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Epithelial Pathology – A Overview

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ABSTRACT

Epithelial pathology encompasses a broad spectrum of disorders affecting the epithelial tissues, ranging from benign hyperplasias to malignant neoplasms. The oral epithelium, a dynamic and frequently exposed tissue, is particularly prone to pathological changes due to environmental, genetic, and microbial factors. Common epithelial pathologies include hyperkeratosis, dysplasia, carcinoma in situ, and invasive squamous cell carcinoma. Premalignant conditions such as leukoplakia, erythroplakia, and oral submucous fibrosis exhibit varying degrees of epithelial dysplasia, with potential for malignant transformation. Infectious diseases like oral candidiasis and viral papillomas also alter epithelial integrity, leading to hyperplastic or erosive changes. Autoimmune disorders, including lichen planus and pemphigus vulgaris, cause epithelial atrophy, blistering, and desquamation. Histopathological evaluation is essential for diagnosing epithelial pathologies, assessing dysplasia, and guiding management. Biomarkers such as p53, Ki-67, and E-cadherin aid in distinguishing benign from malignant lesions. Early detection and intervention are crucial, as epithelial malignancies, particularly oral squamous cell carcinoma, have high morbidity and mortality rates. Advances in molecular pathology and immunohistochemistry have improved diagnostic accuracy and therapeutic strategies, emphasizing the need for continuous research in epithelial pathology.

KEY WORDS : dysplasia, leukoplakia, erythroplakia, oral submucous fibrosis

SQUAMOUS CELL PAPILLOMA

INTRODUCTION

A papilloma is a non-cancerous (benign) growth that originates from an epithelial layer and typically expands outward. Most often, a papilloma pertains to squamous cell papillomas, which manifest as frond-like growths that can occur in various locations on the body where squamous epithelium is present.[1]

ETIOLOGY

Most papillomas are linked to human papillomavirus (HPV). There are more than 170 different subtypes of the virus. Typically, types 6, 7, and 11 are primarily associated with papillomas and are considered low-risk types since they usually do not lead to precancerous changes and rarely develop into cancer. HPV has been observed to cause papillomas to develop in nearly any area of the body that has stratified squamous epithelium, including the skin, conjunctiva, oropharynx, larynx, upper trachea, and the anogenital regions.

EPIDEMIOLOGY

The global prevalence of HPV infection, which is the primary cause of papillomas, ranges from 11% to 12%. Nevertheless, obtaining accurate surveillance data regarding the prevalence of warty lesions is challenging. In the case of non-genital warts, two significant population-based studies reported prevalence rates of 0.84% in the United States and 12.9% in Russia, with the highest rates observed in children and young adults. For genital warts, the annual incidence in developed nations was estimated to be between 0.1% and 0.2% of the population. The highest prevalence was noted among teenagers and young adults.

HISTOPATHOLOGY

• In skin papillomas, epithelial cells are typically organized, with squamous surface cells while the proliferation remains limited to the innermost layers.

• The inner section consists of a fibrovascular core that contains well-developed blood vessels.

• The outer layer features infolded epithelium, characterized by acanthosis, papillomatosis, and hyperkeratosis.

TREATMENT

• Topical treatments or procedures like cryotherapy or laser surgery are used to manage skin and genital warts.

• Skin warts can also be eliminated through excision, which can involve cutting with a scalpel or cauterization.[1]

• Surgical removal is the main approach for treating papillomas located in the brain, breast ducts, and respiratory system.[1]

DIFFERENTIAL DIAGNOSIS

- Acrochordon
- Adenoma
- Basal cell carcinoma
- Chancroid
- Condyloma latum
- Corns & calluses
- Cysts[1]

CONDYLOMATA ACUMINATA

INTRODUCTION

Condylomata acuminata (singular: condyloma acuminatum) are warts located in the anogenital area that result from infection with human papillomavirus (HPV). The strains of HPV most frequently associated with these warts are types 6 and 11. HPV is a double-stranded DNA virus that is mainly transmitted through sexual intercourse. Factors such as age, lifestyle choices, and sexual behaviors influence an individual's likelihood of developing condyloma acuminata.[2]

ETIOLOGY

Condyloma acuminata is caused by an HPV infection. More than 100 types of HPV have been recognized, with 40 of these strains affecting the anogenital region. The most common strains responsible for condyloma acuminata are HPV types 6 and 11. Different strains of HPV can lead to plantar warts, which appear on the hands and feet.

EPIDEMIOLOGY

HPV is the most widely spread sexually transmitted infection around the globe, affecting 9 to 13 percent of the world's population. The age group most frequently impacted by this infection is individuals between 20 and 39 years old. The likelihood of infection rises with a greater number of lifetime sexual partners, a past history of chlamydia and gonorrhea infections, smoking, and a diagnosis of human immunodeficiency virus (HIV).[2]

HISTOPATHOLOGY

Condyloma acuminata are usually diagnosed based on clinical findings, making histopathological evaluation of the lesions largely unnecessary. Microscopic assessment of the tissue reveals acanthosis accompanied by hyperkeratosis. Unique cells known as koilocytes can be identified. Koilocytes are enlarged keratinocytes with plentiful cytoplasm and small, pyknotic nuclei. These distinctive cells are frequently found in the upper layers of the epidermis. Furthermore, condyloma acuminata can be distinguished from verruca vulgaris based on the type of hyperplasia observed. In verruca vulgaris, spiked verrucous hyperplasia is present, whereas condyloma acuminata exhibits papillomatosis[2]

TREATMENT / MANAGEMENT

Patients have access to various treatment options including topical therapies, cryotherapy, and surgical excision. There is no established treatment algorithm; the choice of therapy is based on the lesion's location, appearance, and the patient's preferences. Fleshy papules can be treated using podophyllotoxin in either a 0.5% solution or a 0.15% cream. Podophyllotoxin is applied twice daily for three consecutive days, followed by a four-day pause. Lesions may resolve after a period of four weeks. Imiquimod cream at a 5% concentration is another topical option, demonstrating lower recurrence rates compared to podophyllotoxin. Imiquimod should be applied three times per week on alternate days, with resolution seen over sixteen weeks. Another topical option is sinecatechins ointment at 15%, which is used three times a day for up to sixteen weeks. The use of 5-aminolevulinic acid (ALA) combined with photodynamic therapy is a developing option for treating condyloma acuminata. This treatment has been shown to be more effective, easier, and associated with lower recurrence rates than CO2 laser treatment. Photodynamic therapy with ALA may serve as a valuable adjunct to other conventional treatment approaches.

DIFFERENTIAL DIAGNOSIS

- Condyloma lata
- Molluscum contagiosum
- Lichen planus
- Psoriasis
- Malignancy
- Pearly penile papules
- Acrochordon
- Sebaceous cysts
- Buschke-Lowenstein tumor[2]

MULTIFOCAL EPITHELIAL HYPERPLASIA

INTRODUCTION

Multifocal epithelial hyperplasia (MEH) is a rare, benign familial condition characterized by numerous soft, well-defined, sessile nodules on the oral mucosa, primarily linked to human papillomavirus (HPV) types 13 and 32. This condition is more commonly found among North, South, and Central American-Indians, particularly the Waimiri-Atroari Indians, and is less frequent in Caucasians. In younger patients with MEH, multiple nodular lesions are typically observed, while older individuals may present with fewer or even a single lesion that appears flat and papular. Koilocytosis is consistently observed in these lesions.[3]

ETIOLOGY

The precise cause of Heck's Disease remains unclear, although some authors have pointed to factors such as tobacco use, electrogalvanism, and Vitamin A deficiency. A viral cause, specifically HPV types 13 and 32, has been proposed based on findings from microscopic, electron microscopic, and immunofluorescent analyses. Additional risk factors appear to include lower socioeconomic status, inadequate oral hygiene, overcrowded living situations, malnutrition, and HIV infection. While previous studies have noted a familial pattern, our patient did not indicate similar occurrences among family members. Nevertheless, habits like chronic smoking may have contributed to the development of the disease.

EPIDEMIOLOGY

Heck's disease can occur in both males and females, but research indicates a higher prevalence in females, primarily affecting children and individuals in their teenage years and early twenties, with the lower lip being the most frequently affected area. Other locations that may be involved include the buccal, labial, and lingual mucosa. In our case, the condition presented at an atypical age of 65 years, affecting multiple regions such as the buccal mucosa on both sides and the upper

CLINICAL FEATURES

MEH is clinically defined by the presence of numerous well-defined, discrete, soft, flattened or raised, and round papulonodular lesions found on the oral mucosa, exhibiting a color similar to that of the surrounding mucosa. In rare instances, the lesions may display changes with a papillary surface. Each individual lesion is relatively small, ranging from about 3 to 10 mm in size, and they often group together, creating a cobblestone-like appearance. Areas subjected to mechanical irritation may have their lesions enhanced, leading to a whiter appearance due to frictional keratosis. In our case, the posterior right buccal mucosa displayed grayish regions mixed with white nonscrapable keratotic areas resulting from frictional keratosis.[3]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes molluscum contagiosum, condyloma acuminatum, lymphangioma, Cowden syndrome, and tuberous sclerosis due to their shared clinical features like lesion type, color, and location. Molluscum contagiosum manifests as multiple papules primarily found in children and young adults, affecting the neck, trunk, and genital areas. Condyloma acuminatum appears as clustered papules with a papillary texture, commonly located in the floor of the mouth and on the ventral tongue due to sexual contact with an infected individual. Oral lymphangiomas often involve the anterior two-thirds of the tongue and have a pebbly appearance resembling a group of translucent vesicles. Cowden's syndrome is characterized by multiple hamartomas, while tuberous sclerosis may present with cutaneous hypopigmentation, subungual fibromas, enamel anomalies, epilepsy, or cognitive impairment.[3]

HISTOPATHOLOGY

The diagnosis of Heck's disease is confirmed through histopathological examination. Key microscopic characteristics include significant acanthosis, parakeratin layering, koilocytic degeneration, mitosoid cells, and elongated rete ridges, some of which form horizontal anastomoses while others exhibit a club-like appearance referred to as “bronze age battle axe” or “clubs.” In our case, histological sections stained with H and E revealed abrupt acanthosis, mild hyperkeratosis, and slight focal koilocytosis. Although a biopsy is considered the gold standard for diagnosis, molecular techniques like DNA in situ hybridization for HPV types 1, 6, 11, 13, 16, 18, and 32 can also be used to achieve a precise diagnosis of Heck's disease.

TREATMENT

Management of MEH is not always necessary as they are often asymptomatic and can resolve on their own. Treatment becomes crucial in cases where aesthetics are affected. The primary methods of treatment consist of excisional biopsy for lesion removal, along with cryotherapy, CO2 laser, electrocoagulation, or electrodessication. For cases with widespread involvement, topical or systemic interferon can be effective. Other treatment options include levamisole, topical podophyllin resin, or vitamins. Given the multifocal nature of the condition, CO2 laser ablation was recommended for the patient. Nevertheless, the patient chose not to pursue treatment due to the asymptomatic nature of the lesions. Additionally, long-term follow-up was recommended to keep track of the lesion's status.[3]

SINONASAL PAPILLOMA

Sinonasal inverted papilloma (IP) is a relatively uncommon and benign tumor found in the nasal cavity and paranasal sinuses, initially described by Ward in 1854. The incidence of IP ranges from 0.2 to 1.5 cases per 100,000 individuals annually, making up 0.5%–4% of all sinonasal tumors.2, 3, 4 IP typically develops from the lateral nasal wall or the maxillary sinus, arising from the schneiderian sinonasal epithelium. This condition shows a preference for males, with a male-to-female ratio of 3.4:1. Although the morphological and clinical aspects of IP have been thoroughly documented, its causes and associated risk factors continue to be debated.[4]

HISTOPATHOLOGIC CHARACTERISTICS OF IP

According to the World Health Organization (WHO), sinonasal papillomas are categorized into three distinct histopathological types: exophytic papilloma (which includes fungiform, septal, and squamous papillomas), inverted (or inverting) papilloma, and oncocytic papilloma (comprising cylindrical cell and columnar papillomas). Among these, inverted papilloma (IP) is the most prevalent, typically presenting as a sizable, polypoid mass with a grayish hue and a rough, multinodular surface. Histologically, it is marked by a thickened neoplastic epithelium that is inverted into the deeper connective tissue while maintaining an intact basement membrane. The epithelium of the tumor is made up of well-differentiated columnar or ciliated respiratory epithelium, which may exhibit varying degrees of squamous differentiation.

The initial phase in the formation of a papilloma is transitional metaplasia of the respiratory epithelium, representing an intermediary transition between pseudostratified columnar ciliated epithelium and stratified squamous epithelium. IP demonstrates pronounced inverted or endophytic growth of non-keratinizing transitional cells. Subsequently, the epithelium undergoes squamous maturation and inverts into the stroma

while preserving a distinct basement membrane that separates the epithelium from the underlying connective tissue stroma. Although surface keratinization and a granular cell layer have been noted, these features are rare. The histopathological traits of IP are intimately linked to the tumor's clinical behavior, with an increase in inflammatory infiltrates generally signaling benign, lower-grade lesions.

ENVIRONMENTAL FACTORS

Tobacco use is regarded as the primary risk factor for both the onset and return of tumors in the head and neck region. Additionally, it has been suggested that exposures related to occupation and industry may play a role in the cause of IP.[4]

ANGIOGENIC FACTORS

Numerous cellular components related to angiogenesis have also been linked to the growth of inverted papilloma (IP). Osteopontin (OPN) is a secreted phosphoprotein that is vital for the formation, movement, and invasion of different tumor cell types. Vascular endothelial growth factor (VEGF) is crucial in facilitating neoangiogenesis during tumor development by encouraging the proliferation and migration of endothelial cells, enhancing vascular permeability, and aiding in blood vessel formation. Liu et al found that staining intensity, mRNA expression, and protein levels for both OPN and VEGF were elevated in IP tissues compared to control tissues, with a significant correlation between expression levels and disease severity. These findings indicate that the relationship between OPN and VEGF plays a role in tumor development by promoting angiogenesis, potentially influencing the clinical advancement of IP. Angiomotin is an additional protein that regulates angiogenesis by down-regulating angiostatin, a circulating angiogenesis inhibitor. Byun et al reported that, according to PCR and Western blot analyses, angiomotin was significantly overexpressed in IP tissues relative to normal sinus mucosa, implying a link to the progression and growth of IP through angiogenesis.[4]

INFLUENCE OF CHRONIC INFLAMMATION

Numerous cellular components related to angiogenesis have also been linked to the growth of inverted papilloma (IP). Osteopontin (OPN) is a secreted phosphoprotein that is vital for the formation, movement, and invasion of different tumor cell types. Vascular endothelial growth factor (VEGF) is crucial in facilitating neoangiogenesis during tumor development by encouraging the proliferation and migration of endothelial cells, enhancing vascular permeability, and aiding in blood vessel formation. Liu et al found that staining intensity, mRNA expression, and protein levels for both OPN and VEGF were elevated in IP tissues compared to control tissues, with a significant correlation between expression levels and disease severity. These findings indicate that the relationship between OPN and VEGF plays a role in tumor development by promoting angiogenesis, potentially influencing the clinical advancement of IP. Angiomotin is an additional protein that regulates angiogenesis by down-regulating angiostatin, a circulating angiogenesis inhibitor. Byun et al reported that, according to PCR and Western blot analyses, angiomotin was significantly overexpressed in IP tissues relative to normal sinus mucosa, implying a link to the progression and growth of IP through angiogenesis.

CONCLUSION

Sinonasal inverted papilloma (IP) is an uncommon, non-cancerous tumor found in the sinonasal region, and it is significant clinically due to its high likelihood of recurrence and potential for malignant change. Although the exact cause is still debated, the reviewed studies suggest that factors such as viral infections, cell cycle dynamics, angiogenesis, environmental and occupational exposures, along with chronic inflammation may play a role. More research into the risk factors and the interactions among these various inflammatory mediators, as well as those involved in cell proliferation and apoptosis, is needed to inform clinical practice and pinpoint therapeutic targets.[4]

MOLLUSCUM CONTAGIOSUM

INTRODUCTION

Molluscum contagiosum, commonly known as water warts, is a non-cancerous skin condition. The skin bumps associated with molluscum contagiosum are referred to as mollusca. A typical lesion is characterized by a dome shape, a round form, and a pinkish-purple hue.[5]

ETIOLOGY

A double-stranded DNA virus known as molluscum contagiosum virus (MCV) is responsible for causing molluscum contagiosum. There are four recognized subtypes of the molluscum contagiosum virus; MCV-1, which accounts for 98% of cases, is primarily observed in children, whereas MCV-2 is mainly associated with skin lesions in individuals with HIV. MCV-3 and MCV-4 are found in regions of Asia and Australia. At present, it is not feasible to culture the molluscum contagiosum virus.

Molluscum contagiosum lesions are spread through direct skin-to-skin contact (including sexual contact) or indirect contact (such as through towels, underclothing, toys, razors, or tattoo equipment). Additionally, molluscum contagiosum can spread via autoinoculation to unaffected skin following the scraping of lesions by the individual. While sharing swimming pools and other moist environments could facilitate transmission, this has not been conclusively established. Cases of transmission in utero and prepartum have been occasionally documented, leading to congenital molluscum contagiosum or lesions appearing in the first few months of life.

EPIDEMIOLOGY

Molluscum contagiosum is a prevalent medical issue. In 2010, approximately 122 million cases were reported. This condition occurs globally but appears to be more prevalent in warm and humid climates. Molluscum contagiosum is primarily diagnosed in children between the ages of two and five, but it can also affect sexually active teens, adults, and individuals with weakened immune systems. The presence of atopic dermatitis may heighten the likelihood of developing molluscum contagiosum due to its impact on skin barrier and immune function. Among those living with HIV (human immunodeficiency virus), the incidence of molluscum contagiosum can reach as high as 18%. There is no observed gender preference.

TREATMENT

The primary method of physical removal involves cryotherapy using liquid nitrogen or curettage, and these techniques may be combined. Laser therapies, such as carbon dioxide or pulsed dye lasers, can also be utilized but are not the first choice for treatment. Physical removal tends to be painful and may necessitate local anesthesia. There is a possibility of postoperative scarring. For treating molluscum contagiosum, topical trichloroacetic acid can be applied, leading to minimal scarring. [5]

Physicians suggest various topical treatments for molluscum contagiosum. Home treatments include podophyllotoxin (which is not safe for pregnant women), potassium hydroxide, salicylic acid (either alone or in conjunction with povidone-iodine), benzoyl peroxide, and tretinoin, which must be applied directly to each individual lesion.

DIFFERENTIAL DIAGNOSIS

- Keratoacanthoma
- Lichen planus
- Epidermal cyst
- Pyoderma[5]

VERRUCIFORM XANTHOMA

Verruciform xanthoma appears as a growth that resembles a papilla or cauliflower, primarily found in the oral mucosa. Shafer first documented it in 1971. This rare lesion occurs in approximately 0.025-0.05% of all pathology cases, leading to common misdiagnosis as papillomas. Lesions found outside the oral cavity are often linked to additional conditions, including lymphedema, epidermal nevi, and Congenital Hemidysplasia with Ichthyosiform Erythroderma and Limb Defects (CHILD) syndrome[6]

CLINICAL FEATURES

The gingiva, alveolar mucosa, and hard palate are the primary intraoral locations where it commonly appears. Typically, it manifests as a solitary lesion that can be either sessile or pedunculated, featuring a rough or pebbly surface. Usually asymptomatic, the lesion ranges from approximately 2 mm to 1.5 cm in size and may present in normal, pale, white, or red hues. It has been observed predominantly in adults aged 40 to 70 years.

ETIOPATHOGENESIS

Mostafa et al. have proposed that the epithelial hyperplasia observed in verruciform xanthoma is merely a perception rather than a genuine proliferation of epithelial cells with downward rete peg growth; instead, it is thought to stem from an upward exertion caused by accumulated macrophages pressing toward the epithelium. The authors suggest that this phenomenon also accounts for the thinning of the epithelium that covers the macrophages situated within the connective tissue papillae. However, Mostafa et al. failed to identify degenerated epithelial cells through either ultrastructural or immunohistochemical methods. The hyperplasia of the epithelium is part of a damaging loop connected to persistent inflammation. Chronic inflammation activates T-cells, which release cytokines that lead to hyperplasia. The hyperplastic epithelium exhibits the expression of human leukocyte antigen-DR (HLA-DR) and interleukin (IL)-8 molecules. Stimulated keratinocytes that present HLA-DR molecules subsequently secrete cytokines that enhance T-cell migration. Conversely, IL-8 molecules facilitate the exocytosis of HLA-DR+ neutrophils into the parakeratin layer. The interaction of increased T-cells and neutrophils further stimulates T-cells to release cytokines that promote epithelial hyperplasia. Consequently, this cycle perpetuates itself.[6]

ORAL MELANOACANTHOMA

Oral melanoacanthoma is an uncommon, non-cancerous macular brown-black lesion that is typically asymptomatic and characterized by its sudden emergence and quick growth. It is believed to occur as a result of tissue injury and tends to resolve on its own. According to the literature, as many as 75% of documented cases are classified as reactive. Histologically, it displays thickening of the superficial epithelium along with an increase in dendritic melanocytes.[7]

CLINICAL FEATURES

Oral melanoacanthomas are primarily found in the buccal mucosa, but they may also appear in the labial mucosa, palate, gingiva, alveolar mucosa, and oropharynx. There are two identified phenotypes: multifocal and singular, with the singular phenotype being the more prevalent of the two.

ETIOLOGY

Chronic trauma or exposure to chemical irritants activates melanocytes, leading to either oral pigmentation or the development of a melanoacanthoma. Continuous exposure to petroleum-based products present in toothpaste and mouthwashes may serve as irritants. These substances include sodium lauryl sulfate, phenolphthalein, nitrophenol, chlorophenol, phenylenediamine sulfate, amine fluoride, and cocamidopropyl betaine. Mouthwashes containing hydrogen peroxide can also provoke irritation of the oral mucosa, potentially resulting in melanoacanthoma. Additionally, silver amalgam has been identified as a possible cause of morphological changes and pigmentation, as well as dental restorations using other materials. Factors such as bruxism, cheek biting, ill-fitting removable prostheses, implant procedures, and non-specific chronic trauma have been noted prior to the occurrence of oral melanoacanthoma. Other contributing factors include patients undergoing treatment for chronic asthma and long-term use of ferrous lactate for iron-deficiency anemia.[7]

HISTOPATHOLOGY

A biopsy is essential for the diagnosis of oral melanoacanthoma and will reveal dendritic melanocytes alongside spinous keratinocytes. In this case, the dendritic melanocytes will be distinctly defined and located within an acanthotic epithelium. This differs from oral melanoma, where the melanocytes penetrate the lamina propria. Typically, dendritic melanocytes are identified using the Masson-Fontana silver impregnation stain. In most cases, the surrounding connective tissue shows signs of inflammatory infiltrate[7]

DIFFERENTIAL DIAGNOSIS

Multifocal hyperpigmented melanocytic lesions may arise from various conditions, including HIV, syndromes such as Peutz-Jeghers, neurofibromatosis, McCune-Albright syndrome, Addison's disease, Laugier-Hunziker syndrome, and certain medications like azathioprines, antimalarials, cytotoxic drugs including bleomycin, and contraceptives.

Non-melanocytic diffuse pigmentation could result from exposure to heavy metals, trauma, or hemochromatosis.

In cases of focal pigmentation, differential diagnoses encompass melanotic macules, which are the most prevalent, followed by melanocytic nevi, and less commonly, oral melanoma.[7]

MELANOCYTIC NEVI

INTRODUCTION

Pigmented skin lesions are often referred to as freckles. These lesions encompass solar lentigo, congenital nevi, mucosal nevi, and unique nevi found on the palms and soles. This activity will assist in distinguishing between the different types of pedal nevi and acral lentiginous melanoma from a clinical standpoint. Plantar

melanomas are typically diagnosed at a later stage, exhibit a poorer treatment response, and have a notably higher mortality rate in comparison to melanomas located more proximally[8]

ETIOLOGY

Experiencing a serious burn during childhood is closely correlated with a heightened likelihood of developing melanoma, whereas more gradual exposure in a work setting does not seem to increase that risk. These results bolster the theory that the risk of melanoma is primarily influenced by occasional intense sun exposure, which disrupts normal immune function and damages atypical melanocytes. Sunburns during adolescence can impair lifelong immune function and interfere with the natural process of eliminating neoplastic cells. Additionally, genetic predisposition might contribute to the occurrence of melanoma in areas with more shade. It is estimated that around 10% of melanoma cases could be associated with inherited genetic defects.

EPIDEMIOLOGY

The real rise in melanoma cases is probably attributed to a general surge in exposure to ultraviolet (UV) light. While melanoma is commonly considered to be uncommon, its occurrence across the globe is increasing significantly, and even with enhanced screening initiatives, mortality rates have not seen substantial improvement. In the United States, melanoma ranks as the fifth most common cancer in men and the seventh in women, with its incidence having doubled over the past decade.

PATHOPHYSIOLOGY

Melanocytes, which are unique dendritic cells originating from the neural crest, can disperse across the entire body surface. This capacity for spreading may explain why melanoma has the ability to metastasize through various tissues, blood vessels, nerves, and lymphatic systems. This capability for extensive spread contributes to melanoma's increased lethality compared to other skin cancers that are restricted to local areas. Despite the fact that the foot receives less sun exposure, melanoma located on the foot is more dangerous than melanoma found on the upper thigh. While the five-year survival rate for melanoma on the calf is 94%, the rate drops to 77% for melanoma on the foot. Acral melanoma shows a notably worse prognosis compared to other melanoma subtypes.

TREATMENT / MANAGEMENT

An atypical nevus located on the sole can be sampled using a straightforward 2 mm punch biopsy. If a wide excision is the preferred approach, it is advisable to include a 1 to 2 mm margin of normal skin tissue along with a portion of sub-dermal fat. Once a melanoma is identified through either the punch biopsy or complete excisional biopsy, a more extensive excision with surgical margins of 1 cm for tumors that are between 0 and 2 mm thick, and up to 5 cm for tumors exceeding 2.1 mm in thickness, can be planned. This procedure may result in significant tissue loss, potentially necessitating amputation. Generally, small excision sites for plantar melanoma are allowed to heal by secondary intention. After primary healing occurs, methods such as plastic skin grafts and flaps can be employed to restore the function for weight-bearing. Mohs microsurgery can also be utilized to reduce tissue loss. Having a qualified oncology team is crucial for enhancing patient outcomes. The Melanoma Staging database is derived from the clinical experiences of over 38,900 melanoma patients and includes a tumor, node, metastasis (TNM) classification system. This system is based on the evaluations of the primary tumor (T), nearby lymph nodes (N), and distant metastatic areas (M). The Breslow depth mainly determines the T classification, which is adjusted according to the tumor's mitotic rate. The 10-year survival rate progressively declines, starting at 96 percent for primary lesions less than 0.5 mm

thick and dropping to 54 percent for lesions ranging from 4.01 to 6 mm thick. The N classification, which evaluates regional lymph node involvement, significantly affects long-term survival rates. A sentinel lymph node biopsy (SLNB) is advised for tumors that are 0.75 mm thick or greater. If the biopsy result is positive, a complete lymph node dissection is recommended.[8]

DIFFERENTIAL DIAGNOSIS

- Atypical mole
- Basal cell carcinoma
- Café au lait spots
- Cockade nevus
- Cutaneous melanoma[8]

LEUKOPLAKIA

INTRODUCTION

Oral premalignancy is viewed as a transitional phase. It is divided into two main categories: premalignant lesions and premalignant conditions. A premalignant lesion is described as “a morphologically altered tissue where the likelihood of developing oral cancer is greater than in its apparently normal counterpart.” An example of this is leukoplakia. A premalignant condition is described as “a generalized condition that is linked to a notably higher risk of cancer.” Oral submucous fibrosis serves as an example. The World Health Organization (WHO) has recently grouped premalignant lesions and conditions together under a category called Potentially Malignant Disorders. Oral leukoplakia is classified as a potentially malignant disorder that affects the oral mucosa and is defined as “essentially a white lesion of the oral mucosa that cannot be classified as any other identifiable lesion.”[9]

ETIOLOGY

The causes of oral leukoplakia are varied, and many are unknown. One of the most prevalent risk factors is tobacco use, whether smoked or chewed. Moreover, the consumption of areca (betel) nut preparations, particularly in certain regions of South and Southeast Asia, significantly increases the risk, along with the use of snuff and other smokeless tobacco products. Chronic candidiasis has been associated with the emergence of leukoplakia, especially nonhomogeneous forms of the condition. This association may be connected to the high potential for nitrosation in some forms of candidiasis, indicating the production of endogenous nitrosamines. In certain cultures, retaining smoke from the burning end of a cigarette or similar device within the mouth can result in various oral mucosal lesions, including leukoplakia. In these groups, the likelihood of malignant transformation in such leukoplakias is 19 times higher compared to cultures where tobacco is consumed in different ways.

The main histopathological changes seen are: Keratinization of the epithelium (hyper ortho-keratinization or hyper para-keratinization)

- Increased thickness of the epithelium
- Acanthosis
- Basement membrane becomes thin
- The inflammatory component in connective tissue
- Change in the cellular layer
- Increased nuclear-cytoplasmic ratio
- Hyperchromatic nuclei
- Nuclear hyperplasia
- Abnormal mitotic figures
- Increased mitosis
- Pleomorphic nuclei
- Basilar hyperplasia
- Drop-shaped rete pegs
- Loss of polarity[9]

ORAL ERYTHROPLAKIA

INTRODUCTION

Oral erythroplakia is an uncommon yet serious premalignant lesion found on the oral mucosa, marked by a red, velvety area that cannot be linked to any other condition. From a histopathological perspective, it is important due to its considerable risk for malignant transformation.[10]

CLINICAL FEATURES

The WHO's publication 'Histological typing of cancer and precancer of the oral mucosa' characterized the clinical features of oral erythroplakia (OE) by stating: "Some erythroplakias present as smooth lesions, while others appear granular or nodular. Frequently, there exists a clearly defined border next to normal-looking mucosa." Shear expanded on the various clinical forms of OE: "The erythroplakic lesions might exhibit a smooth, velvety surface, but can also possess different morphological traits. The soft palate, floor of the mouth, and buccal mucosa are the areas most often affected by OE. In men, the floor of the mouth is the most prevalent location for OE, whereas in women, the most frequently impacted sites include the combined mandibular alveolar mucosa, gingiva, and sulcus. For men, this particular combined area was the least commonly affected site. The retromolar region is affected in both genders.[10]

EPIDEMIOLOGY

Oral erythroplakia predominantly affects middle-aged individuals and the elderly. The largest proportion of cases is found in the 45-54 year age group. It has been noted recently that oral erythroplakia is more prevalent in men.

ETIOLOGY

The causes and mechanisms behind OE are not well comprehended. The factors that contribute to its development are largely unclear, but it has been proposed that the consumption of tobacco and alcohol likely plays a significant role in many instances.

HISTOPATHOLOGY

Epithelial Atrophy:

• The epithelium tends to be more delicate, in contrast to leukoplakia, which may exhibit hyperkeratosis.

• There is a reduction in typical epithelial maturation and layering.

Loss of Keratinization:

• In contrast to leukoplakia, erythroplakia typically does not have a dense keratin layer, leading to its reddish coloration.

DIFFERENTIAL DIAGNOSIS

- Squamous Cell Carcinoma
- Verrucous Carcinoma
- Pyogenic Granuloma[10]

TREATMENT

Oral erythroplakias are associated with a significant risk of becoming malignant, making prompt and effective treatment of these lesions essential. The suggested approach for oral lesions that are at risk for malignant changes involves surgically removing those with severe epithelial dysplasia or carcinoma in situ, along with ongoing follow-up assessments of lesions that show no to moderate epithelial dysplasia in their histological evaluation.

CONCLUSION

This review has indicated that the idea of oral epithelial dysplasia (OE) has been largely overlooked in recent years, leading to a complicated and unclear situation. This could be attributed to the inadequacy of the existing terminology, which requires significant revision or clarification. Clinicians require clinical indicators, while pathologists seek enhanced objectivity in their reporting to accurately diagnose and grade oral epithelial dysplasia histologically.[10]

SMOKELESS TOBACCO

INTRODUCTION

Smokeless tobacco is made up of various chemical carcinogens, including the polynuclear hydrocarbon benzo[a]pyrene, nicotine, and tobacco-specific N-nitrosamines, which are linked to cancers of the esophagus, stomach, and mouth. Since smokeless tobacco is placed inside the mouth, these substances can cause dysplastic alterations in the oral mucosa. Pathological conditions related to these products include smokeless tobacco keratosis, leukoplakia, erythroplakia, verrucous carcinoma, and squamous cell carcinoma.[11]

ETIOLOGY

Smokeless tobacco keratosis occurs due to the continual frictional irritation caused by smokeless tobacco on the oral mucosa, leading to the development of keratosis. The rate at which this forms is influenced by the frequency of use, the amount consumed, and the specific brand of tobacco. Various causes contribute to leukoplakia, including tobacco, alcohol, betel nut/sanguinaria, UV exposure, microorganisms, and/or physical trauma. Erythroplakia is closely linked to tobacco use and alcohol intake, with some association noted with the chewing of betel quid.

EPIDEMIOLOGY

Smokeless tobacco keratosis was the most common pre-malignant condition observed in 50.4% of the studied population. Leukoplakia usually occurs in individuals over 40 years old, with the average age of diagnosis being 60 years. About 70% of these lesions are located on the vermilion border, buccal mucosa, or gingiva.

HISTOPATHOLOGY

Smokeless tobacco keratosis might show a non-specific appearance, featuring hyperkeratotic and/or acanthotic squamous epithelium. Intracellular edema and increased vascularity beneath the epithelium could also be observed. It is important to note that parakeratin chevrons may typically be seen above or within the upper layers of the epithelium. Consequently, histological analysis of these lesions should assess for the presence of epithelial dysplasia.

Leukoplakia is characterized by hyperkeratosis, which indicates a thickened layer of keratin, possible acanthosis, and an enlarged spinous layer. The term leukoplakia is solely a clinical designation, and a biopsy is necessary to establish a conclusive diagnosis. The biopsy should be taken from the area exhibiting the most severe changes.[11]

TREATMENT / MANAGEMENT

Smokeless tobacco keratosis typically resolves on its own once the usage is stopped. Initially, patients can be encouraged to alter the placement of the tobacco, followed by an evaluation of the affected region after two weeks. During this time, lesions that have developed to a mild or moderate degree should heal on their own, while more severe lesions may require a longer period to resolve or could need to be examined for possible malignancy. The clinician should recommend that the patient stop smoking, as moving the tobacco could heighten the risk of dysplastic changes in other areas of the mouth.

DIFFERENTIAL DIAGNOSIS

- Frictional keratosis
- Leukoplakia
- Squamous cell carcinoma[11]

ORAL SUBMUCOUS FIBROSIS

INTRODUCTION

OSMF is marked by limited mobility and a loss of papillae on the tongue, a pale and leathery appearance of the oral mucosa, a gradual decrease in the ability to open the mouth, and a shrunken uvula. Other names that refer to OSMF include idiopathic scleroderma of the mouth, juxtaepithelial fibrosis, idiopathic palatal fibrosis, diffuse oral submucous fibrosis, and sclerosing stomatitis.[12]

EPIDEMIOLOGY

The estimated prevalence of OSMF in India ranges between 0.2% and 2.3% among males and from 1.2% to 4.6% among females, affecting individuals from ages 11 to 60 years. A noticeable increase in incidence has been noted following the extensive promotion of commercial tobacco and areca nut products, commonly referred to as Gutkha, which is available in single-use packages. Presently, it is believed that 10% to 20% of the global population consumes areca nut in various forms.

ETIOLOGY

The disease's etiopathogenesis is complex and influenced by multiple factors, with the main triggering agent identified as the consumption of areca nut in any form. Additional risk factors that have been proposed include the use of smokeless tobacco, excessive consumption of chilies, elevated copper levels in food and chewing products, deficiencies in vitamins, malnutrition leading to decreased serum protein levels, anemia, and genetic susceptibility.

CLINICAL FEATURES

The diagnosis of OSMF relies on clinical indications and symptoms such as a burning sensation, discomfort, and ulcer formation. Other typical characteristics include gradual limitation in the ability to open the mouth, whitening of the mucous membranes, loss of papillae on the tongue, and reduced pigmentation.

DIFFERENTIAL DIAGNOSIS

- Oral Leukoplakia
- Squamous Cell Carcinoma
- Scleroderma

TREATMENT / MANAGEMENT

While there is a consensus on clinical staging, the management strategies for patients differ significantly. Various treatments have been documented. Supportive measures like vitamin and iron supplementation, a diet rich in minerals, the consumption of red fruits, green leafy vegetables, and green tea are frequently suggested, yet there is a lack of high-quality research validating their effectiveness.[12]

ACTINIC KERATOSES

INTRODUCTION

Actinic keratoses, which are also referred to as solar keratoses or senile keratoses, are non-cancerous intra-epithelial growths that are commonly assessed by dermatologists. Frequently linked to prolonged sun exposure, individuals affected by actinic keratosis may exhibit irregular, red, scaly bumps or plaques in areas of the body that have been exposed to the sun. Prompt identification and the establishment of a treatment strategy are vital, as actinic keratosis has the potential to develop into invasive squamous cell carcinoma.[13]

ETIOLOGY

Actinic keratoses mainly develop as a result of the long-term impact of ultraviolet (UV) radiation on the skin, resulting from a person's lifetime of sun exposure.

EPIDEMIOLOGY

•Older age: Actinic keratosis is more commonly seen in the elderly due to their extended lifetime exposure to sunlight and insufficient sun protection practices.

•Male sex: Actinic keratosis has a higher prevalence among men than among women.

•Individuals with fair skin (Fitzpatrick Skin Phototypes I and II): Those with pale or light skin have a lower amount of melanin, which increases their vulnerability to sunburn and the harmful effects of UV radiation.

HISTOPATHOLOGY

The main histopathological characteristic of actinic keratosis is the existence of abnormal keratinocytes in skin that has been damaged by the sun, which is confined to the lower third of the epidermis.

TREATMENT / MANAGEMENT

Treatment methods for actinic keratosis can be divided into therapies aimed at individual lesions and those targeting the broader area. The common saying associated with actinic keratosis treatment is "no pain, no gain," suggesting that effective therapies may entail some level of discomfort or side effects.

Lesion-targeted therapies concentrate on addressing single actinic keratoses. Common methods include cryotherapy, curettage, or surgical removal. These treatments are efficient for focusing on specific visible lesions.

Conversely, field-targeted therapies provide the benefit of addressing multiple, widespread, and subclinical actinic keratosis in an area affected by chronic sun exposure. These treatments focus on the entire damaged skin region rather than just individual lesions. Field-targeted therapies may consist of topical treatments (such as chemotherapy creams or immunomodulators), light-based therapies like photodynamic therapy

(PDT), or laser resurfacing. These approaches effectively treat both visible actinic keratoses and subclinical lesions that may not be detectable to the eye.[13]

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