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The role of viruses in the development of ocular surface squamous neoplasia and pterygium

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ABSTRACT

High prevalence of infections with human papillomavirus (HPV) and human immunodeficiency virus (HIV) is reportedly associated with an increased frequency of ocular surface squamous neoplasia (OSSN). The present review article aimed to evaluate the relationship between viruses such as HIV/HPV with OSSN and HPV with other possible related viruses with a pterygium. HIV infection increases the frequency and severity of OSSN, although the documented report on the involvement of HPV is inconclusive. The research findings evaluating both mucosal and cutaneous subtypes of HPV infection suggested an association only between the cutaneous subtype and the increased risk of OSSN. Despite uncertainties on the function of oncogenic viruses in pterygium development, the present literature found a clear disparity. The available data elucidate the potential of these viruses in the pathogenesis of pterygium, at least in a certain group of patients.

Keywords: *Human immunodeficiency virus, human papillomavirus, ocular surface squamous neoplasia, pterygium*

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INTRODUCTION

Ocular surface squamous neoplasia (OSSN) embraces a wide range of tumors in corneal and conjunctival epithelium, from mild dysplasia to carcinoma in situ, as well as invasive types of cancers. The OSSN shows varied signs from no symptoms to high severity pain and decreased vision. However, the most prevalent manifestations have been reported to be eye redness, eye irritation, or mass lesion formed on the ocular surface.[1] OSSN most frequently originates at the limbus and can extend into the inter-palpeblar conjunctiva. The OSSN has multifactorial causes, but there is no exact information on its etiopathogenesis. Meanwhile, even though several pathological processes may cause pterygium and OSSN (e.g., genetic factors, inflammation, and viral infection), the precise pathology is still unknown. Nevertheless, human papillomavirus (HPV) can be reportedly one of the major factors to develop pterygium and OSSN.[2–4] In fact, human immunodeficiency virus (HIV), HPV, and UV irradiation are possible OSSN risk factors. Kaposi sarcoma, OSSN, and non-Hodgkin lymphoma are malignancies occurring especially in human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) cases. The OSSN is observed in 4–8% of these patients.[5] The World Health Organization (WHO) in 2018 declared about 37.9 million HIV/AIDS cases around the world. Numerous researchers know that HIV is the main risk factor for OSSN in sub-Saharan Africa, probably due to the high prevalence of HIV/AIDS. Also today, another important OSSN risk factor has been reported to be chronic immunosuppression.[6] Even though the incidence rate of HIV has declined in the past few years, the prevalence of OSSN has been on a rise in the HIV-infected population due to the linear correlation between the two diseases in recent decades. In fact, the significant increase in HIV during the pandemic has gradually changed the age at referral to the clinic, clinical process, and OSSN management.[7] Not only does HIV increase the risk of OSSN, but it also affects the prognosis and severity of the disease.[7]

Several authors have suggested an indirect relationship between pterygium and neoplastic lesions. In addition, a number of studies have been conducted to indicate the existence of oncogenic viruses, like HPV, herpes simplex virus (HSV), and others in the formation of pterygium and conjunctival neoplasia. While studies have found a link between pterygium and HPV, the hypothesis that HPV is a risk factor for pterygium is rejected in another study.[8] Moreover, Gothai and colleagues[9] suggested a probably different etiology between developing and industrialized regions. To further assess, Piras and colleagues[10] analyzed pterygium in two different geographic regions to screen HPV DNA based on the polymerase chain reaction (PCR) technique. According to their observations, HPV was present in 100% and 21% of Italian and Ecuadorean pterygium cases, respectively.[10] Therefore, their findings approved the importance of geographical differences in the prevalence of HPV in pterygium. Furthermore, environmental conditions and the genetic structure of different lifestyles may be implicated in the etiology, pathological, and prevalence role of HPV in pterygium.[11] Therefore, in this narrative review we updated the review on the correlation of HPV and HIV infections with OSSN, also HPV, and other viral roles in the pathogenesis of pterygium.

MATERIALS AND METHODS

In this review paper, we aimed to find articles related to evaluating the relationship between viruses such as HIV and HPV with OSSN, also HPV and other possible related viruses with a pterygium. To this end, the search strategy was to screen the relevant articles published on authentic databases (Google Scholar, PubMed, Science Direct, MEDLINE, and Scopus) based on the main keywords ("HPV," "HIV," and viruses combined with "OSSN" and "Pterygium"). The analysis was

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performed on original articles and peer-reviewed reviews, and letters, case reports, editorials, and posters were excluded. Priority was given to human studies, and if necessary, animal studies were also reviewed. Full-text articles in English published from inception until October 1, 2022, were reviewed for eligibility. Due to the huge number of relevant articles, we tried to incorporate unique articles in our final analysis. In the end, the results were classified into categories of the relationship between OSSN and pterygium with HPV and HIV infections.

RESULTS

OSSN is associated with a concurrent viral infection, particularly HIV and HPV play a role in some studies. HPV can cause pathology of conjunctival epithelium from papillomas to squamous cell carcinoma (SCC).[12–14] Viral-like intracellular components can be found in a pterygium; in spite of uncertainties on the involvement of oncogenic viruses in the pterygium pathogenesis, the existing literature exhibits disparities on the topics.[15]

Relationship between OSSN and HIV/HPV

OSSN is the first symptom of HIV/AIDS in 26–86% of patients, with seropositivity of 38–92%. Despite a proper explanation of current OSSN management among the general population, the current OSSN management in patients positive for HIV is on the basis of few medical studies. There are limited data on different therapeutic methods for OSSN or their results in HIV patients. In general, OSSN treatment in HIV/AIDS cases is dependent on the laterality, extent, and invasion of tumor into surrounding regions and overall systematic status. However, the most prevalent therapy for resectable tumors (less than two quarters) with distinct lesions is surgical management via broad excision.[16]

Etiology

The OSSN has multifactorial causes, but there is no exact information on its etiopathogenesis. HPV, HIV, and UV irradiation are possible OSSN risk factors. The association of OSSN with vitamin A deficiency, smoking, and allergic eye illness has been reported previously. The high prevalence of OSSN in sub-Saharan African people can be attributed to concurrent HIV/AIDS and HPV infections and UV irradiation. The overlap of these factors in some points of the world with the rapidly growing prevalence of OSSN means their possible interaction with one another.[17] The high OSSN prevalence among sub-Saharan Africans can be related to multifactorial causes like UV irradiation, sunlight exposure, and HPV/HIV co-infection.[18]

Sunlight

In a subtle study, McCarty and colleagues[19] found the declined prevalence of OSSN down to 49% for each 10-degree elevation in latitude ($P < 0.0001$). Therefore, UV exposure has an association with the development of OSSN even though other factors, such as HIV and HPV infections, are significant in the increase of disease risk in Africa.[20]

HIV

Evidence suggests the association of immunosuppression with a high risk of cancer. One meta-analysis reported a higher relative risk of cancer in both patients with HIV and organ transplantation-mediated chronic immunosuppression.[21] The OSSN prevalence in Uganda has more than tripled since the beginning of the AIDS epidemic. The OSSN in sub-Saharan Africa is prevalent among 4–8% of patients with HIV infection, representing a 5–6% elevation over HIV-uninfected patients.[22] Also, there is a controversial impact of highly active antiretroviral treatment on OSSN. The screening of HIV is highly recommended for all OSSN subjects to rule out undetected HIV infection.[23–25] HIV can enhance the OSSN risk and affect the prognosis and severity of the disease.[26–28]

HPV

Scientific evidence revealed no association between OSSN and mucosal types of HPV, whereas

other studies detected an unclear involvement of cutaneous types of HPV in OSSN. A systematic review reported an association between the cutaneous subtype of HPV and high OSSN risk.[21] Based on some studies, while HPV might act as the main risk factor for OSSN, the assumption that it causes the disease is questionable. Other studies reported that HIV is a predisposition to OSSN through the formation of a "permissive environment" related to oncogenic HPV action, which eventually plays a role in neoplastic development as a cofactor. As such, it might be difficult to describe only one factor as its risk factor.[21]

Clinical features

The OSSN shows varied signs from no symptoms to high severity pain and decreased vision. However, the most prevalent manifestations have been reported to be eye redness, eye irritation, or mass lesion formed on the ocular surface.[1]

The disease is followed by a slow-growing lesion among the general population, but with aggressive behaviors among patients with HIV infection in either developed or developing regions. In various individuals, some investigations from Africa reported a longer time between symptom onset and tumor diagnosis, with an average history of 3 months at presentation. This longer period and large extent of the lesion highlight that many sufferers are non-adherent to medical care because of misdiagnosis or because they are undergoing long-term conservative therapy due to other eye diseases. The interpalpebral conjunctiva is usually influenced by OSSN, often arising from the nasal limbus. The patients with HIV infection from the sub-Saharan region exhibited larger tumors, more intensive malignancy, and higher recurrent tumor risk.[21] Shields and colleagues[29] described more invasive and aggressive types of OSSN in HIV-infected patients, and these people had a higher need for extended enucleation/exenteration.

The altered OSSN epidemiology has been reported during the past decades, particularly in developing regions of the world. Despite its reputation as an uncommon tumor among the elderly,[15] there is a possibility of increased prevalence and most likely among the younger age group. In fact, the mean age of OSSN onset has been reported at approximately 35 years in individuals with AIDS/HIV.[21]

The relationship between OSSN and pterygium with HPV

Pterygium as a chronic vision-threatening condition has unclear source and pathogenesis, characterized by the penetration of a fleshy triangular fibrovascular tissue from bulbous conjunctiva into the cornea, with many vessels and covered by squamous epithelium. The epithelium may show broad proliferative and degenerative alterations. Some pathological traits of epithelium seen in the pterygium are the same as in HPV-induced features in epithelia elsewhere, some studies investigated the potential effect of HPV in the pterygia pathogenesis. Recent studies have suggested the possible role of HPV in the pathogenesis of at least a subcategory of pterygium.[24,30,31]

HPV includes a single-closed circular double-stranded DNA that is carried in the icosahedral capsid shell. Belonging to the Papillomaviridae family, HPVs are severely tissue-limited species and have a preferential tropism for epithelial tissues. Today, approximately 100 HPV genotypes have been characterized, and more HPV are being constantly found. All known HPV need to differentiate terminals for the proliferation and production of the virion. HPV develops diseases ranging from benign warts to invasive tumors. In general, they are classified into three subcategories: mucosal, cutaneous, and autosomal dominant epidermodysplasia verruciformis (EV). In addition, mucocutaneous HPV are subdivided into low and high risk defined by their risk of progression to malignancy.[32]

Papillomaviruses as non-enveloped icosahedral small viruses possess a circular double-strand 8-kb DNA, with three parts of early (E) region

encoding E1–E7 proteins essential for viral replication, late (L) region encoding L1 and L2 structural proteins essential for virion assembly, and the predominantly non-coding part called long control region (LCR) carrying cis elements essential for viral DNA replication and transcription. Only HPV-encoded E6 and E7 genes play a crucial role in cell transformation through interaction with p53 tumor suppressor genes and retinoblastoma family of pRb proteins, which are implicated in the control of cell proliferation. Viral proteins may help more potential abnormalities in cell genetic matters.[13]

Over the past decades, HPV showed malignant and benign lesions in anogenital region, ocular surface, skin, respiratory tract, and oropharynx, with various genotypic tropisms in different anatomical locations. The ocular surface epithelium is in contact with the environment and thus is sensitive to infection, especially in cases of endangering the protective barriers of mucin, superficial cellular layer, and tears. It is implicated in the pathogenesis of ocular surface conditions like conjunctival papillomas, lacrimal sac papillomas and carcinomas, OSSN, conjunctival intraepithelial neoplasia (CIN), conjunctival pterygium, and conjunctival SCC.[5] A total of identified 80 different HPV genotypes exist in the east, of which HPV6 and HPV11 and HPV16 and HPV18 are related to benign lesions and SCC, respectively.[18] The results obtained by Piecyk-Sidor and colleagues[11] confirmed the presence of HPV DNA in most of the conjunctival papillomas, and indicated the involvement of types 6, 11, and 16 in the pathogenesis of such lesions. Their results also revealed the existence of HPV DNA in 50% of studied pterygium cases and the presence of widely similar types of HPV in both pterygium and papillomas. Additionally, type 6 HPV was prevalent, and type 16 HPV was rare in both lesions. The pterygium pathogenesis can be attributed to inflammation at the junction of Bowman's membrane and conjunctival blood vessels, in which the autolytic trend of inflammatory responses leads to the production of amino acid mixture from protein degradation.[20] The aforementioned mixture is proposed to be able to absorb conjunctival vessels on the cornea. Some of the possible risk factors are some herpes viruses and long UV irradiation.[1,21]

Recent results support a model whereby pterygium development is due to the impaired process of normal apoptosis. Cells produce high amounts of p53 and apoptosis inhibitory proteins. According to one study, HPV was present in pterygium and the overexpression of apoptosis inhibitory proteins, such as cIAP-1, clusterin, and XIAP, can partially explain the etiopathology of this disease.[32]

Diagnosis of HPV and other viral etiologies in pterygium

As part of a multistage pathophysiology, viruses can develop pterygium, as one of the dimensions of "second hit" theory in which oncogenic viruses provoke the development of pterygium in genetically susceptible people.[33] The HPV and HSV may have a potential function in the pterygium pathogenesis, based on multiple studies that observed them in pterygium samples.[33–37] The HPV prevalence in pterygium varies from very low to 100%. A meta-analysis reported an overall prevalence rate of 18.6% for HPV infection in pterygium.[38] Such differences in these statistics can be due to diverse study tools detection of viruses, various lifestyles, and diverse geographic area. Types 16, 18 HPV, as high-risk viruses for the development of cancer, have been frequently isolated from pterygium-associated genotypes.[39] The HPV-induced pterygium can occur due to viral E6 and E7 factors that influence the normal p-53 performance. HPV is responsible not only for the pterygium pathogenesis but also for postoperative pterygium recurrence. Such a disparity can be seen in studies that detected herpes viruses in pterygium. A research found cytomegalovirus and HSV among 45% of affected people, while another research in Taiwan detected HSV in only 5% of pterygium cases.[33,34] Epstein–Barr virus (EBV) DNA was isolated from 10% of study cases. Uncertainty in the literature on the action

of oncogenic viruses in the pterygium pathogenesis confirms a disparity in this regard, highlighting the heterogeneous pathophysiology of pterygium.[40] The available data elucidate the potential of these viruses in the pathogenesis of pterygium, at least in a certain group of patients.

HPV has been extensively studied as a possible common pathogen. There is no consensus among studies in this regard. For instance, while McCarty and colleagues,[19] Chen and colleagues,[41] and Gothai and colleagues[9] found no HPV in pterygium, Sjo and colleagues[42] and Takamura and colleagues[43] observed an ultra-low viral incidence in the range of 3–4.8%. Conversely, some earlier investigations identified HPV successfully. In fact, the mean HPV prevalence in human pterygium has been reported at 18.6%. This lack of consistency between the results of studies might be due to the difference in sampling and methods used. Piras and colleagues[10] suggested that these results might be explained by the role of geographical differences in the viral incidence in different regions of the world and support multifactorial pathogenesis.

Viral infection diagnosis is based on HPV-DNA detection. Diverse methods of identification with different specificity and sensitivity compromise the observations significantly. Direct isolation of HPV-DNA can occur from clinical samples, which can be detected by Southern blot, in-situ hybridization (ISH), or dot-blot hybridization. Nevertheless, such methods have been reported to be insensitive and laborious. Conversely, extremely false positive findings are yielded by the PCR because it is greatly sensitive. The viral load can be rapidly recognized and quantified by real-time PCR.[44] Reverse-transcriptase PCR (RT-PCR) can qualitatively measure the expression level of viral gene based on the reverse transcription. The aforementioned methods can be combined to achieve qualitative and quantitative data on the expression level of viral genes.

Conjunctival papillomas can recur following the surgical removal, which might show a permanent viral infection. Moreover, the postoperative recurrence rate of pterygium has been reported to be 46% following the follow-up periods of 7 years. According to these results, the involvement of HPV in the manifestations of such lesions causes persistent HPV-induced infection in the conjunctiva results in recurrent pterygium, and recurrent pterygium must be analyzed for HPV DNA.[45] Furthermore, the involvement of HPV in the recurrence of pterygium suggests the application of antiviral therapy for prevention of the recurrent lesions. In a study, Tsai and colleagues[39] found the HPV DNA in the pterygium and supported the involvement of HPV may change epithelial cells in the pterygium and that the virus can be involved in the pathogenesis of primary pterygium and its recurrence.

Several studies have reported an increased risk of recurrence and more invasive pterygium as a result of HPV intervention. In addition, a significant association has been found between genital HPV infection transmission via infected hand and ocular HPV infections. Nonetheless, this hypothesis remains suspicious and debatable. Cervical cytology, also known as a Pap smear, is a gold standard to screen genital HPV-induced infection. According to documented evidence, the urine analysis is more effective and accurate than the pap smear for the diagnosis of HPV infections from both female and male genital tracts. Some of the advantages of HPV detection by urine sample are ease of use and high potency for HPV DNA detection in the male genital tract.[46]

In a study, Uthaithammarat and colleagues[30] evaluated the incidence rate of HPV present in initial and recurrent pterygia. They also assessed the role of autoinoculation in HPV transmission from the genital tract to the eye. In their protocol, the association of fleshiness was explored with pterygium extension and also the level of cytokines such as interleukin (IL)-6, vascular endothelial growth factor (VEGF), and IL-18 was compared in the tears among patients with primary and recurrent pterygium and without any eye diseases. Therefore,

a cross-sectional study was conducted on 25 healthy individuals and 116 pterygium patients. Real-time PCR was used to detect HPV DNA in collected pterygium and conjunctival swabs and first-void urine specimens like genitalia samples. The tear samples were examined for the presence of IL-6 and IL-18 cytokines and VEGF, and the results showed that no HPV DNA was found in pterygium or conjunctival swabs. Moreover, there was no relationship between HPV DNA in conjunctival or pterygium swabs and urine samples. There was significantly a greater level of tear VEGF in pterygium patients than in healthy individuals,[32] without significant difference in their levels between primary and recurrent pterygium. Therefore, it could be concluded that HPV had no role in the pathogenesis of pterygium; this finding nullified the hypothesis of HPV transmission from the genitals to the eyes.

There are numerous reports on HPV DNA identification in pterygium specimens using a variety of approaches like Southern blot, PCR, ISH, immunohistochemistry, and hybridization II. Varied HPV prevalence has been found in these studies, between 0 and 100%, and also varied HPV DNA strains have been reported by many different studies. As such, no consensus was reached on considering HPV as a potential cofactor for pathogenisis.[46] The exfoliative cytology, a swab method, has been used in numerous investigations for HPV DNA detection in normal conjunctiva, pterygium, and conjunctival epithelial neoplasia. According to Chen K and colleagues, HPV is transmitted from the genital tract through finger contact, and many studies have mentioned the autoinoculation of HPV from genitalia to eye, including the pterygium.[41]

The best surgical therapy for pterygium has focused on the minimal risk of side effects and recurrence, short duration of recovery, and acceptable cosmetic outcomes. Therefore, there are diverse surgical procedures like the bare sclera method, limbal conjunctival grafts, autologous conjunctival grafts or amniotic membranes, and sliding flaps.[4] The adjuvant treatment using mitomycin C (MMC), anti-VEGF, thiotepa, 5-fluorouracil (5FU), cyclosporin A (CsA), β-irradiation, and interferon (IFN) alpha-2b eye showed satisfactory outcomes on postoperative recurrence, without consensus on illness relapse and dangerous side effects like scleral necrosis, corneal dellen, and melting, cataract.[19]

Other viruses like EBV, HSV, and CMV are reportedly the main risk factors for pterygium onset and recurrence, so it is essential to determine their performance in pathogenesis and in postoperative recurrence.[40]

Diagnosis of HPV in conjunctival papilloma

HPV infection is related to benign lesions (such as laryngeal papillomatosis and anogenital warts) and malignant lesions in the cervix, penis, anus, vagina, and oropharynx.[11] In addition, HPV persistence after treatment is accompanied by the recurrence of some pathology, such as sinonasal papilloma, SCC, high-grade vaginal intraepithelial neoplasia (VAIN), and CIN. On the other hand, one of the preventive methods for the recurrence of laryngeal papillomatosis is the use of adjuvant HPV vaccination.[32]

One of the benign tumors acquired is conjunctival papilloma due to the stratified squamous epithelium of conjunctiva. There is possible to see dysplasia but it rarely undergoes a malignant transformation. Although they tend to recur after surgical removal, spontaneous regression is also possible. Exophytic, mixed, or rarely inverted types are there for conjunctival papillomas, depending on their growth profile. The exophytic one is pedunculated or sessile. Even though the issue may arise in both adults and children, it mostly emerges in people within the age range of 20–39 years, due to the peak age of genital HPV infection among sexually active people. It seems that papilloma is associated with a male preponderance, with a decreased prevalence with age. Their existence has been reported in the inferior and medial conjunctiva.[47]

The exact pathogenic performance of them is still unclear. HPV infection via autoinoculation

due to contaminated hands can be related to their development. The pediatric conjunctival papilloma can be due to an HPV-infected birth canal within the fetal passage. The HPV function has been extensively reported in the conjunctival papilloma pathogenesis, in most of which, the low-risk types 6 and 11 HPV present in condylomata accuminata have been the most common in HPV-infected conjunctival papillomas, having variable incidence rates between 50 and 100%.[47] In a study, the researcher pointed out the types 6 and 11 HPV detection in an infant with conjunctival papilloma, with the mother experienced vulvar HPV infection within the pregnancy, thereby suggesting the possibility of vertical transmission within childbirth.[46] Benign nature of conjunctival papillomas lesions could be explained by the low-risk HPV identification. Moreover, epithelial lacrimal sac papillomas and carcinomas have shown the presence of HPV. These lesions can be developed due to tear flow on HPV-infected conjunctiva.[48]

Surgical removal, carbon dioxide laser, and cryotherapy are among the main options for the treatment of conjunctival papillomas. Edible cimetidine, localized interferon-α, and topical MMC are used to manage these benign lesions. Despite different treatment techniques, there is a high recurrence rate in these lesions.[49]

DISCUSSION

Comprising diverse conjunctival lesions, histologically ranging from in situ carcinoma and dysplasia to invasive SCC, the OSSN is the prevalent eye malignancy that affects the interpalpebral region due to limbus, and even the cornea. The prevalence rate of OSSN is completely different from the high prevalence rate in regions of the world with epidemic HIV infection. A robust relationship has been found between HIV infection-induced immunosuppression and OSSN mainly due to the fact that different investigations determined a 10-fold elevation in OSSN among such patients. Old age, UV irradiation, male gender, atopic eczema, immunosuppression, and xeroderma pigmentosum can cause OSSN. The most severe type of OSSN is presented by conjunctival SCC so its ignorance can lead to death.[47] The metastasis to lymph nodes is a prevalent event in a HIV-infected patients, thus it is essential to consider any aggressive therapy using exenteration or enucleation.

Prolonged illness-free survival of HPV-infected OSSN patients was reported by Chauhan and colleagues.[50] Meanwhile, a low incidence of cutaneous HPV and no relationship between mucosal HPV and OSSN were mentioned by De Koning and colleagues.[51] Furthermore, Tornesello and colleagues[49] pointed out a lack of high-risk and low prevalence of EV-associated types and did not find a significant relationship between HPV infection with abnormal p53 gene-product expression in OSSN. Such inconsistencies in diverse investigations render the HPV function in uncertain OSSN.[33]

The localized mitomycin, interferon, 5FU, UV irradiation, and cryotherapy may alleviate the incidence of metastasis and recurrence.[49,50]

HPV is one of the reasons for the intraepithelial injury that results in mucosal surface squamous neoplasms. Various precancerous and cervical carcinoma lesions can occur due to HPV infection. Moreover, a relationship can be found between HPV and dysplastic and malignant squamous lesions of the oropharynx. At the same time, there is no full knowledge of the relationship between HPV and squamous neoplasms of the eye and conjunctiva. The HPV genotype and relevant risk factors seem to play a considerable action in the pathogenesis of lesions. Koilocytosis is histologically one of the consequences of HPV infection.[52] Koilocytes as intermediate or superficial mature squamous cells are characterized by densely stained peripheral cytoplasm and perinuclear vacuolation with nuclei with rope-like chromatin patterns and undulating nuclear membranes. The antigens of viruses can be found in the nucleus of koilocyte using wide-spectrum antibodies of papillomavirus.[53]

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HPV has been found in a number of ocular lesions. There is a positive relationship between conjunctival papilloma and types 6 and 11 HPV. The variable numbers of HPV-associated papillomas can be attributed to differences in genetic factors, environmental factors, and lifestyle. In pterygium cases, there is no clear association between the virus' presence. Reportedly, HPV can serve as a pathogenic co-factor alongside genetic factors such as a mutation in p53 gene,[20] and also environmental causes like UV exposure and HIV co-infection.[18] Although there are clear controversies between existing studies, HPV is the main co-morbidity in sensitive people. Repeated pterygium recurrences after surgical removal can be due to HPV infection. The suggested underlying pathogenesis reveals the inactivation of p53.[54]

In spite of a clear relationship between HIV and OSSN risk, HPV involvement is inconclusive. Reportedly, the cutaneous HPV, not mucosal subtype, has a relationship with OSSN. Moreover, it seems that older people are more prone to the development of these lesions. The lack of consistency between the results might be due to selection bias in various parts of the world and diverse techniques of HPV isolation.[10] In a study by Chalkia and colleagues,[32] the exfoliative cytology studied by PCR was introduced as a precise HPV identification approach in ophthalmic pterygium, and others applied exfoliative cytology for conjunctival papilloma and OSSN.

CONCLUSION

According to the results of the present study, HIV infection significantly increased the OSSN risk. Despite inconclusive evidence for HPV involvement, the findings of investigating mucosal and cutaneous subtypes of HPV revealed that just cutaneous HPV is related to the high risk of OSSN. There is a need for further studies for the determination of pathogenic pathways of HPV in diverse eye diseases, and information may have clinical significance regarding the development of targeted treatments or preventive actions like the HPV vaccine. Overall, the OSSN risk can be elevated following the HIV infection up to eight times, while the existing data on the impacts of HPV revealed a relationship only between cutaneous HPV and high OSSN risk. On the other hand, the performance of these agents relates to "second hit" theory, in which pterygium is developed by the oncogenic viral infections in genetically susceptible patients.

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