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Clinical Manifestations of the Human Papillomavirus

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1. Introduction

1.1. Skin injuries

1.1.1. Benign skin lesions

The global prevalence of papillomavirus in the 4- to 18-year-old population has been estimated to be 24% (12% for those aged 4 to 6 years and 24% for those aged 16 to 18 years) [1]. The prevalence is significantly reduced in adults (3.5%) [2]. There are no significant differences related to gender. There is, however, a higher prevalence in rural versus urban schools. While plantar and common warts generally number 1 or 2, flat warts frequently appear as multiple lesions [1].

HPV transmission requires the inoculation of the virus into the basal epithelia cells, which occurs on sites that are particularly predisposed to microtraumas. Therefore, it is not surprising to frequently find common warts on the hands and fingers (Figure 1). Lesion regression is frequently spontaneous, and the immune system plays an important role, as is reflected in practice by the increased HPV susceptibility of immunosuppressed patients. In these cases, the lesions are clinically more exuberant and recalcitrant to treatment [3]. It is important to highlight a particular collective group composed of butchers and slaughterhouse workers who, without immunosuppression, have a higher risk compared to the general population [4, 5]. This group has an increased incidence of the HPV7 subtype, and it is thought that some component of meat favors the replication of this viral subtype [6, 7].

1.1.1.1. Common warts

This infection is fundamentally produced by HPV subtypes 1, 2, 4, and 7 [8]. The lesions are usually asymptomatic, although they can be painful when located in pressure zones. Clinically, they are easily diagnosable; thus, the patient frequently brings up the presence of lesions during a consultation. Common warts can manifest as a single lesion; however, because of the virus's infectious nature, multiple lesions can be found in the same patient [1]. The lesions present progressive growth such that they are initially about the size of the head of a pin, and they are smooth and shiny. Over the course of weeks, they acquire their typical characteristics. On inspection, they present as papules with well-defined borders and with the same color as the skin. The surface is flattened; it may be whiter than the surrounding skin as an expression of hyperkeratosis of the lesion itself, and it may have a multilobulated aspect (Figures 1 and 2). The hyperkeratosis and multilobulate aspect confer a rough surface upon palpation. Occasionally, the exuberant development of hyperkeratosis can produce the formation of a cutaneous horn. Depending on the characteristics of the host and the anatomical location of the cutaneous horn, a histological study of the lesion may be necessary for a differential diagnosis with malignant lesions, such as epidermoid carcinoma. When the lesions are multiple, they can present as distinct isolated lesions, as close-by lesions and even as confluent lesions ("mosaic"). Lesions can be numerous in immunosuppressed patients (i.e., those who are transplanted or HIV-positive or have Hodgkin's lymphoma or leukemia) [3, 8-11]. Characteristically, lesions may be located on the nail fold. This location is particularly associated with the habit of nail biting [12]. Thus, breaking this habit can prevent new lesions in adjacent nails that have not yet been affected.



Figure 1. Erythematous hyperkeratotic papule on the arm: common wart.

Although the clinic is generally sufficient for diagnosis, dermatoscopy is a useful tool that provides complementary information for cases involving clinical doubts. Dermatoscopically, common warts are characterized by the presence of dense papillae, each centered around a



Figure 2. Papule with well-defined borders and with the same color as the skin on the finger compatible with common wart.

central red dot or a loop surrounded by a whitish halo. This combination of characteristics creates a “frog spawn” appearance [13].

Because of their frequency and similarity from a clinical point of view, the main differential diagnoses are nonpigmented seborrheic keratosis, fibrous papule of the nose (angiofibroma), intradermic nevus and warty epidermal nevus.

The histology is characterized by marked hyperkeratosis, acanthosis and papillomatosis. Nevertheless, these features are not specific to this type of lesion. As a characteristic sign of HPV's cytopathic effect, koilocytes (cells with a pyknotic nucleus surrounded by a clear halo) are observed [14].

1.1.1.2. Filiform warts

These are considered a special variant of common warts. They are predominantly localized in the palpebral and perioral regions and in the neck. Their distinctive characteristic is the special filiform or elongated morphology, with a narrow pedicle and pronounced digital projections on the surface (because of this, they are also called “digitiform papilloma”) (Figure 3). The main differential diagnosis is with acrochordons, which can have a similar morphology but are differentiated by their smooth surface (they lack digital projections). The histological peculiarity of filiform warts is that the papillae are more elongated than those of common warts.

1.1.1.3. Plantar warts

HPV 1 frequently causes these lesions, and it occasionally causes Type 4 lesions [14]. They can manifest as single or multiple (“mosaic”) lesions (Figure 4). Trauma plays an important role in the inoculation of the warts, as the most commonly affected sites are the heel and the heads of the metatarsi.



Figure 3. Filiform papule on the upper lip with pronounced digital projections on the surface compatible with filiform wart.

The main differential diagnosis between plantar warts and plantar callus is important because the two disorders are frequently confused in clinical practice. Although the most frequent locations for the emergence of warts are pressure zones, warts can also appear in areas that experience less pressure, such as the arch of the foot. This location, however, is not common for calluses, which are produced as a consequence of pressure on the skin. A clinical maneuver for distinguishing warts from calluses is tangential scraping: in calluses, the detachment of multiple hyperkeratotic layers with a clean central fundus is observed, whereas warts present a multilobulated aspect above the superficial hyperkeratotic layer, accompanied by multiple black dots that correspond to thrombosed capillaries. In contrast, warts are indicated by certain dermatoscopic signs, such as black to red dots, globules corresponding to dilated and thrombosed capillaries of the papillae and interrupted dermatoglyphics in the lesion. Calluses present a translucent central corn or a homogeneous opacity [15].

The use of the dermatoscope has been described as useful for monitoring the need for new treatment sessions for warts because dermatoscopes are more sensitive than the naked eye [15].

1.1.1.4. Flat warts

HPV 3 and 10 commonly produce this lesion. [14] This type of wart is typical in childhood. It is very rare in male adults and has been described in the context of HIV infection [16]. The most commonly affected area is the face, followed by the back of the hands and the shins. [14] The aspect is that of a papule or slightly elevated flat plaques (2-3 mm) and low desquamation (smooth surface). Coloration ranges from light brown to the color of the individual's skin, thus making flat warts hard to detect with simple inspection. Histologically, flat warts are characterized by less acanthosis than common or plantar warts, and papillomatosis is minimal or absent.



Figure 4. Plantar wart: Multiple hyperkeratotic lesion on the sole of the foot with thrombosed capillaries (black dots).

For differential diagnosis in the face, the syringomas, seborrheic keratosis, and papulosis nigra stand out. Warty epidermal nevus, present from early childhood and following the Blaschko lines, is another diagnosis to consider.

1.1.1.5. Pigmented warts

Subtypes 65, 4 and 60 are the main causes of pigmented warts [17]. Egawa was the first to describe these subtypes in 1988 [18]. Although common warts and molluscum contagiosum can transform to a black color [19, 20] in their involutionary phases, pigmented warts are pigmented from the initial phases. They are fundamentally located on the hands and feet. The lesions are morphologically similar to common warts when they are located in the lateral side of the hands and feet and on the fingers and toes (Figure 5); when they are located on the sole, they can have the aspect of flat, pigmented warts with light hyperkeratosis on the surface [17], but with the particularity of their brown-black coloration. Although the clinical diagnosis is not difficult, lesions on the sole can be proposed for a differential diagnosis with acral melanoma. Surface hyperkeratosis usually guides diagnosis. However, when in doubt, histological analysis can be used for diagnosis.

One histological peculiarity of pigmented warts is the presence of intracytoplasmic inclusion bodies consisting of a homogeneous eosinophilic substance together with swollen nuclei, very similar to cases associated with Types 65 and 4. In the case of HPV 60, the inclusion bodies are similar but have a much rounder shape and no edema in the nucleus [17]. In contrast, not all of the other HPV subtypes are associated with inclusion bodies; when present, inclusion bodies are characterized by eosinophilic bodies and not by a homogeneous substance [21].



Figure 5. Pigmented hyperkeratotic papule on the finger: pigmented wart

1.1.1.6. *Epidermodysplasia verruciformis*

This is a rare genodermatosis that is generally autosomal recessive hereditary, although X-associated heritage has also been described. It has been classified as a primary immunodeficiency [22] in which there is a curious and particular susceptibility to infection by HPV- β subtypes [23]. The types most frequently implicated are HPV 5 and 8, although many others have also been associated. Most of the cases are associated with mutations in one of the genes located in the long arm of chromosome 17 (EVER1 or TMC6, and EVER2 or TMC8) [24]. These genes code for transmembrane proteins that are fundamentally found in the endoplasmic reticulum and interact with the zinc transporter (ZT1) [23]. It is believed that a selective inhibition of T lymphocyte immune responses against HPV exists, most likely because of defective viral antigen presentation on keratinocyte surfaces [25].

Clinically, this infection is characterized by the appearance at an early age of multiple flat warts, pityriasis versicolor-type lesions, and other lesions similar to seborrheic keratosis (Figure 6) [14]. However, the major interest is in the high risk of developing squamous cell carcinoma, especially in photoexposed zones (30 to 50% of patients) between the third and fourth decades of life [14, 23]. Based on the risk of developing malignant lesions, two phenotypes have been distinguished. One phenotype is indicated by more benign lesions that are flat, desquamous and hypo- or hyperpigmented in a manner similar to that of tinea versicolor; these lesions are distributed on the neck, torso and extremities. The other phenotype is characterized by seborrheic keratosis-type warty lesions that have a higher malignant potential. These lesions are distributed primarily on photoexposed zones, such as the face and hands, and on the feet. The development of these malignant lesions is usually associated with Types 5 and 8. However, unlike the pathogenesis of other oncogenic HPV, these types do not seem to require integration into the host genome [23].

Recently, epidermodysplasia verruciformis (EV)-like clinical appearances have been described in immunosuppressed patients, such as HIV and transplantation patients [26, 27] This phenomenon has been called “acquired EV form” [26]. It has been hypothesized that these

forms can create minor defects in patients with predisposing genes, and these defects manifest clinically upon immunosuppression [24].

From a histology perspective, EV is characterized by the presentation of hyperkeratosis, hypergranulosis, and acanthosis. However, the characteristic feature is the presence of large keratinocytes with a blue-grey granular cytoplasm in the superior portions of the squamous stratum and in the granulose. As has been noted, the lesions can present a progressive atypia until the development of invasive squamous cell carcinoma [14].



Figure 6. Multiple flat warts and pityriasis versicolor-type lesions in a patient with epidermodysplasia verruciformis

1.2. Malignant skin lesions

1.2.1. Squamous cell carcinoma of the skin

Squamous cell carcinoma (SCC) is the second commonest malignant skin tumor (the first one is basal cell carcinoma). Ultraviolet (UV) radiation is the main risk factor for skin cancer and this tumor usually appears in sun-exposed areas specially the face, neck, arms and hands. Changes in lifestyle over recent decades have led to greater exposure to ultraviolet radiation; this phenomenon increases the risk of developing skin cancer. In the last 25 years there have been an increased in the incidence of this tumor due to sun exposure and increased life expectancy [28]. SCC can complicate other lesions as burn scar, lichen planus, discoid lupus, epidermoid cyst or venous ulcers. Other risk factors include older age, fair skin and immunosuppression. Emerging evidence suggests that cutaneous human papillomavirus (HPV) infection may also be a risk factor for SCC.

Despite the role of HPV in sunlight induced malignancies is uncertain as in squamous cell carcinoma there have been some evidence of the association between some subtypes of HPV and squamous cell carcinoma of the genital area. HPV 16 has been detected in squamous cell carcinoma of the vulva, penis and perianal region. [29] The inactivation of tumor suppressor genes by HPV has been implicated in the development of SCC. In HPV infection, the onco-

protein E7 inactivates the tumor suppressor Rb, leading to p16 upregulation. Recently new studies have shown that Genus-beta HPV (seropositivity) infections were associated with SCC in any locations [30]. Patients with HPV related squamous cell carcinoma are characterized by a higher rate of recurrences but not more metastases compared to ordinary SCC and also many patients present genital lesions containing the same HPV type [31]. Moreover patients with SCC of penis, scrotum and anus are associated with higher risk of metastases. Also immunosuppressed patients for renal transplantation or with epidermodysplasia verruciformis (HPV 5) develop SCC associated with VPH. UV radiation and HPV may play a synergic role in the development of squamous cell carcinoma and a recent study has shown that seropositivity for HPV types in genera alpha or beta increased the risk of SCC associated with poor tanning ability [32].

Clinically SCC presents as shallow ulcers, papules or plaques often with keratinous crust and elevated surrounds commonly in photo-exposed areas (Figure 7). It is not uncommon to find an in situ SCC under a cutaneous horn. Patients rarely complain about pain or pruritus. SCC usually bleeds with minor trauma. The adjacent skin usually shows features of actinic damage (actinic keratosis). Pigmented variants are rare. SCC should be suspected in patients with permanent or bleeding recurrent ulcer. Prognosis depends on the risk of recurrence and metastasis. The overall recurrence rate varies from 3 to 11% and the overall metastasis rate is around 5%. Tumor thickness and desmoplasia are multivariate factors associated with local recurrence and tumor thickness, immunosuppression, ear location and tumor diameter with the risk of metastasis.



Figure 7. Infiltrated and erosive tumor of the helix compatible with squamous cell carcinoma of the skin

Actinic keratosis is a well-established precancerous skin lesion that has the potential to progress to squamous cell carcinoma. Clinically it is presented as a circumscribed scaly erythematous lesions, usually less than 1cm in diameter on the sun-exposed (face, ears, scalp, hands) skin of older individuals. They may remit or remain unchanged for a long time but between 8-20% gradually transform into a SCC. Several clinical variant of actinic keratosis has

been described: hypertrophic, acantholytic, pigmented and lichenoid. Intermittent sun exposure and sunburns during the childhood are strongly associated with the prevalence of actinic keratosis. Recently HPV infection has been associated also with the risk of developing these lesions [33].

A clinical well-differentiated variant of SCC is verrucous SCC which is named different according to the localization, in oral mucosa florid oral papillomatosis, in the genital area giant condyloma of Buschke-Lowenstein and in the soles caniculatum carcinoma. Differential diagnosis includes verrucous hyperplasia, pseudoepitheliomatous hyperplasia and giant condylomas. These tumors present a low rate of metastases but tend to infiltrate easily. Radiotherapy is not indicated as usually recur in a more aggressive manner. The role of human papillomavirus infections in the development of verrucous carcinoma is controversial in the literature, and although some clinical cases have shown and HPV positivity (type 6, 11, 16, 18) a recent study do not support a causal role of HPV in the development of verrucous carcinoma. [34]

SCC of the oral or anogenital mucosa tends to metastasize and be more aggressive than the one originated in sun-exposed skin. Oral carcinoma usually affects lower lips but also in the tongue and inside the oral cavity (palate). Special risk factors for this location are smoking and alcoholism. SCC in oral mucosa begins as an erythroplasia plaque that evolves into a nodular and granulomatous plaque. A recent study which included 172 patients with advanced oral cavity squamous cell carcinoma detected a prevalence of HPV infection in 22% of the tumors [HPV-16 (9%) and HPV-18 (7%)]. A comparison with the group of patients with HPV-16 negative infection revealed that those with a single HPV-16 infection are at higher risk of distant metastases and poor survival despite undergoing radiation-based adjuvant therapy and require a more aggressive adjuvant treatment and a more thorough follow-up whereas HPV-18 infection had no impact on 5-year prognosis [35].

Keratoacanthoma is a rapidly growing skin tumor arising predominantly on the exposed surfaces of the body that should be considered as a variant of SCC rather than a benign or pseudomalignant neoplasm. Clinically they present as a smooth, hemispherical papule that rapidly enlarges over the course of a few weeks with a central keratin-filled crater. Usually involution occurs with tumor resorption and loss of the keratin plug. The role of HPV in keratoacanthoma remains thus elusive but a study showed that 51% of keratoacanthoma presented DNA of HPV. [36]

1.2.2. Bowen's disease

Bowen's disease (BD) is considered a squamous cell carcinoma in situ that predominantly affects sun-exposed areas in middle-aged or elderly patients. It presents as an asymptomatic well-defined erythematous scaly plaque which grows centrifugally resembling psoriasis or dermatitis (Figure 8). It is not uncommon the presentation of Bowen's disease as non-steroid-responsive dermatitis. The clinical differential diagnosis of Bowen's disease includes psoriasis, eczema, superficial basal cell carcinoma or cutaneous Paget's disease. It may affect any part of the integument, mucous membranes or nail bed, but it commonly presents on the trunk, head, extremities or genitalia. Some clinical variants of Bowen's disease include a verrucous,

nodular, eroded or pigmented variant that may be confused with melanoma. Invasive carcinoma develops in nearly 5-10% of untreated cases with a metastatic potential of 13-30% of cases. This complication should be suspected when a rapidly growing tumor is present in a previous scaly lesion. Complete or partial regression has been described in Bowen's disease [37] but this is not a common phenomenon. Some authors proposed that Bowen's disease was considered a marker of an internal malignancy; however a later meta-analysis showed that this association was inconsistent [38].



Figure 8. Well-defined erythematous scaly plaque on the limb clinically and histopathologically compatible with Bowen's disease.

Bowen's disease of the penis is regarded as erythroplasia of Queyrat and this disease is characterized by slightly, erythematous, velvety, bleeding macules or plaques. Perianal lesions present the same clinical characteristics, but they are more common in females than males.

The etiology of Bowen's disease is mainly multifactorial and different factors have been associated as UV light or arsenic. Also HPV have been associated with Bowen's disease, initially periungueal and anogenital lesions, but later studies have shown an association in other locations. Many types of HPV have been associated with BD: HPV 2,16,18,27,31,33,34,39,52,56,58,59,67,76,82... and the implication in the prognosis of the disease remains elusive.[39]

1.2.3. Basal cell carcinoma of the skin

Basal cell carcinoma (BCC) is the most common malignant cutaneous neoplasm and the incidence is rising in the last decades [28]. They usually arise from the lowermost layer of the epidermis, although a small percentage may originate from the outer root sheath of the pilosebaceous unit. It is slightly more common in men than in women and although these tumors metastasize exceptionally rarely they have a tissue destruction potential particularly lesions on the face. This tumor is mainly found on areas of skin exposed to the sun. Up to 70% of all lesions are found on the head and neck and 30% on the shoulders, back, chest and lower

extremities. This tumor has been described in nearly every location of the body, but lesions on the scrotum are of particular importance because of a high rate of metastasis associated. The most common sites of metastasis (less than 0.5% of the cases) include lymph nodes, lung, bone and skin. In sunny climates the clinical presentation is in much younger patients but in less sunny climates it usually happens during the sixth decade [40].

Basal cell carcinoma may develop in some benign lesion as organoid nevi, pore of Winer, rhinophyma, epidermal nevi, "port wine" stain, epidermal cysts, multiple trichoepitheliomas, solar lentigos... The presence of multiples BCC in young people is associated with different syndromes as Gorlin syndrome, Bazex syndrome, cartilage hair hypoplasia syndrome or ROMBO syndrome that should be discarded.

BCC is characterized by a papulonodular lesion with pearly translucent edge and it is usually ulcerated (Figure 9). The lesion is usually indurated and telangiectasias on the surface of the lesion are easily visible. Five main clinical variants have been described: nodular/ulcerative, superficial, pigmented, infiltrative or morpheaform and fibroepithelioma of Pinkus. Nodular variant resembles a cutaneous cyst with telangiectasias on the surface, the sizes varies from 1 to various centimeters. The ulcerative variant usually starts as a small translucent papule with a pearly appearance with a central erosion or ulceration with a rolled margin (*ulcus rodens*). The superficial variant is usually located on the trunk as a slowly enlarging, scaly red patch for a long time. Lesions may be confused with psoriasis, dermatitis or eczema.. These lesions are usually treated with topical corticosteroids but a careful examination of the edges of the lesions shows a rolled translucent border and dermatoscopy may be useful for the diagnosis of these tumors. Infiltrative or morpheaform BCC presents a poorly demarcated and cicatricial lesion which enlarges over several years. BCC may contain pigment on it and in some cases it is necessary to differentiate from melanocytic lesions. BCC tends to enlarge progressively and to be destructive, also atypical forms simulating cervical adenopathies have been described [41-42]. Fibroepithelioma of Pinkus is an uncommon erythematous tumor usually located on the trunk or extremities with typical histopathologic features.



Figure 9. Basal cell carcinoma: papulonodular lesion with pearly translucent edge on the upper back.

UV radiation and sunburns correlates properly with BCC of the head and neck. The history of sunburns during the childhood and recreational exposure during the first two decades of life are associated with higher risk of this tumor. Low phototype is also a risk factor (fair skin and red hair). Primary prevention is very important and recently a study has demonstrated that a programme entirely conducted via Internet significantly reduces by half self-reported sunburn risk (main risk factor of melanoma and BCC) in an adolescent population achieving very high satisfaction rates [43]. BCC can be a complication of PUVA therapy, irradiation, burns, immunosuppression, renal transplant recipients, HIV infection, or leukemia. Mutation in PTCH1 has been found in sporadic and syndromes associated with BCC. The pathogenic role of beta-HPVs in non melanoma skin cancer (NMSC), is not still completely understood, and literature data indicate that they might be at least cofactors in the development of certain cutaneous squamous cell carcinomas. However, only few reports contain data on basal cell carcinoma (BCC). Some studies have shown an overexpression of some protein associated with beta-HPV species [44] but other authors conclude that HPV does not seem to play a fundamental role in the aetiopathogenesis of either nodular or superficial BCC. The presence of HPV appears to be more related to actinic damage and possibly to an alteration of the barrier function associated with ageing [45].

2. Mucosal lesions

2.1. Benign mucosal lesions

Human papillomavirus (HPV) produces a wide variety of lesions in all the mucosae that are in contact with the environment outside the organism. In addition to genitourinary lesions, benign lesions associated with HPV have been described in the oral cavity, nasal mucosa, and ocular conjunctiva [46]. Some serotypes are frequently associated with specific lesions: focal epithelial hyperplasia (13, 32), buccal papilloma (2, 6, 11, 57), condyloma acuminata (6, 11), laryngeal papilloma (11), squamous conjunctival papilloma (6, 11, 16) and nasosinal papilloma (6, 11).

The diagnosis can be made clinically, but some cases require the use of DNA techniques or microscopy techniques to establish the presence of koilocytes (elongated cells with eccentric and pyknotic nuclei that are frequently surrounded by a perinuclear halo).

2.1.1. Focal epithelial hyperplasia or Heck's disease

Although several etiopathogenic factors have been considered, this disease is associated with HPV, particularly Types 13 and 32. However, other factors play a role, as the zones where the disease is most frequently observed (the oral mucosa) are contact areas with dental prostheses [47]. There are also family and ethnic associations (the disease was first described in Inuits and is not common in Caucasians), thus supporting a possible genetic component associated with HLA-DR4 [48]. Sexual transmission is not considered common, as the disease is most common in patients before the second decade of life.

The basic lesion consists of a rounded or oval papule with a soft consistency that is usually multiple (figure 10). Its surface is smooth, not keratinized, and the same color as the mucosa or slightly lighter. Its maximum diameter is usually 5 mm, although it can be confluent; therefore, the sizes reported in the literature vary between 1 and 10 mm, and the lesion may even have a cobbled aspect. It is asymptomatic [47, 48]

Heck's disease lesions have been described almost exclusively in the oral mucosa. The most common location is the lower lip, followed by the jugal mucosa, the upper lip and the tongue. Lesions are also associated with contact zones. Much more rarely, lesions occur on the palate, the floor of the mouth, or the oropharynx.

Histologically, epithelial hyperplasia is observed with elongation and horizontal anastomosis between the interpapillary crests. Also described are hyperkeratosis, parakeratosis, focal acanthosis, koilocytosis and mitosoid figures (cells that present degenerative nuclear changes that simulate mitosis) in superficial keratinocytes [3,4]. When HPV DNA is detected, either by PCR or in situ hybridization, Genotypes 12 and 32 are appreciated in more than 90% of cases and in Types 1 and 11. To date, no malignant potential has been demonstrated [49].

Differential diagnosis is made against other benign lesions produced by HPV, such as the common wart, squamous papilloma and condyloma acuminata, all of which are associated with sexual transmission and with possible abuse, in the case of a minor. It is necessary to differentiate against fibroma and bite papilloma, as lesions occur in a friction zone. Mucosal neuroma, white sponge nevus, florid oral papillomatosis and diffuse epithelial hyperplasia in tobacco chewers are considered in the differential diagnosis. Neurofibromas on the mucosal affection of the neurofibromatosis and the papule or labial papillomas of Cowden's syndrome are usually located in similar zones, thus indicating these systemic diseases [47, 48].



Figure 10. Heck's disease: rounded papule with a soft consistency on the upper lip.

Treatment deserves a brief mention. Because the lesions usually remit spontaneously in months or years, no specific treatment is suggested. However, if treatment is needed in the

absence of remission or because of aesthetics or friction-related nuisance, surgery (cryosurgery, electrosurgery, CO₂ laser) or pharmacological therapy similar to any other HPV lesion can be considered (imiquimod, salicylic acid, podophyllin or trichloroacetic acid)

2.1.2. *Condyloma acuminata*

The prevalence of this entity, which is associated with human papillomavirus, has progressively increased in the developed world, affecting an estimated 6% of the population with an incidence close to 2% [50]. The most common viral types are 6 and 11. These types have a low carcinogenic potential, although others types with a higher carcinogenic potential are also associated with these lesions.

The most frequent mode of transmission is sexual contact, although it is not exclusive. The disease can also be transmitted vertically in the birth canal or by direct contact via the hands. Consequently, its presence in children does not necessarily imply sexual abuse.

In addition to infection by papilloma viruses Types 6 and 11 (HR of 12.42), the risk factors associated with condyloma age (HR of 0.43; if we compare 45-70 years against 18-30 years), high number of female sexual partners (HR of 5.69) and number of male partners (HR 4.53) [51]. Classically, it has been considered that there is an inverse association between circumcision and HPV prevalence in men, although meta-analyses are inconclusive [52].

The incubation period is variable, lasting from 3 weeks to 8 months (2 to 3 months on average) [50]. In addition, the infection can be present and contagious in the absence of lesions (sub-clinical infection). Consequently establishing the source of infection is practically impossible, and it should be assumed that both members of a couple are infected at the time of diagnosis.

In the beginning, the lesion is asymptomatic because it initially affects the basal epidermal cells. With time, a papule lesion appears, and new lesions develop from there. The evolution of the disease depends on viral (type, virulence), host (e.g., age, sex, promiscuity, immune system, toxic abuse) and other factors (location, friction). After infection, evident lesions may appear, or the lesions may be difficult to appreciate, even with the help of 3 to 5% acetic acid (inapparent subclinical forms). In other cases, it is impossible to diagnose the lesion even after histopathological study, and only in situ hybridization (latent forms) can provide a diagnosis. The evolution of the disease allows the coexistence of the three types of lesions.

Clinically, several forms have been described:

- **Classical form:** These lesions are defined as a fleshy mass, exophytic and vegetating, pedunculated, with digitations, classically described as having the shape of a cauliflower (Figure 11). They are keratinized, and the color is variable but generally clear. They are located in humid areas exposed to friction, such as the balanopreputial sulcus, the frenulum and the introitus or meatus of the genitals. When they are located in the oral cavity, the nodules and digitations are frequently softer, but the cauliflower shape is more pronounced [53]. Their most frequent location is on the superior lip, the lingual frenulum, the back of the tongue, the inferior lip and the corner of the mouth. The size is also variable, from 1-2 cm to 15 or 20 cm.

- Spicule form: These lesions are more hyperkeratotic, rough and digitiform than the classical form. They are usually isolated on the preputial mucosa or plate-clustered in the perianal zone.
- Papule form: These lesions are 1-mm papules that are well delimited, non-confluent, cupuliform and disseminated. When located in the penis, they require differential diagnosis from hypertrophic sebaceous glands; heterotypic, pearly papules or hirsutoid papillomas; and Tyson's glands.
- Flat condyloma or leukoplakia: These lesions present a confluence of viral papules. They react poorly to acetic acid and do not respond to treatment.
- Macular form: These lesions take the form of erythematous spots with a vascular or granulomatous aspect, with or without a hypopigmented halo. They have a moist surface with a velvety aspect. They must be differentiated from bacterial or candida chronic balanoposthitis in immunosuppressed patients and from with Queyrat's erythroplasia.
- Micropapillar form: These lesions are small fibroepithelial projection with central capillaries.
- Inverse punctuated form: These lesions present as erythematous spots.



Figure 11. Multiple condyloma acuminata in penis in an HIV patient

All of these forms are usually asymptomatic, although they can produce pruritus, stinging or discrete hemorrhages from trauma. If they are large, they can produce a bad odor or pain. Dysuria, pollakiuria or hematuria can appear if the location is intraurethral, and a ureteroscopy will be necessary. If the lesions are located in the anus, they can produce constipation and dyschezia. An anoscopy with exfoliative cytology is recommended, particularly in passive homosexuals with lesions, as the risk of affecting the rectum is near 50%.

Other forms are much more striking and have benign tumor characteristics but are locally aggressive. These forms are the giant penile condyloma (Buschke-Lowenstein tumor) and the florid oral papillomatosis.

The diagnosis of acuminated condylomas is clinical, requiring a biopsy for confirmation because of atypical lesions, a malignant aspect, no improvement with therapy or immunological problems.

In addition to typical koilocytes, the histopathological study of the epidermis will show strong acanthosis with diverse degrees of papillomatosis, hyperkeratosis and parakeratosis and a total obliteration of the granule cell layer. The crests tend to be elongated and point towards the center of the lesion, and the dermis presents increased vascularization with the presence of capillary thrombosis. In unclear lesions, immunohistochemical staining with peroxidase-antiperoxidase or MIB1 antibody (against the protein Ki-67) allows the direct visualization of a viral presence [50].

Treatment will depend on the size and location of the lesion, and surgery is preferable when lesions are large or are located in the urethral meatus.

2.1.3. Bowenoid papulosis

This disease is fundamentally associated with HPV Type 16, although it is also related to Types 18 and 33 (along with Type 16, these are the most oncogenic types), 32 (in oral mucosa lesions) and, in a small percentage of cases, to Types 31, 34, 35, 39, 42, 48, 51 and 54 [54]. Bowenoid papulosis is most frequent in the second and third decades of life (earlier than for Bowen's disease). It is located in the prepuce and less frequently in the glans. In women, it appears in the labia majora and minora, the clitoris, the groin and around the anus. It is less common in the oral area and is generally associated with HIV, thus possibly posing a differential diagnosis problem [55].

The lesions are defined as macular lesions (less frequent), papular or multiple verruciform. They are less than 1 cm in size and are usually confluent. They are usually hyperpigmented, pink to red-violet or brown (Figure 12). The surface is regular with scales or velvety with a soft consistency. The disease is asymptomatic, and the lesions rarely ulcerate or bleed (unlike in Bowen's disease).



Figure 12. Violaceous papular lesions on the back of foreskin support Bowenoid papulosis

The pathological anatomy has similar characteristics to Bowen's disease and few differences from in situ squamous cell carcinoma. At times, Bowenoid papulosis is considered a low-degree in situ carcinoma [54, 56]. We find hyperkeratosis with parakeratosis foci and hypergranulosis, irregular acanthosis, occasional papillomatosis and vacuolated keratinocytes with mitosis in the same phase. Such findings distinguish these lesions from those of Bowen's disease, in which maturation is disorderly and appears as dysplasia. The basement membrane is intact [9]. However, nuclear alterations can also appear, along with dyskeratosis, atypical mitosis and multinucleated keratinocytes [11]. In fact, some authors propose that there is a risk of neoplastic transformation in 2.6% of the cases, and the frequency is higher if there is some type of immunodeficiency [57].

The main differential diagnosis is made with Bowen's disease but may also involve condyloma acuminata, Queyrat's erythroplasia, lichen planus, psoriasis, seborrheic keratosis, anular granuloma and molluscum contagiosum [54, 57].

Treatment should be conservative because of the high percentage of spontaneous regression, although the terms are variable and the lesions can persist for 2-3 weeks to 2-3 years or longer. Simple partial or total excision has been used, as have ablative treatments and local or systemic pharmacological approaches [54, 56]. A wait-and-see approach with clinical management and/or repeated biopsies is also a good option [54].

2.2. Malignant mucosal lesions

2.2.1. *Queyrat's erythroplasia*

Queyrat's erythroplasia is an in situ squamous carcinoma (intraepidermic) that can evolve into invasive squamous carcinoma in 3 to 5% of cases. Aside from human papillomavirus (principally Serotypes 16 and 18), the risk factors that influence the development of erythroplasia include sun exposure, light skin, radiation, PUVA therapy, immunosuppression, smegma and poor hygiene [58].

Clinically, Queyrat's erythroplasia presents as an erythematous-squamous plate of slow growth and irregular borders (Figure 13), with a smooth surface, hyperkeratotic or warty appearance and pigmentation in less than 2% of the cases. It is usually present in the multiple form, although it can also appear as a single lesion. It is frequently located in the penis, although it can also be found in the urethra, vulva, oral mucosa, tongue and conjunctiva. The diagnosis must be made by a biopsy or the exeresis of the lesion, and cellular atypia with an intact basal membrane is typically observed. Differential diagnosis is required against psoriasis, seborrheic dermatitis, actinic keratosis, invasive squamous cell carcinoma, surface basocellular carcinoma and Paget's disease [59].

2.2.2. *Vulvar cancer*

The vulva is the only visible and external part of the female genital system, and its pathology should be well-known and quickly diagnosed. However, vulvar pathology has been undervalued because it is not very symptomatic or very frequent. Vulvar cancer has a biological and

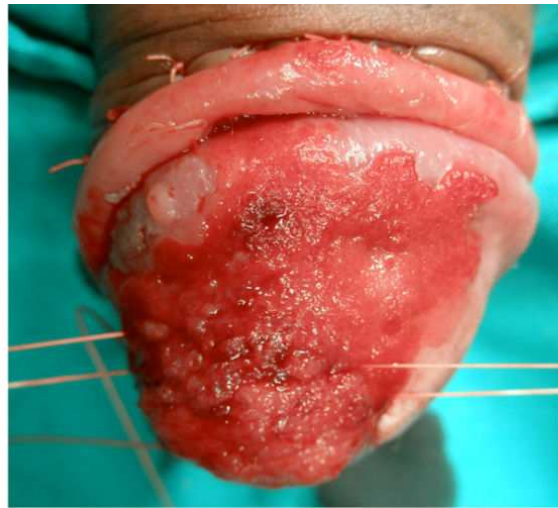


Figure 13. Slightly raised erythematous lesion occupying the glans. Queyrat's erythroplasia

social impact and requires early diagnosis. It represents 3 to 4% of gynecologic cancers; epidermoid carcinoma is the most frequent, representing 90% of malignant vulvar tumors.

Vulvar exploration must be meticulous and exhaustive, especially in women with referred symptomatology. Subclinical lesions frequently require special detection techniques. The study must be performed via simple vulvoscopy and expanded with a complete biopsy of the suspicious lesion. An adequate anamnesis, in which personal background is documented (sexually transmitted diseases, toxic habits, hygienic habits and immunosuppression status) is important. In addition, visual inspection and inspection with panoramic light must be performed to observe coloration, trophism and macroscopic lesions, and the other female genitalia must be examined [60]. The vulvoscopic exam should be undertaken with frequent applications of 5% acetic acid to corroborate the white color reaction. Another applicable study is the Collins test, which involves the application of 1% toluidine blue, followed by washing with 3% acetic acid. However, the most definitive test for diagnosis is a vulvar biopsy with a rongeur, punch, scalpel or scissors.

It has been observed that one of the etiological agents implicated in the development of vulvar cancer is the human papillomavirus, specifically Serotype 16, although other serotypes that influence molecular mechanisms associated with cancer development, such as inactivation of the p53 gene, have also been implicated.

Although epidermoid vulvar cancer is the most common type, other types include warty carcinoma, Paget's disease of the vulva, adenocarcinoma, basocellular carcinoma, Bartholin gland carcinoma and vulvar sarcoma.

Our primary focus will be the clinical description of squamous or epidermoid vulvar carcinoma, which is the type most directly related to human papillomavirus. Squamous or epidermoid carcinoma is characterized by the presence of long-evolution pruritus (between 40 and 50%); flux or vulvar exudate, sometimes with bad odor; bleeding outside menstruation; vulvar pain; dysuria; and tumor formation (in almost 50% of patients). In the initial stages, this carcinoma

is observed as an indurated, overelevated lesion; sometimes it can be hyperkeratotic, with variable coloration ranging from erythematous to white. In the initial phases, it can coincide with other lesions, such as lichen sclerosus, vulvar intraepithelial neoplasia (VIN), genital atrophy, squamous cell hyperplasia and overinfection with lichenification from scratching [61]. In more advanced phases, the squamous carcinoma presents as reddish, ulcerated lesions (Figure 14), either polypoid or nodular, or with white coloration, even when associated with palpable inguinal lesions.

Different stages can be differentiated by tumor size, ganglionic affection and metastatic affection. Stages IA, IB and II are usually the initial stages of the localized disease, and the most frequently affected zones are the anterior part of the vulva, followed by the labia majora and minora, the clitoris and the vulvar fourchette. In more advanced stages, it frequently propagates to neighboring organs, such as the anus, urethra and vagina. Dissemination to other organs such as bone, liver, lungs and brain is rare [62].



Figure 14. Irregular and ulcerated lesion on the vulva histopathologically compatible with vulvar cancer

2.2.3. Penile carcinoma

Penile carcinoma is a rare malignant tumor, but it has a major medical and psychological impact. Amongst the risk factors that influence and contribute to its development are phimosis, balanoposthitis, ultraviolet radiation, smoking, cervical cancer in the partner, sexually transmitted diseases, poor hygiene and human papillomavirus, fundamentally Types 16 and 18, which are highly metastatic.

There are different precursor lesions that carry the risk of developing penile spinocellular cancer or penile squamous-cell invasive carcinoma, such as bowenoid papulosis, balanitis xerotica obliterans, cutaneous horn and Queyrat's erythroplasia that affect the mucous membrane; or Bowen's disease that affects the rest of the genital area.

Penile spinocellular cancer or penile squamous-cell invasive carcinoma is the histological type present in more than 95% of malignant penile invasive neoplasias. Approximately half are well differentiated. They usually metastasize via the lymphatic system, first at the inguinal-femoral

level, then at the pelvis; finally, they migrate to distant areas. The hematogenous spread can affect the lungs, liver, brain, pleura, bone, skin and other organs [63].

Clinically, penile carcinoma initially manifests as an elevated papular-type or pustulous lesion that does not resolve with topical treatment and can evolve into an exophytic, polypous or infiltrating lesion (Figure 15). Erythematous and superficial lesions can also appear. They are usually located in the glans and less frequently in the balanopreputial sulcus. If the patient presents phimosis or if the lesion is under the prepuce or is evolved, it protrudes outside the prepuce. These patients can present initially with an inguinal-level adenopathic lesion resulting from an inflammatory or metastatic reaction. The lesions can be single or multiple, fixed or free and can become overinfected.



Figure 15. Excrecent lesion on the penis, that after surgery, histological study confirmed penile cancer

The natural clinical evolution of the disease normally progresses through several stages. Initially a papillar lesion appears, gradually ulcerates and overinfects, affecting Buck's fascia and potentially invading the cavernous bodies [64]. In a second stage, the lesion disseminates via the lymphatic pathway, especially at the inguinal level. Finally, the disease produces distant metastases that are uncommon upon initial diagnosis.

2.2.4. Anal carcinoma

Anal carcinoma is not very frequent, representing 1 to 2% of digestive system cancers. Among the risk factors that influence the development and genesis of this cancer, in addition to human papillomavirus (fundamentally, Types 16, 18 and 31), are poor hygiene, chronic anal irritation, smoking, seropositivity for herpes virus, seropositivity for human immunodeficiency virus, sexual promiscuity, passive anal sex, anal fistulas and other less-relevant factors.

Generally, the most frequent type of anal carcinoma associated with papilloma virus is squamous or spinocellular carcinoma. There are also other types, such as basaloid, cloacogenic, basal-squamous, epithelioid, trasitional and mucoepidermoid cancer. As observed with cancer in other locations, there may be premalignant lesions with the potential for developing into

anal carcinoma, as in Bowen's disease, Paget's disease, Bowenoid papulosis, leukoplakia and condyloma acuminata [65].

Clinically, anal cancer presents with hemorrhages and constant pain associated with other symptoms, such as changes in defecation, secretion that can be purulent if there is overinfection and pruritus. In more advanced stages, the patient has the sensation of a palpable mass, and the tumor can become ulcerated. In the first stages, during which bleeding, pruritus and pain occur, anal cancer can be easily confused with hemorrhoidal processes, perianal fistulas or anal fissures; thus, it is necessary to carefully explore the area [65, 66].

Exploration of the anal channel must be directed toward identifying the lesion or possible lesions; establishing their size, anatomical limits and relationship with the dentated line; and looking for any other concomitant lesion with different characteristics. Small lesions must be totally resected for study, while bigger lesions require a biopsy.

2.2.5. Cervical cancer

Cancer in the neck of the uterus is the second most common cancer in women (the first is breast cancer). Among the multiple causes related to the development of this neoplasia are smoking, immunosuppression, chlamydia infection, poverty, poor hygienic/dietary conditions, different dietary habits, diethylstilbestrol, promiscuity, early-age pregnancy and infection with human papillomavirus. Different types of human papillomavirus have been implicated in the development of cervical cancer. The most important types are 16, 18, 31, 33 and 45, and the first two are responsible for approximately 2/3 of all cancers in the neck of the uterus.

Cervical cancer can be prevented with cytologic techniques and by applying the Papanicolaou method. The objective is to establish an early diagnosis so that therapy can begin quickly; because the initial stages of this cancer are asymptomatic, frequent and exhaustive reviews are important [67].

As we have previously mentioned, the initial stages of cervical cancer do not produce symptoms; however, when the tumor increases (Figure 16), women present abnormal vaginal bleeding that can occur between menstrual cycles, following sexual relations and after menopause, or the bleeding can prolong menstrual-bleeding periods [68]. Cervical cancer can also be associated with other symptoms, such as pelvic pain and dyspareunia, and it can increase flux and vaginal secretions.

3. Other types of tumors

Next, we will describe other tumoral clinical processes that have been associated with HPV infection. It is important to highlight that the majority of people infected with HPV do not present symptomatology or health-problems related to the infection. In 90% of the cases, the immune system naturally eliminates the virus within two years. However, sometimes HPV infections become chronic, and they can be associated with other lesions or tumors aside from the previously described pathology. These lesions and tumors include warty lesions in the oral

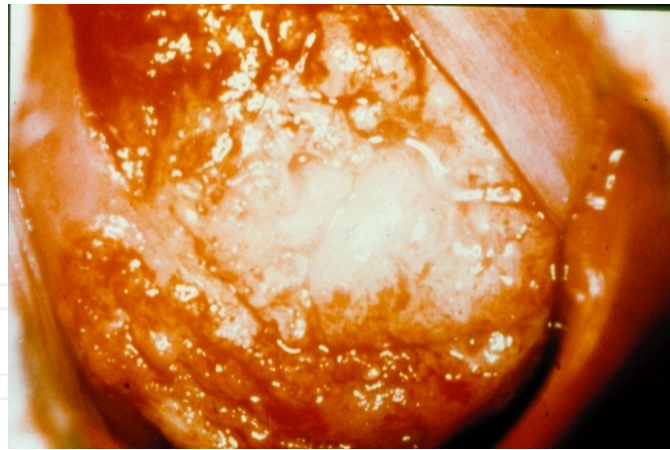


Figure 16. Excrecent ulcerated lesions in cervix clinically compatible with carcinoma

cavity and pharynx (recurrent respiratory papillomatosis [RRP]) and rare but serious cancers such as those of the bladder, lung and oropharynx (the posterior area of the throat, including the base of the tongue and the tonsils).

3.1. Oral and cervical cancer

Eighty-five percent of oral cavity cancers are epidermoid (we will be referring primarily to this type), and their incidence increases progressively with age. HPV 16/18 are the types most frequently associated with oral and cervical cancer, especially in the oropharynx and tonsils [69, 70]. The principal lesions associated with HPV infection in the oral cavity are oral papillomatosis (associated with HPV 6 and 11), focal epithelial hyperplasia (HPV 13 and 32) and erythroplasia (HPV 16).

Causal factors strongly associated with oral and cervical cancer are tobacco and alcoholic beverage consumption. Therefore, investigations to determine the possible etiological role of HPV will need to consider these factors. Several studies that controlled for age, gender, smoking, tobacco chewing and drinking have not observed significant differences among these factors for HPV detection in tumoral tissue, with the exception of smoking. That is, HPV DNA was less likely to be found in the biopsy samples of ex-smokers and smokers than those of people who had never smoked. In comparison, patients with more than a single sexual partner had a higher possibility of HPV DNA detection than those who had a single lifetime sexual partner. Similar observations were obtained when comparing oral sex practitioners versus nonpractitioners. These associations were similar for oral cavity and oropharynx cancer [71].

The clinical manifestations of patients with epidermoid carcinoma are very diverse and depend on the location and size of the lesions. Leukoplakia and erythroplasia are premalignant lesions over which neoplastic lesions can develop. The most common initial presentation is a painful ulcer. Pain appears precociously in lesions that affect the base of the mouth or the gums; however, it is delayed in other locations, such as the base of the tongue. Dysphagia occurs with lesions that affect the oropharynx or that alter the mobility of the tongue. Hemorrhage usually occurs in ulcerated lesions. Other associated symptoms include dysphonia, tooth mobility or

loss, anesthesia or trismus. Clinically, the tumor manifests in exophytic, ulcerative or warty forms (Figure 17). It is important to completely explore the entire oral cavity and to obtain a biopsy of the lesion when it is accessible, or a puncture-aspiration with a fine needle when biopsy is difficult. The neck must be carefully explored to detect adenopathies, and a radiologic or endoscopic study should be performed to establish tumoral extension.

The importance of HPV in oropharyngeal carcinoma patients is increasing. It is important to determine the presence or absence of this virus in patients who present epidermoid carcinoma in the oropharynx or who have cervical adenopathy of uncertain origin to obtain information on the patient's therapeutic attitude, prognosis and survival [72].



Figure 17. Squamous cell carcinoma of the lip: exophytic, ulcerative, warty tumor of the lower lip.

3.2. Recurrent respiratory papillomatosis and lung cancer

Recurrent respiratory papillomatosis (RRP) is characterized by warty lesions produced by HPV infection of the airways. These lesions can obstruct the airways or cause dysphonia, among other symptoms. Two clinical variants are recognized depending on the patient's age at onset: the juvenile (before 5 years) and the adult form (after 40 years). The juvenile variant is more frequent and severe than the adult form. HPV 6 and 11 are the types most frequently involved in this clinical picture [73]. HPV 11 produces a more severe clinical picture than the other viral variants do, and HPV 11 infection more frequently requires tracheostomy. The transmission mechanisms of the infection are not always clear, but sexual transmission should be considered in adults, and mother-to-child transmission should be considered in the juvenile RRP variant. In this regard, some risk factors associated with this variant have been confirmed. These risk factors include a mother younger than 20 years, vaginal delivery and being firstborn. Sexual abuse should also be suspected in diseased children older than 5 years.

The symptomatology of this disease is varied, and diagnosis is generally delayed because of the disease's rareness. The predominant symptoms are related to upper airway obstruction caused by the frequent involvement of the larynx. These symptoms can occasionally threaten the patient's life. Dyspnea, snoring, dysphonia, the sensation of a foreign body in the throat, coughing or wheezing are common clinical symptoms. The diagnosis should be suspected with these clinical data, and appropriate complementary tests should be requested for diagnosis. Such diagnostic tests include bronchoscopy or laryngoscopy, which will show typical warty images on the airway. HPV serotyping is necessary and has prognostic value.

Lung cancer is one of the most common cancers. It has one of the highest mortality rates among cancers and is particularly associated with smoking. The majority of cancerous lung tumors originate from the bronchial epithelia (bronchogenic carcinomas); the rest derive from other cells and constitute a more heterogeneous group. The maximal incidence is from 40 to 70 years, and the disease is more frequent among men. The diagnosis is usually made late, and only 15% of the patients present a localized disease. Usually there is ganglionic or metastatic disease upon diagnosis. Several histological subtypes have been distinguished and have important prognostic implications. These subtypes are squamous cell carcinoma, adenocarcinoma, large cell carcinoma and microcytic carcinoma.

The most important etiological factors are the substances inhaled when smoking cigarettes; thus, the risk increases 60- to 70-fold in an individual who smokes two packs per day. The risk diminishes if the habit is abandoned, but it does not become equal to that of nonsmokers. In addition, genetic alterations in lung cancer patients have been widely studied and corroborate the oncogene activation (Ras, Myc, among others) and inactivation of tumor-suppressing genes (p53). The relationship between lung cancer and HPV infection was initially established in 1975 [74]. More recent studies have suggested a 25% HPV infection prevalence associated with lung cancer, with an important variation between countries [75]. High-risk subtypes that have been detected are 16, 18, 31, and 33; the lower-risk subtypes are 6 and 11. Therefore, it has been suggested that HPV infection is the second-most-important risk factor after smoking. The transmission mechanism is not properly known, but it appears that multiple sex partners and oral and anal sex may be among the transmission factors. A higher-than-expected incidence of lung cancer was detected in cervical and anal cancer patients in whom HPV was implicated [76], suggesting a possible hematogenous dissemination of the virus. The action mechanisms that explain the role of HPV in tumor promotion and development are complex. In addition, it has recently been demonstrated that HPV and smoking can have a synergistic effect on tumor promotion [77].

The symptomatology that the disease produces is associated with growth and obstruction of the lung and neighboring structures. Although in some cases the tumors are diagnosed in their asymptomatic phase using radiography, most of the tumors debut with coughing, hemoptysis, wheezing, stridor or dyspnea. If there is eccentric growth, the tumor can irritate the pleura, leading to pain, coughing and restrictive-origin dyspnea. If the tumor grows towards the thorax, it can produce tracheal obstruction, esophageal compression, snoring (by paralyzing the recurrent laryngeal nerve), hemidiaphragm elevation (phrenic nerve paralysis) or Horner's syndrome, Pancoast syndrome or superior vena cava syndrome. Paraneoplastic syndromes

can also be detected and are associated with the ectopic production of such hormones as PTH and ACTH by microcytic carcinomas. Eaton-Lambert myasthenic syndrome and Trousseau's migratory thrombophlebitis may also be associated with this clinical presentation, although in very low percentages.

Metastasis is observed in 50% of epidermoid carcinoma patients, 80% of those with adenocarcinoma and up to 95% in microcytic carcinoma patients. The metastases can appear in the brain, bones, bone marrow and liver.

3.3. Bladder cancer

Bladder cancer is the malignant tumor that most frequently affects the urinary tract. Its prognosis is highly variable. It is one of the most common cancers among men. The majority of the tumors are transitional cell carcinomas (90%), which have a high tendency to recur after treatment or become invasive and overwhelm subjacent muscular structures. As a consequence, it is necessary to periodically control the urothelium. Pure epidermoid carcinoma constitutes 3% of cases, and adenocarcinoma constitutes 2%.

Tobacco consumption also plays an important role in the development of this tumor; it is thought to contribute to up to 50% of urothelial carcinomas. Other risk factors implicated in the development of this tumor are certain drugs, such as cyclophosphamide and phenacetin; infection with *Schistosoma haematobium*; and external radiotherapy. Genetic alterations have also been detected, including deletions of the RB gene or p53 overexpression. The association between bladder cancer and HPV infection is still controversial, considering that one of the virus's natural reservoirs is the urethra and that it could easily migrate to the bladder. Some authors have strongly implicated the virus in tumors that affect younger patients. A recent meta-analysis of all the published studies on the relationship between HPV and bladder cancer concludes that there is a moderate and clear association amongst both processes and establishes an odds ratio of 2.13 [78]. However, more studies are needed that evaluate the pathogenic relationship between the processes.

The clinical manifestations of this tumor are varied. Hematuria is related to exophytic-growth tumors, whereas irritation symptoms (dysuria, pollakiuria and micturition urgency) are more frequent in patients with localized disease (in situ carcinoma), even though they can also be observed in patients who present tumoral invasion towards the muscle layer of the bladder. However, other important causes of macroscopic and microscopic hematuria must be considered, such as cystitis and prostate problems. When hematuria is found, a complete evaluation should be performed. This evaluation should include urinary cytology, ultrasound (Figure 18) or intravenous pyelogram and cystoscopy. Less common clinical manifestations are pain or nuisance in the renal fossa related to urethral obstruction or pelvic pain and lower extremity edema produced by the obstruction of the iliac vessels. With less frequency, metastatic disease is the first manifestation of these tumors. Once bladder cancer is diagnosed, it is very important to establish whether the muscle layer has been affected. To determine this, ultrasound, CT and nuclear magnetic resonance are of great help.

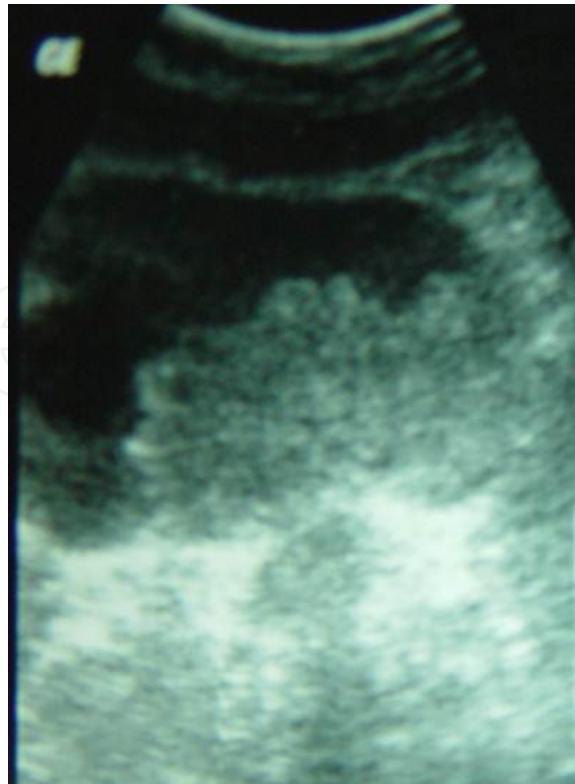


Figure 18. Bladder ultrasound, in which, it can be observed the presence of a lesion that histologically was urothelial cancer.

3.4. Other tumors

Other tumors, including cancers of the larynx, sinonasal tract, nasopharynx, salivary gland, vulva, esophagus and breast, have also been associated with HPV infection [79].

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