), which are associated with "high-risk" HPV types 16 and 18. Low-risk HPV types 6 and 11

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are associated with other premalignant lesions, such as giant condylomata acuminate (GCA) or buschke Lowenstein tumors.

NonHPV-related lesions are primarily linked to genital lichen sclerosus (LS) et atrophicus. However, they are also associated with rarer chronic inflammatory conditions such as penile cutaneous horn, leukoplakia, porokeratosis, extramammary Paget's disease and pseudoepitheliomatous, and keratotic micaceous balanitis (PKMB). Risk of progression of various premalignant conditions to frank malignancy is tabulated in Table 1.[2]

PATHOGENESIS

Although penile cancer only accounts for 1% of malignancies diagnosed in the United States males, the rate is much greater in parts of Asia, South America, and Africa, where it approaches 10%.[3] Premalignant lesions account for approximately 10% of all penile malignancies at first presentation, with the vast majority occurring on the glans. The risk of malignant transformation has been reported to be up to 30% if left untreated.

HUMAN PAPILLOMA VIRUS-INDUCED SQUAMOPROLIFERATIVE DYSREGULATION

A recent systematic review of established polymerase chain reaction techniques has found HPV DNA in approximately 50% of penile squamous cell carcinoma (PeSCC).[4] In this respect, penile tumors appear to share a common pathogenesis and histology with vulval carcinomas and other HPV-related, poorly differentiated, SCCs.[5] "High risk" HPV types 16 and 18 are found in 60%–75% of *in situ* and invasive tumors. The HPV exerts its tumorigenic effect through expression of two viral genes, E6 and E7, which are continuously expressed in cells that have been infected with high-risk types of HPV. E6 and E7 gene products cooperation disturb cellular differentiation, proliferation, and apoptosis through their involvement with the retinoblastoma Rb/E2F and P53 tumor-suppressor pathways. Certainly, their expression is needed to induce and maintain the neoplastic phenotype of cervical cancer cells and similar mechanisms seem to exist in penile cancer.

HUMAN PAPILLOMA VIRUS-INDEPENDENT SQUAMOPROLIFERATIVE DYSREGULATION

Chronic inflammatory processes have been implicated in up to half of the newly diagnosed penile cancers.[6] Unlike HPV related tumors, the progression of these premalignant lesions is large to keratinizing/verrucous PeScc.[7] The associated intraepithelial neoplasia is typically differentiated and can be managed more expectantly compared to full thickness dysplastic lesions. The mechanism of HPV independent carcinogenesis has not yet been fully elucidated.

HUMAN PAPILLOMA VIRUS-RELATED LESIONS

Erythroplasia of Queyrat, Bowen's disease of the penis and Bowenoid papulosis

EQ, BD of the penis (BDP) and BP are three clinical variants of carcinoma *in situ* (CIS) of the penis.[8] Smegma, poor hygiene, immunosuppressed state, trauma, friction at the site, etc., are the risk factors for this disease. The exact etiology of EQ, BDP, and BP is still unclear. However, it is suggested that BP is probably virus-induced epithelial dysplasia associated mainly with HPV 16 and 18.

Table 1: Risk of progression of various premalignant conditions to frank malignancy[2]

Lesions	Progression rate to invasive cancer (%)
HPV-related lesions	
EQ	30
BDP	2.6-5
BP	1
Giant condyloma accuminatum (Bushke-lowenstein tumor)	30
Non-HPV related lesions	
Male genital LS et atrophicus	0-8.4
Extramammary Paget's disease	Not known
Penile horn	30 (low grade)
PKMB	Not known (low grade)
Leukoplakia	10-20
Porokeratosis	Not known

HPV=Human papillomavirus, BDP=Bowen's disease of the penis, EQ=Erythroplasia of queyrat, BP=Bowenoid papulosis, LS=Lichen sclerosus, PKMB=Pseudoepitheliomatous, micaceous and keratotic balanitis

Patients usually complain of pruritus, pain, bleeding, and difficulty in retracting the foreskin. BD of penis presents as red, shiny, slightly pigmented patches or plaques of the keratinized penis while EQ affects the genital mucosa. BP should be used to describe multiple warty-like lesions, which are often pigmented in keratinized sites, and more numerous and more inflamed at "mucosal" sites. BP lesions are less papillomatous, smoother topped, more polymorphic and more coalescent than common genital viral condylomata acuminata, and occur in younger, sexually active men, as opposed to the patches or scaly plaques of EQ and BDP, respectively, seen in older men [Figures 1 and 2]. The differential diagnosis of EQ and BDP includes psoriasis, LS, erosive lichen planus, ZB and extramammary Paget's disease. The differential diagnosis of BP includes lichen planus, common warts, seborrhoeic warts, naevi, and condylomatalata.

A biopsy is indicated in instances where the clinical diagnosis is uncertain. Occasionally, it may be necessary to perform a second biopsy if the initial histology is inconclusive. On histological examination, EQ and BDP show SCC-*in situ*, i.e., atypical squamous cells proliferate through the whole thickness of the epidermis and do not invade the dermis. BP may show scattered atypical cells or full-thickness atypia as well.

The risk for progression to invasive cancer is said to be higher for EQ (approximately 30%) than BDP.[9] The risk of progression of BP to invasive squamous carcinoma is very low (2.6%) unless an immunocompromised state exists. This may also be because most cases of BP are treated as warts with destructive therapy, so the exact number of cases is not known.

Patients presenting with these conditions should be counselled and screened for HPV and other sexually-transmitted diseases, including HIV infection. Cessation of smoking should be advised. Sexual partners should be advised to seek assessment. Long-term follow-up is necessary and should be implicitly explained. Treatment includes topical 5-fluorouracil (5-FU) 5% cream, topical imiquimod, cryosurgery, curettage and electrocautery, excisional surgery, glans resurfacing, Mohs micrographic surgery, laser, and photodynamic therapy (PDT). Circumcision removes a major risk factor for malignancy and provides extensive tissue for histological examination.

Giant condyloma accuminatum (Bushke-lowenstein tumor)

Giant condyloma acuminate also known as buschke-Lowenstein tumor is large, warty, exophytic, cauliflower-like growths which is an HPV -related entity that affect any part of the anogenital region. On the penis, lesions are found around the coronal sulcus, frenulum, penile shaft, and occasionally into the anterior urethra. Extension into the posterior urethra and bladder is usually only seen in immunocompromised patients. Risk factors are immunosuppression, chronic irritation, presence of foreskin, and poor hygiene. Organ transplantation and chronic hidradenitis suppurativa are other predisposing factors.[6] They are caused by infection with low-risk HPV types 6 and 11. Both sexes can be affected. These lesions typically occur in sexually active men in their third decade of life.

In cases of suspicion of carcinoma, a deep surgical biopsy is required. Histopathological examination shows hyperplastic epithelium, parakeratotic scale, atypia, and focal small islands of atypical squamous epithelium.

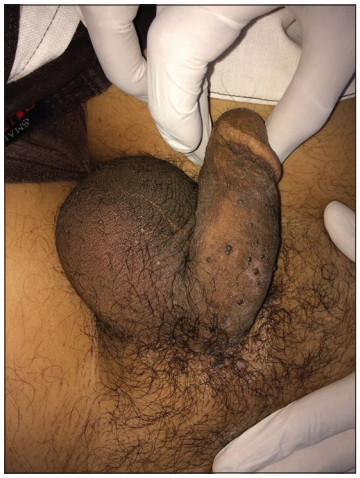

Figure 1: Bowenoid papulosis

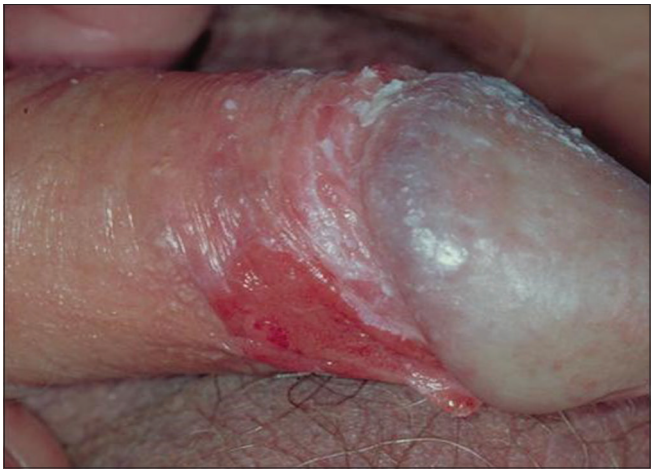

Figure 2: Erythroplasia of Queyrat

Surgical excision is the treatment of choice (glansectomy or penectomy). Mohs micrographic surgery, cryotherapy, laser treatment, interferon-α, radiotherapy or bleomycin, systemic retinoids are alternatives. Radiotherapy should be avoided as it may precipitate transformation to anaplastic carcinoma. The prognosis is poor because the tumour can continue to grow and invade locally. Cause of death is exsanguinations from femoral arterial invasion or cachexia. Even with treatment, recurrence and progressive malignant transformation do occur, so follow-up is necessary.

NONHUMAN PAPILLOMA VIRUS RELATED LESIONS

Male genital lichen sclerosus et atrophicus

Male variant of LS is chronic progressive inflammatory dermatoses of unknown etiology affecting the glans penis, prepuce, and anterior urethra and meatus.[10] It is also called balanitis xerotica obliterans at the end stage. It occurs almost exclusively in uncircumcised men.[11] Its exact etiology remains unclear although a possible autoimmune element has been suggested or even a genetic basis based on human leukocyte antigens. Thus, a multifactorial basis can be suspected. In men, the lesions may be aymptomatic, but if present symptoms may be tightening of the foreskin which can result in phimosis, painful erections, poor urinary stream and obstruction, soreness, and decreased penile sensitivity. On examination, a sclerotic constricting band 1–2 cm distal to the prepuce results in phimosis and paraphimosis. Later porcelain white macules, papules, and sclerotic changes may be present [Figure 3].[12]

Histopathological changes include hyperkeratosis with follicular plugging, atrophy of stratum malpighii with hydropic degeneration of basal cells, flattening of rete ridges, pronounced edema, and homogenization of collagen in the upper dermis and lymphocytic infiltrate in the mid-dermis. The differential diagnosis includes erosive lichen planus, balanoposthitis of various causes, and idiopathic phimosis.

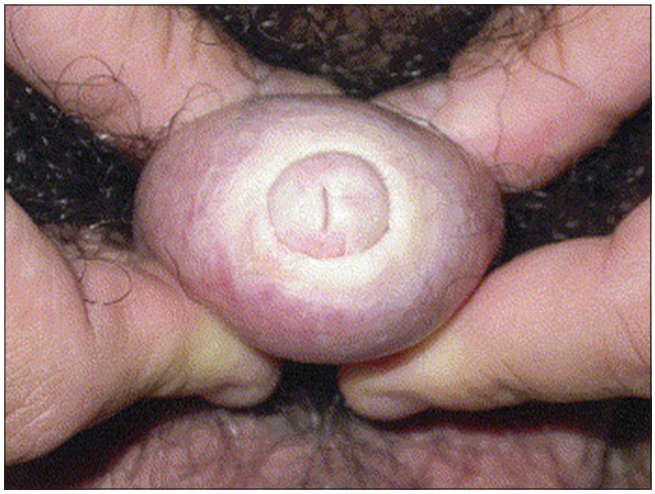

Figure 3: Male genital lichen sclerosus et atrophicus

Treatment focuses on the relief of symptoms by topical corticosteroids, tacrolimus ointment, and antihistaminics. Intralesional steroids can be tried for resistant thick plaques not responding to topical steroids. For postinflammatory pain syndrome after improvement of the skin lesions (i.e., penile dysesthesia) 5% lignocaine ointment can be tried. Certainly, treatment with potent steroids and/or circumcision appears to negate the cancer risk in the majority of men with LS.[11] The development of persistent skin lesions or chronic inflammation in patients with LS should be monitored closely and biopsied to ensure that no concurrent cancer exists.

Extramammary Paget's disease

It is a marginated plaque which resembles Paget's disease clinically and histologically, but occurring in sites rich in apocrine glands, such as the vulva, anogenital region, and axilla. It could be either *de novo* or arising from underlying carcinoma which has given rise to the concept of primary and secondary extramammary Paget's disease. In about 75% of cases, extramammary Paget's disease arises as a primary intraepidermal neoplasm, most commonly from apocrine gland ductal cells or from keratinocyte stem cells. In the remaining 25%, an underlying primary adenocarcinoma is found.

This is a rare disease with women preponderance in the fifth decade or after. It presents as an irritating, itchy, burning, red scaly patch or plaque and maybe multi-focal.[13] The margin is sharp, rounded, and slightly raised. The surface may be scaly and small grayish crusts over erosions. Itching is a prominent feature and there may be excoriations and lichenification. Variable hyperpigmentation which makes it difficult to differentiate between extramammary Paget's disease and superficial spreading melanoma. Characteristic clinical features include the continuous progression and the sharp margin despite of aggressive treatment. As it progresses, the area may become thickened and ulcerated as evidence of invasion downward. The most common area involved is the vulva, followed by the perianal area which is more frequently affected in men than women, the scrotum, penis, and axilla. Appearance depends on the site of involvement. The mucosal surfaces of the labia are

frequently more red than the skin and the change may spread to the thighs, mons pubis and into the vaginal introitus. Perianal lesions may extend up into the anal canal, lesions on the scrotum spread to the thigh or onto the shaft of the penis. The eyelids or ears can also be affected rarely. Lymph node or distant metastases can occur.

The differential diagnosis from eczema, intertrigo and pruritus vulvae is made by the steady spread, lack of response to topical anti-inflammatory agents and the sharp and extending margin. BD, leukoplakia, and superficial spreading melanoma are other differential diagnoses which require biopsy for the diagnosis. Histological appearance in the epidermis is similar to Paget's disease. The epidermis is diffusely infiltrated with large vacuolated cells that have a bluish cytoplasm; these are called Paget cells. These distinctive cells are found in the lower epidermis and may proliferate to the rete ridges and adnexa. The epidermis shows varying degrees of acanthosis, hyperkeratosis, and parakeratosis. The cells stain positively for acid and neutral mucopolysaccharides. Immunohistochemistry shows cells positive for carcino-embryonic antigen, cyclic adenosine monophosphate 5.2 and low-molecular-weight keratins such as cytokeratin 7.

If an underlying malignancy is present, it should be excised together with all clinically abnormal epithelium. Mohs' surgery can be done. The most common cause of recurrence is inadequate excision of the lesion. PDT is also useful, but larger series and longer periods of follow-up are required.

Penile horn

Cutaneous horns also known as Cornucutaneum refers to a well-defined cone-shaped lesion with hyper-keratotic features which arises in the areas of chronic inflammation. Warts, naevi, preputial inflammation, and phimosis are known to play an important role. Horns are most commonly seen on sun-exposed parts so it is rare for the cutaneous horn to affect the penis.

The first case of a cutaneous horn was described in 1854, and since then fewer than 100 cases have been reported. They have a risk of malignant transformation into low grade verrucous or keratinizing SCC in approximately 30% of cases.[14] The malignant change should be suspected in a rapidly growing lesion. Various lesions seen at the base of a cutaneous horn include SCC, actinic keratosis, keratoacanthoma, BD, seborrheic keratosis, basal-cell carcinoma, hemangioma, keratotic and micaeouspseudopapillomatousbalanitis, Kaposi's sarcoma, sebaceous adenoma, Paget's disease of the female breast, pseudoepitheliomatous micaceous and keratotic balanitis, and verrucous carcinoma.[15]

Treatment should be decided after adequate excision and histology of the whole lesion. Microscopically, a cutaneous horn shows marked hyperkeratosis, acanthosis, dyskeratosis, papillomatosis, and chronic inflammatory infiltration of the adjacent dermis. Treatment options include wide surgical excision which involves partial penectomy with or without regional lymph node dissection. Carbon dioxide (CO_2) or Neodymium yttrium aluminium garnet (Nd:YAG) laser are the second line of treatment. Follow-up is mandatory because recurrence may occur.

Pseudoepitheliomatous, micaceous, and keratotic balanitis

PKMB is an extremely rare condition occurring over the glans characterized by silvery white plaque with mica-like crust which is mainly seen in the elderly (over 60 years) [Figure 4].[16] The exact etiology is not known. The pathogenesis of PKMB occurs in four stages: (a) initial plaque stage, (b) late tumor stage, (c) verrucous carcinoma, and (d) transformation to SCC and invasion.[14] The differential diagnosis includes SCC, verrucous carcinoma, keratoacanthoma, giant condyloma, penile horn, and EQ. Histological examination shows hyperkeratosis, parakeratosis, acanthosis, prolongation of the rete ridges and mild lower epidermal dysplasia, with a nonspecific dermal inflammatory infiltrate of eosinophils and lymphocytes. Treatment is based on the stage of the lesion, with the initial plaque stage requiring topical therapy and the advanced stages necessitating more aggressive therapy. Treatment includes topical 5-flourouracil and cryotherapy if

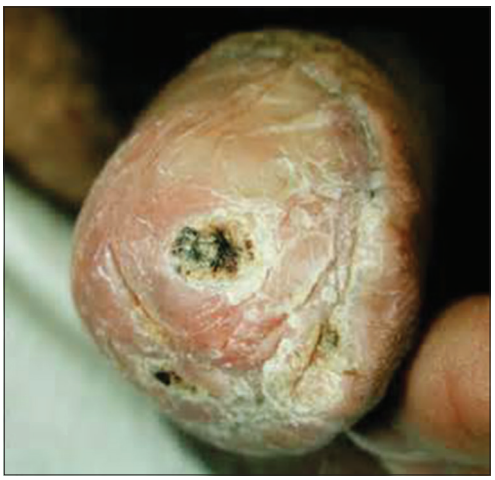

Figure 4: Pseudoepitheliomatous micaceous and keratotic balanitis

there is nomalignancy[16] and surgical excision is required in malignancy. Mohs micrographic surgery can be done.

Leukoplakia

Leukoplakia is rare and presents as a white, verrucous plaque that can arise on mucosal surfaces. Oral lesions have a strong association with chronic tobacco use and have a high risk of malignancy which increases with fissuring, ulceration, and erosion. Genital mucosa is rarely involved. They occur primarily on the glans or prepuce. Diabetics are more commonly affected. Clinically, they can resemble areas of LS. Mainly two clinical types are recognized: Homogenous and nonhomogenous. It doesn't have specific histology, dysplasia may or may not be present. Approximately 10%–20% of penile leukoplakia can show dysplastic changes microscopically.[17] Management involves removal of etiological factors and if the biopsy shows dysplastic changes surgical excision is the treatment of choice.

Porokeratosis

Porokeratosis is a distinct disorder of keratinization. It is generally transmitted as an autosomal dominant mode of inheritance. The exact etiology is not known, but it is proposed that an expanding mutant clone of keratinocytes may be responsible, supported by the fact that an abnormal DNA ploidy is present in the keratinocytes of the porokeratosis. Another theory is an unidentified epidermal antigen causing a mitotic stimulus for epidermal cells. The genetic role is also suggested. Different types of porokeratosis are present such as classic porokeratosis of Mibelli, disseminated forms, punctuate porokeratosis, linear porokeratosis, and other rare variants. It can occur on any site, especially on the face, "v" area of the neck and extensor aspects of the extremities.

Clinically, it presents as hyperkeratotic papules or plaques surrounded by a thread like an elevated border that expands centrifugally. Genital porokeratosis of Mibelli itself rare, but classical lesions have been reported on the penis and scrotum which is common in Asian populations.[18] Pruiritis and ulceration may occur. Characteristic histopathological features are present in the hyperkeratotic ridge. It shows cornoid lamella, a parakeratotic column in which the horny cells appear homogenous and have deeply basophilic pyknotic nuclei. Epidermal cells at the base of the cornoid lamella are irregularly placed, having pyknotic nuclei with perinuclearedema. The granular layer is absent beneath the cornoid lamella. The dermis shows mild infiltration with lymphohistiocytic cells.

Porokeratosis may be confused with psoriasis, BD, granuloma annulare or lichen planus; biopsy differentiates these conditions. Treatment includes the use of emollients and watching for signs of malignant degeneration. Topical 5-FU can induce remission in all cases but recurrences are seen. Topical imiquimod cream was also shown to be effective. Oral retinoids have been tried in immunosuppressed patients who are at a higher risk for malignant degeneration. Excision is most appropriate when malignant treatment develops.

TREATMENT

Several different options and treatment modalities are available for premalignant penile lesions. The choice of treatment should be tailored to the type and site of the lesion, taking into account patient preference and likely compliance with treatment regimes and the need for close follow up with the more minimally invasive techniques.

HUMAN PAPILLOMA VIRUS VACCINATION

Naturally, "prevention rather than cure" is a far more attractive therapeutic proposition in this clinical area. The advent of new HPV vaccines (both bivalent and quadrivalent) has raised an interesting debate for genital cancers in men. The protection from HPV infection is secure up to 5 years after vaccination. Currently, the center for disease control recommends the HPV vaccine for all boys ages 11 or 12 years and catch up vaccination for males from age 13–21 years who have not already received all three doses.[19]

TOPICAL THERAPIES

Topical therapies for premalignant penile lesions can either be by chemotherapy or immunotherapy. They are best suited to immunocompetent patients with well defined solitary lesions. Lesions amenable to treatment with topical therapy include penile intraepithelial neoplasia (PIN), BP, and PKMB. It is not suitable for LS, GCA or cutaneous horn. The most common first-line treatment is topical 5% 5-FU. This antimetabolite chemotherapeutic agent is a pyrimidine analog. It is applied topically for 4–6 weeks every alternate day. Patients are generally advised to apply the cream with or without gloves and thorough handwashing after the application is advised. All are explained that the treated area often becomes encrusted and inflamed during the treatment period. Additional application of topical steroid can be used if the areas become uncomfortable during the treatment period. However, it can take between 4 and 8 weeks for the areas to heal. Nonresponders

or partial responders to this treatment can be treated with immunotherapy using topical 5% imiquimod cream as a second-line treatment for 5 days a week for a period of 4–6 weeks. The frequency of application can be reduced provided that the inflammatory response is maintained.

LASER TREATMENT

Laser therapy is primarily used to treat PIN and BP and is not suitable for LS, large GCA or cutaneous horn. CO_2 and Nd:YAG lasers are used as first-line therapy with reasonable response rates and good results. The CO_2 laser has a tissue penetration of 2–2.5 mm and can be used as a scalpel to excise tissue for histological analysis by direct focusing of the beam. Treated areas generally take 3–4 weeks to heal. The Nd:YAG laser has a tissue penetration of 3–5 mm, but causes tissue coagulation preventing histological diagnosis, which may result in the disease being under staged. Larger lesions can be treated using this laser, but the healing of ablation sites may take 2–3 months also. Treatment with either of these lasers is usually well tolerated, with minor complications ranging from minor pain and bleeding at treatment sites. Laser has a higher recurrence rate and disease progression which may reflect a tendency to tackle larger lesions with this minimally invasive approach compared with those treated by other topical therapies.

Cryotherapy

It can be used across a diverse range of skin conditions with the technique involving the use of either liquid nitrogen or nitrous oxide to generate rapid freeze/slow thaw cycles to achieve tissue damage at temperatures below −20 by the formation of ice crystals, leading to disruption of cell membranes and cell death. Cryotherapy has a greater risk of recurrence in some case when compared to 5 FU and surgical excision after 5 years of follow-up.[20]

Topical photodynamic therapy

PDT for premalignant penile lesions is still in its infancy. Topical photosensitizing cream such as Delta-5-aminolaevulinic acid is applied to the penis for approximately 3 h which are then preferentially taken up and retained by malignant cells. The area is then treated by the illumination of an incoherent light from a specialist PDT lamp leading to photoselective cell death of sensitized cells. Intra- or perioperative side effects of photodynamic diagnosis were not observed.[21]

SURGICAL EXCISION-CIRCUMCISION

It forms an essential part of the management of premalignant conditions to treat and to prevent persistence of an environment suited to HPV infection, chronic inflammation and progression to invasive disease. Surgical excision is the treatment of choice in all premalignant conditions. Primary surgical excision is advocated in extensive lesions, poor compliance, and recurrence.

A total glans resurfacing procedure provides the best surgical approach in which diseased area is excised with an adequate margin followed by split-thickness skin graft.[22] It allows preservation of penile length, form and function, and a good cosmetic appearance.

Partial glans resurfacing

Partial glans resurfacing has also been used as a primary surgical approach for glanular CIS. This approach has the advantage of conserving normal glans skin, allowing better preservation of glanular sensation, and achieving a final appearance closer to the original glans. This approach would be more attractive to younger, sexually active men.

Mohs micrographic surgery

An alternative surgical approach is excision using Mohs micrographic surgery. This involves removal of the entire lesion in thin sections, with concurrent histological examination to ensure clear margins microscopically. While this technique allows maximal preservation of normal penile tissue, it is difficult and time-consuming, requiring both a surgeon and pathologist trained in the technique to ensure adequate oncological clearance and has a higher chance of recurrence.[23]

CONCLUSION

Some genital lesions, which seem to be of an inflammatory nature, may actually be premalignant lesions that can evolve into aggressive tumors. In current clinical practice, the possibility of noninfectious genital lesions is often underestimated with a tendency to attribute a sexually-transmitted origin to any pathological condition affecting the genitalia, especially in young people. It is, therefore, important to be aware of these cases. Their diagnosis is mostly based on typical clinical appearance and in some cases, histopathologic examination, which should always be done based on clinical indications.

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Conflicts of interest

There are no conflicts of interest.

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