

Condyloma Acuminatum with A Focus on Condyloma Acuminatum of the Penis: a Review and Update

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Abstract

Condyloma Acuminatum which is also referred as genital warts is a terminology that is utilized for Contagious HPV related lesion with a clear predilection for the anogenital region of the body. Condyloma Acuminatum tends to be transmitted through skin-to-skin contact during the undertaking of oral, genital or anal sex. Condyloma Acuminatum is most frequently caused by HPV genotypes 6 and 11. Other genotypes that had been identified in Condyloma Acuminatum include HPV 16, 18, 30 - 32, 42 - 44 and 51 – 55. Condyloma acuminatum is a benign lesion. Malignant transformation of condyloma Acuminatum is very rare. The Buschke-Lowenstein tumour emanates from the confluence of multiple condyloma acuminata and it clinically tends to manifest presentation of warty, exophytic, ulcerated lesions that portend an aggressive biological behaviour, rapid growth, invasion, as well as destruction of adjacent structures. Gross examination of specimens of Condyloma Acuminatum tends to demonstrate: Papillary, fungating, wart-like, often multiple lesions and which tend to measure 1 mm or larger. Microscopy pathology examination features of condyloma acuminatum include: Arborescent (tree-like, complex) "condylomatous" spiky papillae that contain prominent central fibrovascular cores, Surface koilocytosis (koilocytes that have hyperplastic epithelium with wrinkled hyperchromatic nuclei, perinuclear halos and frequent bi and multinucleation; sharply defined base without invasion; preservation of orderly maturation of epithelial cell; presence of T lymphocytes with (CD4+ finding; evidence of reactive atypia but no evidence of invasion; variable acanthosis and hyperkeratosis. A number of treatments options are available to treat condyloma acuminatum of the penis including: Medical treatment of Condyloma Acuminatum with utilization of: imiquimod cream, 20% podophyllin antimitotic solution, 0.5% podofilox solution, 5% 5-FU cream and trichloroacetic acid (TCA). Other forms of treatment of Condyloma Acuminatum: freezing, burning (electrocautery), CO2 laser, or surgical excision (if large). Pursuant to treatment of Condyloma Acuminatum, the Condyloma Acuminatum does tend to recur but it does not evolve recurrence into invasive cancer. Some of the differential diagnoses of condyloma acuminatum of the penis include: Pearly penile plaques, Verruciform tumours (verrucous, papillary, and warty carcinomas): Tuberculosis of the penis and Squamous cell carcinoma of penis could also be considered as differential diagnoses of condyloma acuminata especially confluent ones including "The Buschke-Lowenstein tumour". Considering that condyloma acuminatum is very rare, clinicians need to have a high index of suspicion for this clinical entity which can also be encountered in children and not only in adults.

Keywords: condyloma acuminatum of penis; the buschke-lowenstein tumour; histopathology, koilocytosis; oral sex; genital sex; anal sex; hpv genotypes 6 and 11; hpv 16, 18, 30 - 32, 42 – 44; hpv 51 – 55; medical treatment, surgical treatment; recurrence

Introduction

Condyloma Acuminatum is a terminology that is used for Contagious HPV related lesion with a clear predilection for the anogenital region of the body [1] [2]

Condyloma Acuminatum tends to be encountered in sexually active young men, among whom HPV infections tend to be at epidemic proportions. Majority of cases of condyloma acuminatum are sexually

transmitted, as has been underlined by the higher incidence of condyloma among men whose partners have HPV-related cervical lesions. The incidence of condyloma was documented to be about 5% among adults who are aged between 20 years to 40 years. Nevertheless, condyloma acuminatum of the penis has been reported sporadically. If condyloma of the penis is encountered in a child, sexual abuse would need to be strongly considered as well as investigated. Condylomas manifest as either flat or cauliflower-like lesions which usually tend to be found upon the corona of the glans penis, fossa navicularis, or urethral meatus, but involvement of scrotal or perineal skin may also occur. Considering that condyloma acuminatum of the penis is not common and may simulate more common lesions of the penis, there is the possibility that many clinicians globally may not be familiar this uncommon clinical entity. The ensuing article on condyloma acuminatum of the penis has been divided into two parts: (A) Overview which has summated salient features of the General Aspects of Condyloma Acuminatum; and (B) Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Some Studies Related to Condyloma Acuminatum with a Focus on Condyloma Acuminatum of the Penis.

Methods

Internet data bases were searched including: Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: Condyloma Acuminatum of Penis; Penile condyloma acuminatum; Condyloma Acuminatum of urethra. Sixty-seven (67) references were identified which were used to write the review and update of the literature on condyloma acuminatum of the penis which has been divided into two parts: (A) Overview which has summated salient features of the General Aspects of Condyloma Acuminatum; and (B) Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Some Studies Related to Condyloma Acuminatum of the Penis.

Results

[A] Overview

Definition / general statements

- It has been stated that Condyloma Acuminatum is a terminology that is utilized for Contagious HPV related lesion with a clear predilection for the anogenital region of the body [1] [2]

Terminology

- It has been pointed out that an alternative terminology which tends to be used for Condyloma Acuminatum is genital wart. [1]

Epidemiology

- It has been explained that Condyloma Acuminatum tends to be transmitted through skin-to-skin contact during the undertaking of oral, genital or anal sex.[1]
- It has been iterated that Condyloma Acuminatum most commonly affects young males in teenage years and 20s (third decade of life). [1]
- It has been pointed out that Human Papilloma Virus (HPV) represents the most common sexually transmitted disease within the United States of America (U.S A). but many HPV infections do not lead to the development of condyloma acuminatum. [1]

Sites

- It has been pointed out that the most common sites for the development of Condyloma Acuminatum in decreasing

frequency are the glans penis, foreskin, meatus and shaft of the penis. [1]

- Furthermore, it has been documented that Condyloma Acuminatum has often tended to afflict areas near the coronal sulcus and inner surface of the foreskin. [1]

Aetiology

- It has been iterated that Condyloma Acuminatum is most frequently caused by HPV genotypes 6 and 11 [1]
- It has been iterated that other genotypes that had been identified in Condyloma Acuminatum include HPV 16, 18, 30 - 32, 42 - 44 and 51 – 55. [1]
- It has been pointed out that Condyloma Acuminatum is related to verruca vulgaris which is a common wart [1]

Clinical features of Condyloma Acuminatum

Summations related to the salient features of Condyloma Acuminatum include: [1]

- Condyloma Acuminatum is a benign lesion. [1]
- Condyloma Acuminatum lesions tend to be small lesions that are detected with utilization of topical acetic acid
- It has been pointed out that malignant transformation of condyloma acuminatum is very rare. [1]

Treatment

Summations related to the treatment and outcome following treatment of Condyloma Acuminatum had been outlined as follows: [1]

- Medical treatment of Condyloma Acuminatum includes utilization of: imiquimod cream, 20% podophyllin antimitotic solution, 0.5% podofilox solution, 5% 5-FU cream and trichloroacetic acid (TCA). [1]
- Other forms of treatment of Condyloma Acuminatum that had been pointed out include: freezing, burning (electrocautery), CO2 laser [1] [3] or surgical excision (if large)
- It has been pointed out that following treatment of Condyloma Acuminatum, the Condyloma Acuminatum does tend to recur but it does not evolve recurrence into invasive cancer. [1]

Macroscopy Gross Features

It has been pointed out that macroscopy gross examination of specimens of Condyloma Acuminatum tends to demonstrate the ensuing features: [1]

- Papillary, fungating, wart-like, often multiple lesions and which tend to measure 1 mm or larger
- It has been advised that lesions that depict the aforementioned gross features upon examination should be sectioned and the lesions should be examined thoroughly to exclude verrucous carcinoma based upon their pathology examination features.

Microscopic (histology) description

The pathology examination features of condyloma acuminatum have been summated as follows: [1]

- Pathology microscopy examination of specimens of condyloma acuminatum tends to demonstrate: Arborescent (tree-like, complex) "condylomatous" spiky papillae that contain prominent central fibrovascular cores [1]

- Pathology examination of specimens of Condyloma Acuminatum also tends to reveal Surface koilocytosis (koilocytes have hyperplastic epithelium with wrinkled hyperchromatic nuclei, perinuclear halos and frequent bi and multinucleation) [1]
- Pathology examination of specimens of Condyloma Acuminatum also tends to reveal sharply defined base without invasion. [1]
- Pathology examination of specimens of Condyloma Acuminatum also tends to reveal preservation of orderly maturation of epithelial cells. [1]
- Pathology examination of specimens of Condyloma Acuminatum also tends to reveal T lymphocytes (CD4+) present. [1]
- The lesion on microscopy pathology examination may be found to demonstrate evidence of reactive atypia but no evidence of invasion. [1]
- Pathology examination of specimens of Condyloma Acuminatum also tends to reveal variable acanthosis and hyperkeratosis. [1]
- It has been pointed out that in condyloma acuminatum koilocytosis is not evident in some cases but the histological pattern tends to be otherwise characteristic of condyloma acuminatum. [1]

Cytology description

It has been pointed out that cytopathology examination detection of HPV infection in penile samples collected for liquid-based cytology tends to be low [1] [4]

Molecular / cytogenetics description

- It has been pointed out that with regard to the molecular and cytogenetics features of condyloma acuminatum specimens, lesions with HPV 6 and 11 by in situ hybridization are usually found to have perinuclear halos and nuclear atypia. [1]
- It has also been pointed out that lesions with HPV DNA by PCR only may contain only a focally thickened granular layer associated with epithelial crevices [1] [5]

Differential diagnosis

Some of the differential diagnosis of condyloma acuminatum that had been documented include: [1]

- **Pearly penile plaques:** These lesions had been stated to be HPV negative, and in the lesions, hyperkeratosis may be present but no koilocytosis tends to be seen upon microscopy examination and no significant inflammation tends to be seen. [1]
- **Verruciform tumours (verrucous, papillary, and warty carcinomas):** invasion is stated to be evident upon pathology microscopy examination. [1]

It would be envisaged that some clinicians would consider the following to have features upon macroscopy examination that could provisionally be considered to constitute differential diagnoses of condyloma acuminatum:

- **Tuberculosis of the penis.**
- **Squamous cell carcinoma of penis.**

[B] Miscellaneous Narrations And Summations From Some Case Reports, Case Series And Studies Related To Condyloma Acuminatum.

Weis et al. [6] reported a 46-year-old man who had human immunodeficiency virus who had manifested with a condyloma that had formed over a period of 6 months and which had encased his penis,

scrotum, and perineum. Visible condyloma growth began when the patient who was an immunocompromised patient started highly active antiretroviral therapy, and it grew rapidly as his viral load plummeted. The patient did undergo resection and reconstruction with skin grafting. Pathology examination findings of the surgical specimen revealed benign condyloma acuminatum. This rapid progression of condyloma growth was documented to represent a cutaneous manifestation of immune reconstitution inflammatory syndrome.

Iturralde Codina et al. [7] reported an uncommon case of giant penile condyloma. The patient was treated surgically by denudation and fulguration due to the extent of the penile lesion before the undertaking of treatment with topical podophyllin. The histopathological examination of the specimen was determinant in the diagnosis of giant condyloma of the penis and the postoperative results were excellent. Iturralde Codina et al. [7] concluded that they would recommend to commence treatment with topical podophyllin and that if the lesion does not improve, resection and fulguration of the condyloma should be undertaken as well as that the patient should be followed closely for recurrence.

Uchida et al. [8] reported two cases of giant condyloma of the penis which treated with penis-sparing methods. In the first case, the papillomatous tumour had disappeared with topical utilization of fluorouracil ointment. In the second case, the tumour was treated with topical use of fluorouracil or bleomycin hydrochloride, which was followed by the resection of tumour.

Dupin et al. [9] stated that genital warts are an epidermal manifestation attributed to the epidermotropic human papillomavirus (HPV) and that over 100 types of double-stranded HPV had been isolated and completely sequenced thus far by the time of publication of their article in 2004. Dupin et al. [9] also iterated that HPVs are grouped into low-risk (non-oncogenic) types such as type 6 and type 11, which cause benign anogenital warts (condyloma acuminata), and high-risk (oncogenic) types, such as types 16, 18, 31, and 45, which occasionally lead to cancer. Bryan et al. [10] Cancer-associated human papillomavirus (HPV) types are detected in genital warts that had been removed from immunosuppressed individuals more commonly in comparison with those occurring in otherwise healthy individuals. They also stated that the prognosis of genital warts containing cancer-associated HPV types was not known. Because it had been assumed that genital warts are benign lesions, they are usually treated by destructive therapies without prior knowledge of histopathology report of the lesion. Bryan et al. [10] undertook a study which was aimed to determine whether genital warts from individuals with or without human immunodeficiency virus (HIV) contain high-risk HPV types or areas of dysplasia. The study design was reported to be a non-randomized analysis of genital warts which had been removed by excision biopsy from 15 HIV-infected patients and 15 HIV-negative patients. The tissue was analysed for HPV DNA by hybrid capture, and microscopy pathology sections of each biopsy were examined for areas of dysplasia. With regard to the results, Bryan et al. [10] reported that Genital warts from HIV-infected patients contained cancer-associated ("high risk") HPV types in 9 of 15 cases, including 1 that contained only a high-risk type. High-grade dysplastic abnormalities were found present in 2 of the 15 lesions from this group, both of which had contained high-risk HPV types. Four genital warts removed from HIV-negative patients were found to have contained high-risk HPV types; however, none contained dysplastic abnormalities. Bryan et al. [10] iterated that genital warts from HIV-infected patients often contain high-risk HPV types and that such lesions may exhibit dysplastic changes. They also pointed out the following:

- The frequency of dysplastic changes in genital warts from HIV-infected patients was not known.
- Biopsy of genital warts might be indicated preceding additional therapy in HIV-infected patients, and surgical removal should be considered as a preferred treatment option in these patients.

Voltz et al. [11] undertook a study to ascertain the prevalence of the Human Papillomavirus (HPV) in Human Immunodeficiency Virus (HIV) infected men, using clinical examination and molecular hybridization in situ. With regard to the patients and methods, Voltz et al. [11] reported that from May 1995 to May 1997, they had studied the prevalence, clinical and histological characteristics, the types and the evolution of the HPV lesions among 121 HIV-infected men. The HPV DNA was determined by molecular hybridization in situ, using biotinylated probes which recognized HPV types 6/11, 16/18 and 31/33/35 in 79 p. 100 (5/19) of the patients (17 biopsies). Voltz et al. [11] summarized the results as follows:

- Sixteen per cent (19/121) of the patients were HPV infected: genital warts in 37 patients. 100 (7/19), anal warts in 37 patients. 100 (7/19), and ano-genital warts in 26 patients. 100 (5/19) of the patients.
- In every case of anal condyloma, intracanal lesions were found.
- In 47 patients. 100 (9/19) of the cases, histological examination showed an intra-epithelial neoplasia.
- The HPV types 6/11, 16/18 and 31/33/51 were positive in 53 patients. 100 (9/17), 35 patients. 100 (6/17) and 35 patients. 100 (6/17) biopsies respectively.
- High-risk types of HPV had been noted in 71 patients. 100 (12/17) of the biopsies.
- The evolution of the clinical lesions was: recovering in 47 patients. 100 (9/19) of the patients (after 3 months of treatment), recurrence in 16 patients. 100 (3/19) of the anal warts (after 1 to 3 months of treatment), stabilization in 16 patients. 100 (3/19) of the genital warts (after 6 months of treatment) and extension in 11 p. 100 (2/19) of the anogenital warts (after 3 months of treatment).

Voltz et al. [11] made the following conclusions:

- The high prevalence of condyloma and dysplasia emphasizes the importance of the anogenital exam in HIV-positive patients
- In the case of anal lesions, anoscopy and biopsy would be required.
- They do insist on the need to closely follow these patients with HPV lesions in order to adapt the treatment.
- Anal cytology and HPV-DNA detection by Hybrid Capture Assay, should be developed for the screening and prevention of the malignant transformation of HPV lesions in this population.

Kang et al. [12] reported a 72-year-old man who had a genital mass, which appeared to be composed of multiple papillomatous masses, who was referred for surgical resection. The lesion was first noticed 6 months earlier and had grown rapidly. CO₂ ablative laser therapy was undertaken twice at a primary clinic, but the mass had recurred. With regard to intervention and outcomes, Kang et al. [12] reported that excisional biopsy of the mass had revealed the presence of coexistent EMPD and CA. Additional wide excision was undertaken, and postoperative biopsy of the specimen confirmed no residual tumour. Two years after surgery, no recurrence had occurred. With regard to lessons that should be learnt, Kang et al. [12] stated the following:

- CA could co-occur with several types of skin malignancies, and a skin malignancy coexisting with CA is difficult to diagnose visually.
- In view of this, even if a skin lesion in the genital region is considered to be CA, they recommend the undertaking of punch biopsy before treatment because it can benefit the prognosis.

Kang et al. [12] made the ensuing iterations:

- It has been stated that extramammary Paget's disease (EMPD) is a rare skin cancer which does arise by epidermotrophic spread from an in situ or invasive neoplasm arising in an adnexal gland within dermis. [13]

- In view of this, the sites that are most commonly afflicted by EMPD are rich in apocrine glands, such as perineum, vulva, axilla, scrotum, and penis. [13], [14], [15]
- The commonest manifesting symptom of EMPD is pruritis, and clinically it is usually visualized as a demarcated, thickened, eczematoid, or crusted lesion with an irregular border.[13]
- It had been pointed out that the lesions had been noted to be occasionally hyper- or hypo-pigmented.[13]
- In addition, EMPD has tended to be difficult to distinguish visually from other skin lesions such as eczema, contact dermatitis, or Bowen's disease, [13] [16] and therefore, its diagnosis is quite often delayed.
- Pathologically, neoplastic cells that depict glandular differentiation tend to be observed in the form of intraepithelial (usually intraepidermal) infiltrations, [13] and thus cytokeratin 7, which is expressed in sebaceous glands and the secretory coils of eccrine glands, is a specific immunohistochemical marker for EMPD.[17]
- Condyloma acuminata (CA; anogenital warts) had usually been caused by human papillomavirus strains 6 or 11, though uncommonly by strains 16, 18, 31, 33, or 35. [18]
- CA had usually tended to be asymptomatic, even though this depends upon the size of the lesion as well as the anatomical location; however, it could be pruritic or painful. [9], [18], [19], [20]
- Clinically, CA has usually been encountered as a papillomatous eruption in genital mucosa and it is usually diagnosed by visual inspection.
- Only on rare occasions its diagnosis is confirmed by biopsy.
- At the time of publication of their article, available treatments for CA had focused upon wart removal rather than eradication of the underlying viral infection. [19]
- CA is treated utilizing topical agents (podophyllotoxin, imiquimod cream, or sinecatechins), by destructive or surgical treatments (trichloroacetic acid, cryotherapy, CO₂ laser ablation, or surgery), or by systemic interferon treatment. [9], [18], [19], [20]
- Only 3 cases of coexistent CA and EMPD had been reported. [21], [22], [23]
- They were reporting a rare case of coexistent EMPD and CA.

Kang et al. [12] reported a 72-year-old Asian male patient who had hypertension and who visited their urology department with multiple papillomatous masses of his penis and scrotum. The patient had reported that he first noticed the lesion 6 months preceding his presentation and that the lesion later had increased considerably in size. Initially, he visited a primary clinic where the masses were diagnosed as CA by visual inspection. CO₂ ablative laser therapy was administered twice, but the mass had recurred. Accordingly, he was referred to their institute for excision and reconstruction. Physical inspection had demonstrated a hypopigmented eczematoid plaque lesion (that measured about 8 cm × 6 cm in size) and a verrucous papule above the lesion ([Fig. 1](#)). Excision of the lesion and defect coverage with a local flap was planned, and his surgery was undertaken under spinal anaesthesia. Nevertheless, postoperative biopsy results following pathology examination of the excised penile lesion revealed the presence of coexistent CA and EMPD ([Fig. 2](#)), the presence of residual tumour in all excised margins, and that the tumour was confined to the epidermis. Chest and abdominopelvic

computed tomography were undertaken to exclude possible distant metastasis, but none was found. An oncologist who was consulted regarding the need for adjuvant therapy recommended that additional lymph node dissection and adjuvant therapy were not required and that treatment could be terminated after complete resection. Kang et al. [12] decided to excise remaining EMPD with a margin of 2 cm, and the excision was undertaken until examination of frozen biopsy showed that the surgical resection margins were negative for EMPD (Figure. 3A). In

addition, defects in scrotum and abdomen were covered utilizing a scrotal dartos musculocutaneous flap, and the penile shaft was covered utilizing a full-thickness skin graft (Figure. 3B and C). No recurrence was identified 2 years after the undertaking of the surgery (Figure. 4A), and no wound complication was encountered. In addition, full-thickness skin graft reconstruction of the penile shaft had provided sufficient elasticity to preserve erection function (Figure. 4B).



Figure 1: Preoperative photograph. 8.0 × 6.0 cm lesion on penis and scrotum with hypopigmented plaque and multiple papillomatous masses.

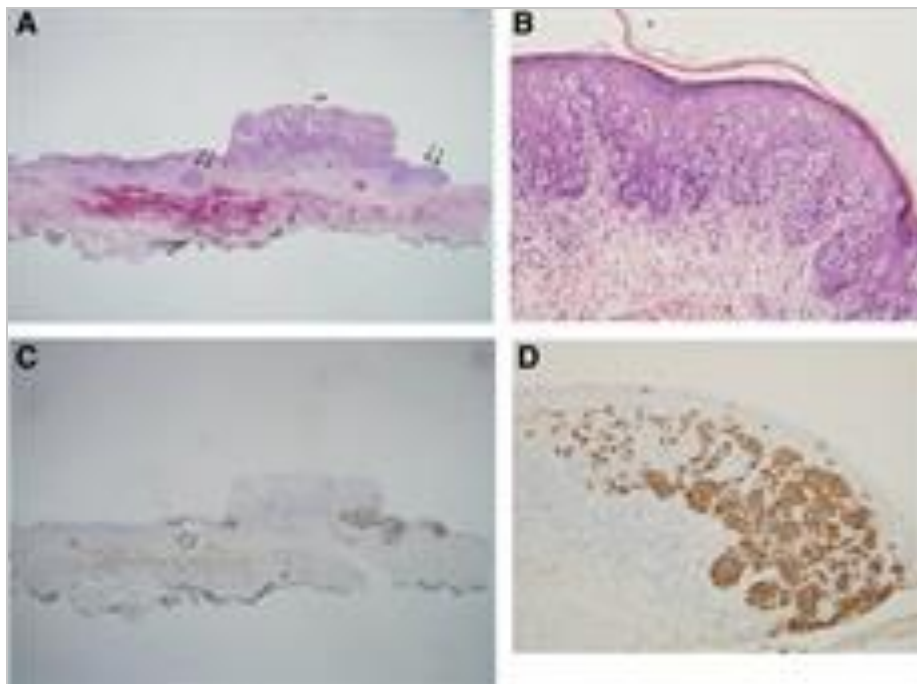


Figure 2: Histologic features. (A) A polypoid lesion of condyloma acuminatum was noted (asterisks), and the adjacent surface and follicular epithelium were thickened (arrows) (H&E, ×40). (B) At high magnification, large, atypical cells with abundant cytoplasm (Paget cells) were observed in thickened epithelium (H&E, ×200). (C, D) Immunohistochemical staining for allowed Paget cells, which presented as single cells or nests, to be easily identified at the periphery and base of the condyloma and adjacent thickened epithelium (CK7, ×40/CK7, ×200). CK7 = cytokeratin 7.

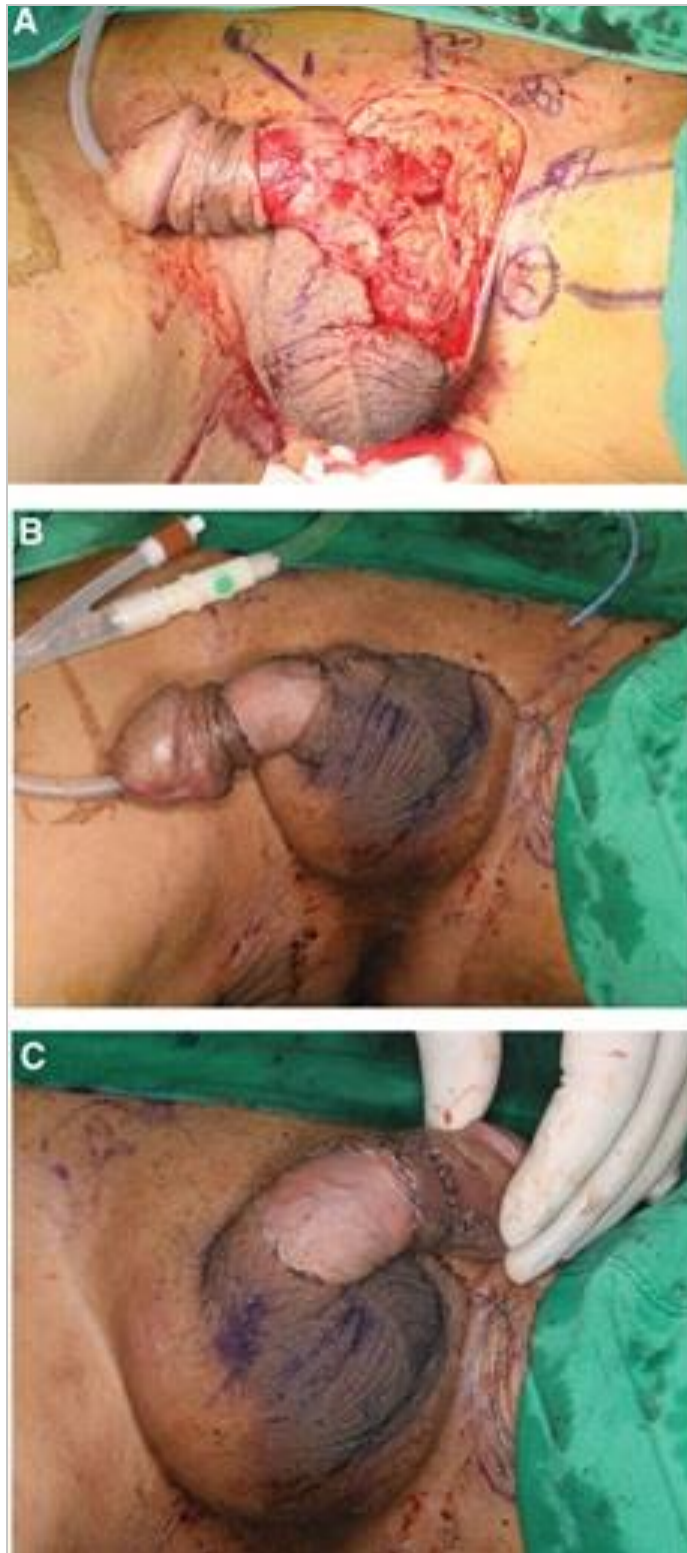


Figure 3: Intraoperative photographs. (A) Wide excision was performed with a margin of 2 cm. Excision was performed until the entire margin was negative, as determined by frozen biopsy. (B, C) Defects in the scrotum and abdomen were covered using a scrotal dartos musculocutaneous flap, and the penile shaft was covered using a full-thickness skin graft.



Figure 4: Postoperative photographs. (A) No recurrence occurred during 2 yr of postoperative follow-up, and no wound complication was encountered. (B) FTSG reconstruction of the penile shaft provided sufficient elasticity to preserve erection function. FTSG = full-thickness skin graft.

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Kang et al. [12] made the ensuing summing discussions:

- Only 3 cases of coexistent condyloma acuminatum and EMPD had been previously reported by the time of the report of their case. [21], [23], [23]
- EMPD is a slowly insidiously progressive intraepithelial skin cancer, and if it is left untreated and distant metastasis occurs the prognosis had tended to be poor.
- EMPD is difficult to differentiate from other skin lesions visually and it should be diagnosed based upon the undertaking of biopsy. [13], [15]
- Various treatment modalities had been suggested, including wide excision, laser ablation, radiotherapy, chemotherapy, and topical agent application, ^[1,3,13] but in non-invasive EMPD cases, wide local surgical excision with an adequate resection margin (2–3 cm) is the treatment of choice. [15], [24]
- If distant metastasis is suspected, sentinel lymph node biopsy and lymph node dissection may be undertaken, [24] ^[13] and depending upon the situation, radiotherapy or chemotherapy may be utilized.
- Non-invasive EMPD could be cured by wide local excision alone, but the prognosis of invasive EMPD is dismal.
- According to a recent study, the 5-year mortality rate of EMPD exhibiting deep dermal invasion was noted to be 85.71%. [25] In view of this, early detection and treatment are critical.
- CA could be treated with topical agents, laser ablation, cryotherapy, or surgery, even though most primary clinics initially adopt a method that is less invasive than surgery.
- Biopsies are rarely undertaken. Nevertheless, though less invasive methods destroy do CA and the encompassing tissues, they may mask a coexistent skin malignancy. In view of this, in cases of coexistent CA and skin cancer (EMPD, Bowen's disease, basal cell carcinoma, or squamous cell carcinoma), a diagnosis of skin cancer is likely to be delayed.
- Many reports of Bowen's disease, basal cell carcinoma, or squamous cell carcinoma accompanying CA had been issued. [14], [22], [26]
- The Centers for Disease Control and Prevention guidelines for anogenital warts had recommend that biopsy should be performed when a lesion is atypical (e.g., pigmented, indurated, affixed to underlying tissue, bleeding, or ulcerated) [18]
- When skin cancer is missed, the diagnosis had tended to be inevitably made in a more advanced state.
- In addition, visual diagnosis of a skin malignancy coexisting with CA without a biopsy is difficult to make, and thus, they would recommend the undertaking of a biopsy before treating condyloma non-surgically.
- In previous case reports, authors had discussed the possibility that CA and EMPD may interact synergistically during disease progression. [21], [22], [23]
- In their case, a pathology examination had shown CA and EMPD lesions were clearly demarcated, which had suggested it was unlikely that CA influenced the occurrence of EMPD, but as EMPD weakens nearby cell immunity, human papillomavirus infection may have initiated CA. [21], [27]

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

- CA could co-occur with several types of skin malignancies, but it is difficult to diagnose a skin malignancy coexisting with CA visually.
- In view of this, even if a skin lesion in the genital region is considered to be CA, they would recommend the undertaking of punch biopsy before treatment because it could substantially benefit the prognosis.

Chuang et al. [28] stated the following:

- The understanding of condylomata acuminata (genital warts) had been enhanced by the recent development of diagnostic methods.
- Forty-two types of human papillomavirus had been identified up to 1985, and at least sixteen types were noted to be involved in genital warts.
- The incidence of genital warts is about 0.1% in the general population and more than 0.5% in young persons.
- The incidence is known to be increasing rapidly and exceeding the incidence of genital herpes.
- Females are more prone to be affected.
- The epidemiology evidence supporting the relationship between genital warts and genital cancer has been overwhelming.
- The evidence had also spoken for a strong correlation between genital warts and verrucous carcinoma of the genitalia, bowenoid papulosis, and laryngeal papilloma.
- The person having genital warts might also have other cutaneous warts. This observation is compatible with the finding that types of human papillomavirus involved in other cutaneous warts were found in genital warts.
- In view of the newer and easier ways of diagnosing non-conspicuous condyloma acuminatum and the potential for the malignant transformation of condyloma acuminatum, it is strongly recommended that patients should be followed up periodically for early detection of neoplasia.

Atabay et al. [29] stated the following:

- The diagnosis of condyloma acuminatum generally relies upon the presence of characteristic clinical features.
- Nevertheless, atypical cases of condyloma acuminatum could cause diagnostic problems.
- With the development of the molecular biological techniques, the condyloma acuminatum disease can be readily diagnosed.

Atabay et al. [29] reported a case of atypical condyloma acuminatum in a 25-year-old male who had manifested with mid-penile hypospadias and a mass which had extended from his scrotum to his corona through his chordee deformity. The clinical diagnosis was condyloma acuminatum. A tissue specimen obtained from the mass was obtained for histopathological examination and in-situ hybridization assay for human papilloma virus. Histopathological examination of the specimen revealed papilloma. The immunohistochemical staining studies of the mass was negative for human papilloma virus. Nevertheless, in-situ hybridization for human papilloma virus was found to be strongly positive. Atabay et al. [29] stated and the following:

- Condyloma acuminatum should be suspected in hypospadias patients who have atypical papillomatous lesions on their chordee deformity.
- In-situ hybridization is extremely useful for the establishment of the diagnosis.
- In view of the fact that condyloma acuminatum is the cause of viral contamination and malignant transformation, it is worth considering histopathological examination and molecular biological techniques in order to protect both the patient and the sexual partner.

Juan et al. [30] stated that Giant condyloma acuminatum (GCA) is a rare, sexually transmitted disease with a high rate of local recurrence and malignant transformation. Nevertheless, the optimal treatment for patients in whom GCA coexists with penile cancer had not been well defined. Juan et al. [30] reported a case that was treated successfully with preservation of the penis. Wide tumour excision was undertaken and the patient received adjuvant intra-arterial chemotherapy with methotrexate. Juan et al. [30] evaluated the efficacy and functional outcome of penile preservation management for GCA with penile cancer transformation. In their reported case, no recurrence of penile tumour or of condyloma was found during follow-up for more than 12 months after treatment. The patient was very satisfied with the cosmetic and functional results following preservation of his penis.

Pineda-Murillo, et al. [31] stated the following:

- The Buschke–Löwenstein tumour is an epithelial tumour that was initially described in 1925.
- It tends to manifest within the fifth decade of life with a male-to-female ratio of 2.7:1.
- Data had shown that approximately 3 million to 4 million cases of genital warts in men occur each year with a peak rate of 500 per 100,000 in the 25–29-year-old age group. [32]
- There is an etiologic relationship with the human papillomavirus (HPV).
- More than 30 genotypes of HPV could infect the genital epithelium.
- Genital warts that are due to HPV are mainly associated with genotypes 6 and 11 (low risk), while anogenital squamous cell carcinoma is associated with genotypes 16, 18, 31 and 33 (high risk).
- Multiple investigations had been undertaken to differentiate verrucous carcinoma (VC) from giant condyloma of Buschke–Löwenstein (GCBL) and its relation to HPV2. [33]
- Risk factors do include lack of personal hygiene, promiscuity, smoking, chronic irritation, presence of foreskin and immunodeficiency (congenital and acquired). [30]
- The tumour comes from the confluence of multiple condyloma acuminata and is clinically manifested by warty, exophytic, ulcerated lesions, with aggressive behaviour, rapid growth, invasion and destruction of adjacent structures.
- In men, it is usually located within the penis (81–94%), anorectal region (10–17%) and urethra (5%), but it could be found in the scrotum and urinary bladder.[34]
- Within the penis, lesions typically occur around the coronal sulcus, frenulum and glans.
- Despite benign histology, the malignant transformation of Buschke–Löwenstein tumour had been reported in 30% to 56% of cases. [35] [36] [37]

Pineda-Murillo, et al. [31] reported a 57-year-old man who had type II diabetes mellitus, high blood pressure and a history of high-risk sexual behaviour with multiple partners, who was evaluated in the urology

department for multiple penile lesions of verrucous appearance and fetid odour of 10 months of evolution, which had prevented the foreskin retraction. His clinical examination demonstrated several confluent penile lesions of exophytic morphology including the prepuce, glans and coronal sulcus (Figure. 5). The results of his serology tests were negative for various sexually transmitted infections, including human immunodeficiency virus (HIV) infection. Along with his clinical examination, he had a computed tomography (CT) scan of his abdomen and pelvis which demonstrated the location and extension of the lesion as well as the involvement of inguinal lymph nodes, which were not affected. Biopsy of the lesion was undertaken and pathology examination of the specimen revealed a giant condyloma acuminatum that was associated with HPV. Conservative treatment with imiquimod cream (5%) was administered 5 days a week for a period of 1 month without any effective response, for which a partial penectomy was undertaken (Figures. 6, and 7). Management of the neourethra was crucial, being dissected from the corpus spongiosum distally for a distance of

approximately 1 cm and transected. It was spatulated on its dorsal surface in order to facilitate reconstruction and prevent the development of stenosis. The spatulated urethra was approximated to the penile skin to create an oblique meatus with its open side at the 12 o'clock position. The length of the shaft of penis that shaft remained after the surgical procedure was about 3 cm, which was considered to be an acceptable length to maximize functional outcomes. At his follow-up assessment, it was noted that the patient had preserved the ability to void in the standing position with effective capacity to direct the urinary stream. His sexual function was maintained due to a penis length that was greater than 2 cm, which is considered the minimum length to allow intercourse. The patient had remained with satisfactory evolution in close surveillance due to the high risk of recurrence, with consultations within the outpatient clinic every 3 months during the first year in which physical examination of the penis, urethral meatus and inguinal region is undertaken in search of new lesions, stenosis and adenopathies.



Figure 5:

Penile lesion of verrucous morphology including the prepuce, glans and coronal sulcus; Reproduced Under Copyright: **Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>),

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Figure 6:

Partial penectomy. **a** Urethral repair. **b** Closure of cavernous bodies. **c** Remaining penile tissue. Reproduced under Copyright: **Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License

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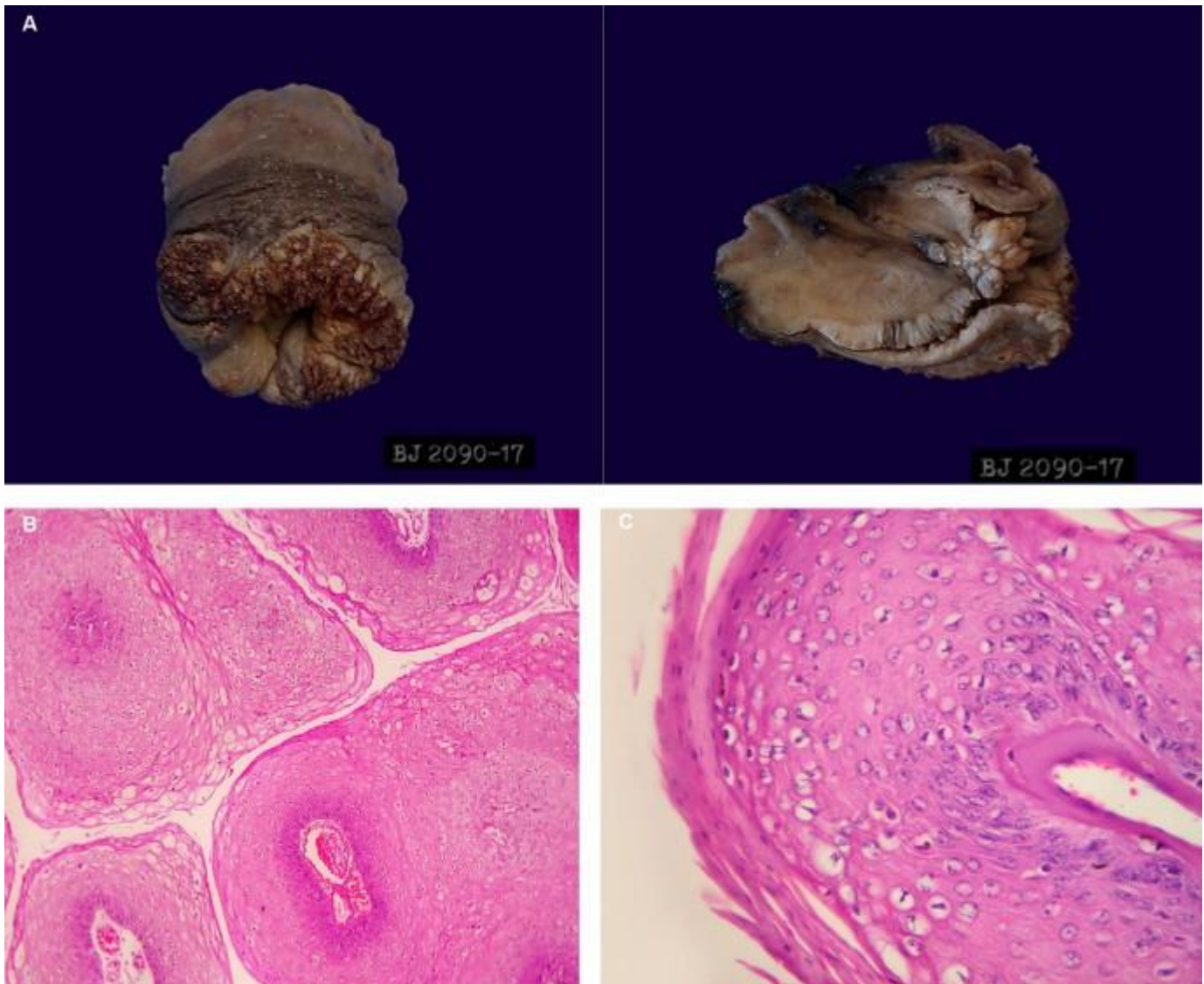


Figure 7:

a Macroscopic product of partial phallectomy. **b** Papillary projections coated by stratified squamous epithelium with acanthosis. **c** Cytopathic changes associated with human papillomavirus (HPV). Reproduced under copyright: **Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

Pineda-Murillo, et al. [31] made the ensuing summing discussions:

- GCBL had been treated by several modalities of treatment, which can be classified into three types: topical therapy (e.g., podophyllin, fluorouracil or radiotherapy), tumour removal (e.g., cryotherapy, CO₂ laser therapy or surgical excision) and immunotherapy (e.g., imiquimod).
- Nevertheless, the variety of treatment regimens that currently being applied at the time of publication of their article did not allow the formulation of definitive therapeutic guidelines.
- The application of imiquimod (5%), podophyllin (25–30%), trichloroacetic acid, 5-fluorouracil and bleomycin alone or combined with cisplatin or methotrexate has had variable results.
- Treatment with interferons 2 α and 2 β combined with laser therapy (Nd:YAG) had been described, as well as cryosurgery with some cases of success.
- Radical surgical excision with wide surgical margins has remained the first line of treatment, with a higher success rate (63–91%) and a lower rate of relapse. [38]
- However, penile skin loss and repair of the urethra could be a challenge for urologists.

- Surgical options include one-stage or two-stage procedures, utilizing either single or multiple tissue transfer [39] [40].
- Preputial and various penile skin flaps, such as a longitudinal flap, the hockey stick flap, the penile island flap and the circumferential/circumpenile flap, had been utilized for penile urethral reconstruction as good options when needed. [41] [42].
- A large representative biopsy specimen is important to judge the structure of the lesion in order to establish the diagnosis and to exclude VC. [43]
- In microscopy examination, invasion of the subepithelial tissue is seen by expansion rather than by infiltration, leaving the basement membrane intact.
- A well-stratified epithelium was shown with minimal cellular dysplasia or atypical cells, rare mitotic figures, acanthosis and hyperkeratosis and no evidence of neural or vascular invasion. [44]
- The risk for the development of recurrence after excision is 60% to 66%, with an overall mortality of 20–30%. [45]
- Close follow-up of these patients is crucial given the complexity and tumour recurrence.

Pineda-Murillo, et al. [31] made the following conclusions:

- The Buschke–Löwenstein tumour is a rare disease which is typified by giant slow growing condyloma acuminatum that is locally aggressive and destructive.
- Even though there had been reports of successful treatment with conservative modalities, the only consistently effective therapy is wide surgical excision of the tumour with clear margins with or without adjuvant chemotherapy.

Meliti et al. [46] stated the following:

- Condyloma acuminatum is an anogenital lesion caused by the human papillomavirus infection.
- It is a common, sexually transmitted disease.
- It usually affects the external genitalia, while urethral and bladder involvement has tended to be uncommon.
- Human papillomavirus types are classified into three categories depending on their oncogenic potential: low risk (type 6, 11, 42, 43, 44, 59, 66, 68, and 70), intermediate-risk (type 30, 31, 33, 34, 35, 39, 40, 49, 51, 52, 53, 57, 58, 63, and 64) and high risk (type 16, 18, 45, and 56). High-risk and intermediate-risk human papillomavirus DNA types, together with other co-factors still to be defined, account for over 90% of anogenital pre-malignant and malignant tumours.
- They were reporting a unique case of condyloma acuminatum positive for human papillomavirus -6 involving the penile urethra, presents as the primary and only site of the disease in a diabetic type-2 patient. [46]

Meliti et al. [46] reported a 47-year-old male patient, who was a known case of diabetes mellitus and hypertension, well-controlled on medications. He was known to have bilateral renal stones for which he underwent percutaneous nephrolithotomy (PCNL) and bilateral ureterorenoscopy (URS) with laser lithotripsy. The patient manifested to their hospital with visible haematuria, he underwent cystoscopy examination which demonstrated a papillary-like lesion that was suspicious for malignancy within his mid penile urethra extending

distally. However, his urethral meatus, prostatic urethra, and urinary bladder neck were normal endoscopically. Apart from bilateral kidney stones, the patient did not have any previous history of genitourinary pathology. Clinical examination of his external genitalia was unremarkable for gross abnormality. The urethral lesion was removed through urethrocystoscopy biopsy and submitted for histopathologic examination. Gross examination of the specimen showed a minute papillary-like tan tissue fragment. Microscopic examination of the specimen showed a fragment of papillary proliferation that was composed of hyperplastic non-keratinizing stratified squamous epithelium. In areas HPV-related changes were evident, including koilocytotic atypia (nuclear wrinkling with perinuclear halos), and binucleation (Figure 8(a) and (b)). Nevertheless, no convincing histopathological evidence of papillary urothelial carcinoma was found. P16 immunohistochemistry staining was positive (Figure 8(c)). In-situ hybridization (ISH) was positive for HPV-6 (Figure 8(d) and negative for HPV-16. Altogether, the histology features and molecular studies were adjudged to be diagnostic of condyloma acuminatum of the penile urethra. The postoperative stay of the patient was reported to be uneventful with a short hospital stay. The patient had been put on follow-up regularly at the outpatient urology clinic. He was healthy with excellent functional performance status at 5 months.

Meliti et al. [46] made the ensuing summing discussions:

- Condyloma acuminatum does uncommonly affect the male genital system, particularly the urethra.
- The involvement of the male urethra usually occurs in an association with external genitalia condylomata.
- A literature review had revealed few reported cases of isolated male urethra condyloma acuminatum.
- Olsen and colleagues had presented one example of condyloma acuminatum of the prostatic urethra without associated lesions on the external genitalia, but these condylomas were extensively involving the urethral meatus. [47]
- Fralick and colleagues studied 114 biopsy-proven HPV infection of the external genitalia, of which 14 were intraurethral lesions. Only 8 patients had presented with a single urethral lesion, and the remaining 6 with multiple lesions; all were confined to anterior urethra. [48]
- Their reported case represented an isolated penile urethral papillary growth without previous or concurrent evidence of external genitalia involvement. The initial clinical impression had raised the suspicion of a malignant urothelial neoplasm, particularly papillary urothelial carcinoma. Nevertheless, the histopathology examination revealed classic features of condyloma acuminatum. Confirmatory ancillary studies were positive P16 and HPV-ISH, which further supported the histology impression.
- Few studies had suggested that chronic diseases with long-standing immunosuppression such as diabetes mellitus could be the initiative causative factor for urinary bladder malignancy.
- Pathophysiology of long-standing insulin resistance, along with the metabolism of body fat, is more likely to generate an environment of cellular destruction. Ultimately leading to random genetic mutations and cell proliferation that can contribute to metaplasia and dysplasia-carcinoma sequence. [49]
- The morphological differential diagnosis of their reported case includes papillary urothelial carcinoma, squamous cell carcinoma (SCC), and verrucous carcinoma. High-grade papillary urothelial carcinoma predominantly exhibits significant disordered proliferation with loss of polarity, high N/C ratio, prominent nuclei, and atypical mitosis. SCC shows unequivocal malignant features either of keratinizing or non-keratinizing subtype with anaplastic cytonuclear changes. On the other hand; verrucous carcinoma could arise upon the

external genitalia, exhibits an exophytic, non-infiltrative growth pattern with bushing borders.

- The role of HPV testing might not be necessary for condyloma acuminatum diagnosis as the cytomorphologic features are usually sufficient for determination. Nevertheless, it is essential not to misdiagnose condyloma acuminatum as a malignant lesion to avoid overtreatment.

Meliti et al. [46] made the following conclusions:

- They had reported a unique case of isolated penile urethral condyloma acuminatum
- . Condyloma acuminatum does involve not only the external genitalia but also on rare occasions it could involve the prostatic urethra, urinary bladder, and ureter.
- Urologists and practicing pathologists should be aware of this uncommon event as a diagnostic pitfall and should always consider condyloma acuminatum in the differential diagnosis for malignant urothelial neoplasms to further enhance the clinical management plans safely.

Olsen et al. [47] stated that Condylomata in the urethra usually tend to occur as a complication ensuing genital warts upon the external genitals and they are most often situated within the distal part of the urethra. Olsen et al. [47] reported of a male patient who had recurring papillomatous transitional cell tumours, stage pTa and pT1, grade 2 and 3 in his urinary bladder and his right ureter, who had presented with extensive condylomatosis within his urethra from the meatus to the verumontanum, without simultaneous presence of condylomata at the external genitals. Olsen et al. [47] also reported that Condylomatous fragments were also found present in the TUR specimen from his urinary bladder, but may have been displaced from the urethra during cystoscopy. Using PCR technique and in situ hybridisation, HPV types 6/11 were detected in the condylomata, but no virus was present within his transitional cell tumours. The lesson that clinicians need to learn from this case summation is the fact that condyloma of the urethra which has been regarded as a benign lesion most of the time could be found associated with transitional cell carcinoma of the urinary bladder and the ureter.

Fralick et al. [48] stated that in order to develop guidelines as to which asymptomatic male patients who have genital human papillomavirus (HPV) infection need to undergo further evaluation of the urethra, they studied two screening methods: urethroscopy and voided urethral cytology. With regards to the methods of their study, Fralick et al. [48] reported that over a four-year period, 135 asymptomatic men had undergone complete screening for HPV infection, who were evaluated because of HPV-related genital disease in their female sex partners or visible genital lesions, or both. Fralick et al. [48] summarized the results as follows:

- Out of the 135 patients, 21 patients that amounted to 16% of the patients had no clinical, subclinical, cytological, or urethroscopic evidence of disease, and 114 of the patients that amounted to 84% of the patients had biopsy-proven HPV infection.
- Out of these 114 patients, only 14 patients that amounted to 12.3% of the patients had intraurethral condyloma.
- All of these 14 patients had current or historical evidence of meatal or peri-meatal "sentinel" lesions. They constituted 29.8 percent of 47 such patients with sentinel lesions.

- In 5 patients that amounted to 4% of the patients, the results of their voided urine cytology were positive for condyloma cells, but only 1 of these had visible intraurethral disease.
- Out of the 14 patients who had urethral disease, only 1 patient that amounted to 7% of the 14 patients had positive results of urine cytology.

Fralick et al. [48] concluded that these observations had indicated that any asymptomatic male patient undergoing screening for condyloma acuminatum who has a history of or demonstrable subclinical or grossly visible peri-meatal or meatal HPV infection should undergo the undertaking of urethroscopy as well as that voided urine cytology is not a reliable or cost-effective test for the detection of visible intraurethral disease.

Timm et al. [50] made the following summatory introductory iterations:

- Isolated urethral condylomata acuminata (CA) is an unusual subgroup of genital warts which had been encountered in 0.5–5% of cases. [51]
- It has been stated that HPV is sexually transmitted and the low-risk groups, DNA types 6 and 11, most commonly cause genital, perineal and anal lesions, which lend themselves to topical treatment. [52]
- Urethral lesions do tend to present a challenge in application particularly if the proximal urethra has been involved.
- First described by Dretler & Klein in 1975, [53] 198.administration of 5-fluourouracil (5FU) to the urethra had been utilized for the treatment of urethral CA with promising outcomes, even though exact administration details had been stated to be vague. [54]
- Surgical treatment of intraurethral warts by laser had been successful, even though it carries with it the risk of fibrosis and in the younger age population they believed the risk of stricture formation is too high. [55]
- They had described their technique for distribution of topical 5FU treatment to the entire urethra for the treatment of extensive pan-urethral CA and its outcomes in a patient where maximum flow rate (Qmax), post void residual (PVR) and cystoscopy evaluation were used as measures of response.

Timm et al. [50] reported a 28-year-old immunocompetent male who had manifested with increasing difficulty voiding over 6 months upon a background of previous cystoscopy investigation which had denoted no cause for obstruction. He was noted to be sexually active without concurrent sexually transmitted infection and no history or examination findings of genital warts. He underwent repeat cystoscopy following result of a Qmax of 7ml/s and PVR of 31ml upon his urine flow study. He underwent cystoscopy which demonstrated circumferential, pan-urethral polyps from the navicular fossa to his urinary bladder neck, (Figure. 8). The lesions were biopsied and pathology examination of the specimens demonstrated acanthopapillomatosis, surface hyperkeratosis and developed koilocytes, which pathologists had agreed was consistent with condylomatous histology (Figure. 9). Immunohistochemical staining studies of the specimen with p16 was found to be positive which is highly suggestive of human papilloma virus (HPV) infection.

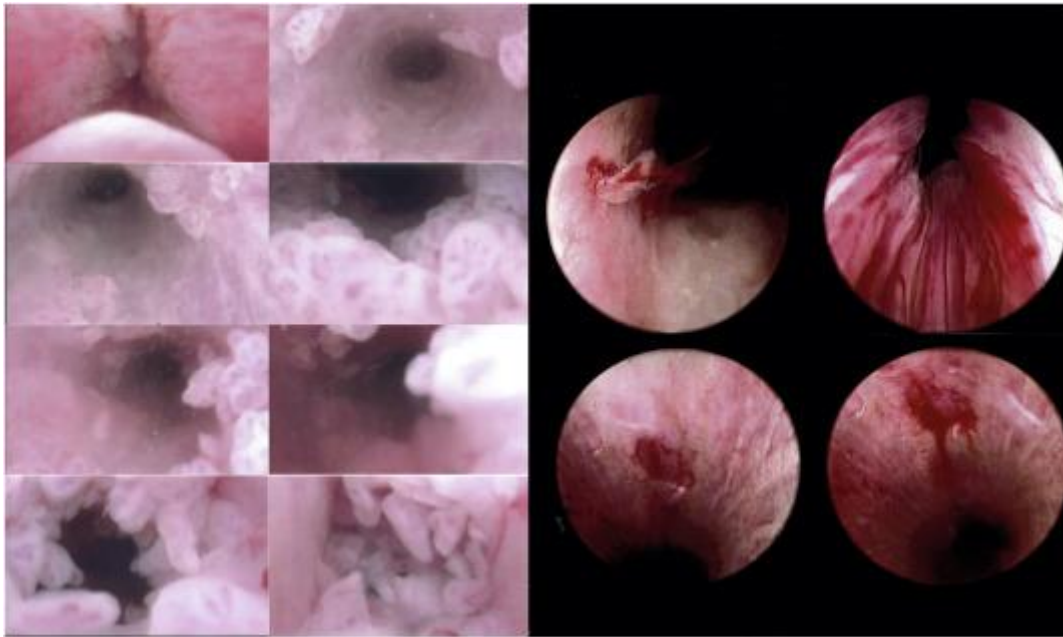


Figure 8: Cystoscopy findings pre-treatment and post treatment with urethral 5FU and focal surgical treatment. Reproduced from: [50] under Copyright. © 2020 The Authors. Published by Elsevier Inc. **Welcome to RightsLink**

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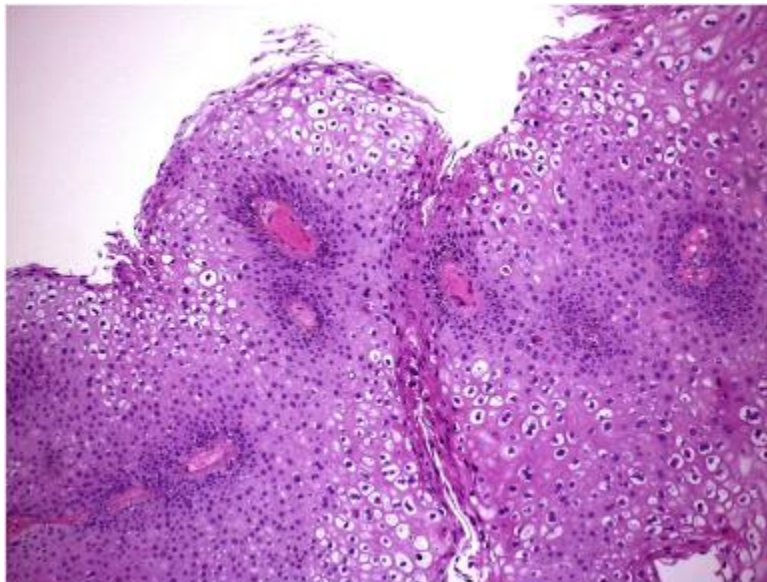


Figure. 9: H&E 100x magnification, features suggestive of condylomata acuminata -papillomatosis, surface hyperkeratosis and koilocytic change. Reproduced from: [50] under Copyright. © 2020 The Authors. Published by Elsevier Inc. **Welcome to RightsLink**

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Timm et al. [50] made the ensuing summing discussions:

- Condylomata acuminata are a frequent manifestation of the most common sexually transmitted disease, HPV.

- It has been stated that CA is associated with low-risk HPV (strains 6 and 11) in up to 90% of cases. [55]
- Whilst CA is associated with low-risk HPV, it does not exclude the possibility of malignancy and hence histopathology assessment is advised.
- A treatment protocol had been developed in coordination with the Melbourne Sexual Health Centre. Weekly rather than daily instillation of 5FU was elected for treatment as more significant

side effect profiles have been encountered with daily application. [51] [52] [54]

- The previous report by Wein et al. which had utilized self-instillation described as a “squeeze” of 5FU via urethral applicator after every void caused significant meatal ulcers, erosions and burning following treatment. [51]
- Their induction treatment of 10g of 5FU weekly for 8 weeks avoided complications and was associated with only mild irritative symptoms.
- Combination therapy of surgical and topical treatment had demonstrated improved outcomes compared with single modality treatment alone in recurrent urethral CA. [55]
- Extensive surgical treatment may lead to stricture formation and therefore we advocate for debulking medical treatment prior to surgical intervention in extensive pan-urethral disease.
- Equipment that was required for their 5FU instillation method: 2% lignocaine gel 10ml, 5FU 10g, Sterile gloves, normal saline, penile clamp, dressing pack (gauze and plastic pots/forceps).

NB – all surfaces must be non-metal to preserve function of 5FU.

- The procedure: Tube of 5FU is weighed to ensure correct dosage (If > 10g tubes available, able to be split and stored for multiple applications - in consultation with pharmacy). Sterile drape is placed upon scales including a sterile pot from catheter tray and contents of tube of 5FU are squeezed into pot and weighed to ensure correct dosage. A 10 ml Lignocaine gel 2% is then added to pot with 5FU and mixed with plastic forceps. Utilizing lignocaine syringe, mixture is drawn up and applicator tip is replaced (Figure. 10). The glans penis is then cleansed with normal saline and Lignocaine syringe is inserted gently into the urethral meatus where the mixture is slowly instilled. The meatus is manually occluded while the remaining volume of mixture is re-collected and administration is completed. A penile clamp or patient compression at distal glans penis is applied for 30minutes. Following release, the glans is cleansed with normal saline soaked gauze and the patient returns home to void and shower in an effort to avoid irritant side effects.



Figure 10: Equipment set up and administration preparation by our practise nurse. NB – Importance of all plastic utensils to avoid metal ion binding and making the 5FU less effective. Reproduced from: [50] under the Creative Commons Attribution License.

- Pursuant to the 8-week induction course, an improvement in Qmax and PVR was demonstrated, most notably prior to the third instillation. Measures of Qmax and PVR following

instillation at 1st, 2nd and 8th instillation were 7ml/s, 15ml/s, 19ml/s and 311ml, 230ml and 160ml respectively.

- Subjective and objective improvement in flow was notable following a single instillation.
- Increased sloughy debris was found following fifth treatment, even though testing for infection was negative.
- Surveillance cystoscopy at 9 weeks had demonstrated significant volume reduction of the lesions; nevertheless, a small volume of residual CA at the neck of the urinary bladder and navicular fossa remained (Figure 8). These were removed by cold cup biopsy forceps without cautery or laser. The application of 5FU over 8 weeks was repeated a further time in an effort to reduce the risk of recurrence. At check cystoscopy there remained a single papilloma at the navicular fossa which was removed again by cold cup biopsy forceps.
- Both Wallin et al. and Wein et al. had encountered similar difficulties with clearance of CA within the navicular fossa using 5FU. [51] [54]
- Pursuant to the findings of recurrence of CA in the navicular fossa after 2 courses of 5FU, they had adopted the patient occluding the most distal portion of the glans in an effort to improve instillation time of 5FU and reduce risk of glans irritation.

Timm et al. [50] made the following conclusions:

- In the absence of readily available premixed 5FU compounds for intraurethral application, sterile combination of 5% 5FU with lignocaine 2% gel allows for a technically feasible and tolerable treatment regimen to minimise disease burden.
- This decrease in disease volume diminishes the need for extensive surgical intervention which may lead to the development of urethral strictures in the younger populations.
- Notably since the introduction of Quadrivalent HPV vaccination in 2007 there had been a declining incidence of genital warts, and, in time, urethral warts are likely to be relegated to the annals of historical curiosities.

Vageli et al. [56] stated the following:

- Penile warts in infants are rare and cases of condylomata acuminata at the urethral meatus are rarer.
- Their reported case was the first report of a 2.5 years infant with a condyloma acuminatum at the urethral meatus of penis which was found positive for HPV 6, by PCR analysis.
- The Infant's mother presented warts on her hands, which had suggested a possible transmission of virus from mother to infant via extragenital contact, without excluding a vertical transmission.
- It has been documented that Genital warts in children are not frequent while penile warts are even rarer [57] [58] [59] [60] [61]
- The youngest documented case of this type of lesion was a 7-month-old circumcised Caucasian boy who had manifested

with a rapidly progressing giant penile condyloma acuminatum which had been surgically removed followed by a fatal course of Neisseria meningitis. This case has served as a warning, concerning the course of condyloma acuminatum in infants, since the infant had died from meningococemia five days after undergoing surgery. [61]

- Condyloma acuminatum of the urethral meatus is very rare while there was only a single report of a 5-year-old child who had presented such a lesion without HPV infection history. [61]
- They were reporting a HPV infected penile condyloma acuminatum at the urethral meatus, of a 2.5 year old infant, with a possible virus transmission from mother to infant.

Vageli et al. [56] reported a 2.5-years-old infant, who had manifested with a penile condyloma acuminatum at his external urethral meatus, who attended the Paediatric Surgery Clinic of General Hospital of Larissa (Figure 11). His mother had mentioned that she had presented warts on her hands. The condyloma was surgically removed and two years after surgery the child was still healthy. The condyloma mass was subdivided to a part that was taken for the standard histopathology examination while the remaining tissue was immediately immersed into stabilization solution and frozen to -20°C. DNA was extracted from tissue using Puregene® Cell and Tissue extraction kit (Gentra Systems, Inc., USA) and an HPV detection molecular method was applied, as was previously described. [62] [63] In brief a multiplex PCR (MPCR) was employed for the detection and discrimination of HPV types 6, 11, 16, 18 and 33 (specific E6 gene) utilizing a commercial kit (MPCR kit, Maxim Biotech) which included specific primers for each HPV type and corresponding positive control samples. The results of HPV-positive sample were reconfirmed by a PCR analysis utilizing specific primers for each HPV type only (Maxim Biotech). Vageli et al. [56] utilized non-template negative control samples, in each PCR reaction to exclude false positive results. The PCR products were electrophorized through 2% agarose gels, stained with 0.5 mg/ml ethidium bromide and visualized on a UV light transilluminator. The detection of specific sizes bands indicated the presence of target sequences, which corresponded to HPV type specific, in their specimen (Figure 2). Vageli et al. [56] undertook a melting curve analysis of PCR products to confirm HPV 6 genotype. Vageli et al. [56] undertook melting Curve analysis in Corbett RotorGene instrument as they had have described previously. [62] [64] utilizing SYBER Green (QuantiTect kit, Qiagen) and ramping 65-95°C (raising by 0.2°C each step). With regard to the results, Vageli et al. [56] stated that PCR analysis for HPV detection and typing had revealed that the DNA sample, derived from the penile condyloma acuminatum of the infant, was positively stained for HPV type 6 (Figure 12). Specifically, agarose gel electrophoresis of our specimen showed a 263-bp amplified PCR product, like HPV-6-positive control, corresponding to PCR amplified specific E6 gene of HPV type-6 (Figure 12). Confirmation of HPV6 genotype was undertaken performing a melting curve analysis of penile condyloma and HPV6 positive control PCR products. Both samples had shown melting peaks that corresponded to HPV6 genotype (Figure 13).



Figure 11: A condyloma acuminatum at the urethral meatus of an infant's penis.

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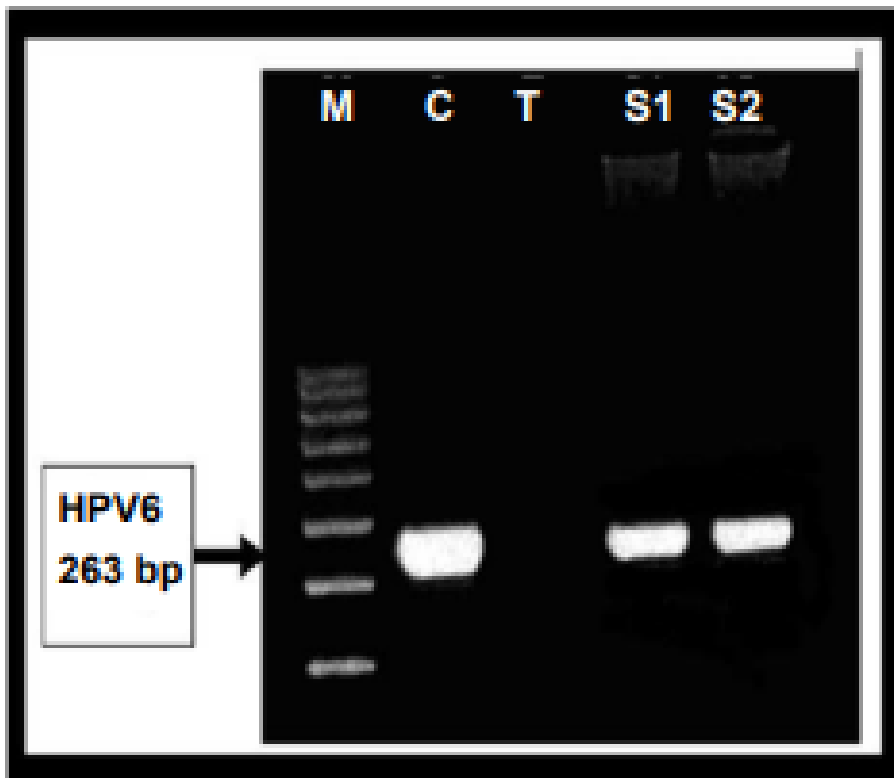
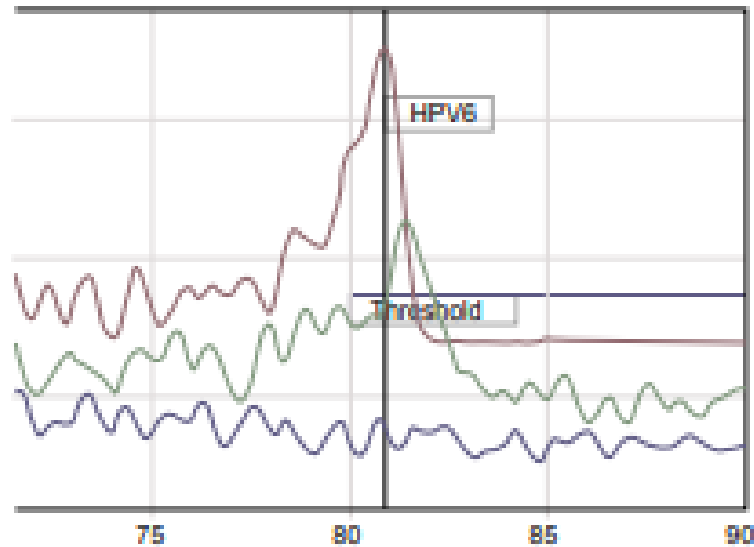


Figure 12: Detection of HPV 6 DNA, in a condyloma acuminatum derived from the urethral meatus penile of a 2.5 years infant, using HPV6-genotype specific primers. Lane M: DNA Molecular Weight Marker (100bp ladder); Lane C: HPV6 positive control; Lane T: Non-template negative control; Lanes S1 & S2: HPV6 positive amplified PCR products of DNA sample derived from the infant's penile condyloma. Reproduced from: [56] Under Copyright: doi:10.4172/2157-7412.1000157 Copyright: © 2013 Vageli DP, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

Melt data for Melt A.FAM/Sybr

No.	Colour	Name	Peak 1
1	Red	HPV 6 Positive Control	80.9 (HPV6)
2	Green	Penile Sample	81.4 (HPV6)
3	Blue	NTC	
Std. Dev.			0.35



This report generated by Rotor-Gene Real-Time Analysis
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Figure 13: Melting curve analysis of a HPV 6 positive sample, derived from a 2.5 years infant's penile condyloma acuminatum and a HPV6 positive control. Melting peaks at 81°C correspond to HPV6 genotype. Reproduced from: [56] Under Copyright: doi:10.4172/2157-7412.1000157 Copyright: © 2013 Vageli DP, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

Vageli et al. [56]] made the ensuing iterations:

- They had reported a rare case of an infant who had a penile condyloma acuminatum at his urethral meatus that had been analysed by PCR method and which was found to be positive for HPV type 6.
- In bibliography, it had been referred to a single case of a condyloma acuminatum of the urethral meatus in an infant, without a history of HPV infection. [61]
- Genital HPV infection in children appeared to behave as a sexual transmitted via abuse [65] or vertically transmitted or extragenital contact transmitted. [66] [67]

Conclusions

- Until recently, condyloma acuminatum has been regarded as benign growth with no malignant potential.
- The histopathology features though similar, but byet clinically different, giant condyloma acuminatum (Buschke-Lowenstein tumour) has been defined as a mass with downward growth which does not depict any histologic malignant changes, even though the clinical course might be malignant.

- It should be noted that condyloma acuminatum of the penis could be associated on rare occasions with other lesions of the penis including malignant tumours within the penis therefore a thorough histopathology examination of all cases that are provisionally diagnosed as benign condyloma acuminatum should be biopsied and thoroughly examined by a well-trained pathologist to ascertain if the lesions are solely condyloma acuminatum or the condyloma acuminatum is associated with a malignant penile tumour.
- On rare occasions malignant degeneration of condyloma acuminatum or the Buschke-Lowenstein tumour might precede or be associated with squamous cell carcinoma.
- Condyloma acuminatum of the urethra could also be associated with urothelial carcinoma of the urinary bladder and ureter and hence clinicians who see patients who have condyloma acuminatum of the urethra should thoroughly assess their patients to ascertain if the patients have other lesions including urothelial carcinoma.

Conflict of interest – None

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