Introduction

Lichen planus is a chronic mucocutaneous inflammatory disease detected in 1% - 2% of the general population. It is common in females more than males especially over 40 years old [1]. About 0.5% to 2% of the general population suffers from OLP which can present in many forms as reticular, papular, plaque, atrophic, and erosive types. The latter two types are the most symptomatic which carry the risk of malignant transformation (MT) [2-4].

The etiology of lichen planus is unknown, and its pathogenesis still needs more studies. It is known as an autoimmune disorder mediated by T-lymphocytes [5]. Several hypotheses were reported regarding the etiopathogenesis of OLP. The most common causes are cell-mediated immune response through T-lymphocytes and chronic inflammation. Besides, Microbial agents as fungal and viral infections as well as psychological stress were also implicated in OLP [6,7].

Many studies reported MT of OLP into squamous cell carcinoma (SCC) [4,8]. Some authors consider OLP as potentially malignant disease despite its MT is controversial and data are less extensive about the risk factor of MT [9].

MT of OLP with epithelial dysplasia as histological evidence can occur at any age [4,10]. Several studies measured the incidence of MT of OLP into oral squamous cell carcinoma (OSCC). It was ranged from 0% [11] to 10% [8,11,12]. Several pathogenic mechanisms were assumed to clarify the relation between malignancy and OLP. They include chronic inflammation [13], free radicals released in inflamed tissues, inflammatory mediators that affect survival and mutations of cells and some of the growth factors [13,14].

The progression from premalignant lesions to OSCC is a chronic, complex, multistep process with gene mutation and changes of protein expression of genes causing abnormal cell growth [15]. To our knowledge, this is the first review discussing the possible detected risk co-factors involved in MT of OLP. MT of OLP remains a controversial question in the literature.

Abstract

Oral lichen planus (OLP) is an autoimmune chronic inflammatory disease. The potential risk of malignant transformation in OLP remains controversial. The aim of the present study was to review original clinical studies published in indexed databases, which assessed the potential risk cofactors which were implicated in the malignant transformation of oral lichen planus. We focused our search to include most of the studies that reported malignant transformation of oral lichen planus using different combinations of the following key indexing terms: oral lichen planus, malignant transformation, smoking, alcohol, chronic inflammation, candida, human papillomavirus (HPV), hepatitis C virus (HCV) and immunosuppression. The animal studies were excluded from our study. Despite a dearth of studies on this topic we have identified consumption of tobacco and/or alcohol, the presence of erosive and/or atrophic areas, infection with candida, HCV, HPV, and immunosuppression as significant cofactors. Patients with OLP with these risk co-factors are at risk of malignant transformation should, therefore, be followed up for an extensive period or even for life.
Methods

We included the articles published until the search dates; papers written in English; studies that presented the words “OLP” and “the risk factors of malignant transformation of OLP in their titles, abstracts, or keywords; and observational studies evaluating the association between OLP and those risk factors. Using scientific databases (Scopus, PubMed, and Science Direct), a literature search was conducted between December 2019 and August 2020 to include only the clinical studies of OLP.

Results and discussion

In an attempt to identify and analyze the possible risk factors of that might induce the malignant transformation of OLP in the available scientific evidence in the literature to answer the research question. We have identified the following factors:

Smoking and alcohol

Smoking is categorized as the major risk factor of oral cancer [16]. Stimulation of carcinogenesis through smoking was attributed to the presence of three pre-carcinogenic components which are nitrosamines, benzopyrenes and aromatic amines. These chemicals induce carcinogenesis through the production of oxidative enzymes, which cause the final product to be poor in electrons and bond covalently with DNA, producing an adduct mutated region [17]. Furthermore, alcohol acts in harmony with tobacco smoking in causing oral cancer. Alcohol can induce oral carcinogenesis through atrophying oral epithelium and increasing permeability of epithelial cells. Furthermore, it can dissolve lipid components of oral mucosa as well as it can interfere with the synthesis and repair of DNA. It was reported that alcohol has a genotoxic and mutagenic effect and its chronic use can impair innate as well as acquired immunity resulting in increased susceptibility to infections and neoplasms [18].

Many studies of OLP reported smoking and alcohol consumption among their studied population. Aghbari, et al. reported a significant increase of OLP MT among smokers and alcoholics in comparison to nonsmokers and non-alcoholic OLP patients [19]. Recently, Gonzalez-Moles, et al. studied the possible risk factors of OLP MT and they found that tobacco and alcohol consumption were associated with a significantly higher risk of MT in OLP patients in comparison to the controls ($p = 0.002$) [4].

Some authors listed Smoking and alcohol as exclusion criteria of MT in OLP patients [20]. However, Gonzalez-Moles et al didn’t agree with that. They suggested that smoking and alcohol may potentiate the MT risk of OLP and oral lichenoid lesions (OLLs) in individual patients [9,21], and there could be a summative oncogenic effect (tobacco and alcohol plus OLP, OLLs) as reported for other oral potentially malignant diseases (e.g, leukoplakia) [21].

Chronic inflammation

The association of chronic inflammation with a variety of epithelial malignancies has been documented in the literature [22]. OLP is a chronic inflammatory disorder and it was used by researchers as a unique disease model to study the correlation between chronic inflammation and cancer. Liu, et al. considered OLP as a pure inflammatory disorder in which chronic inflammation predisposes the lesion to MT [23]. These findings proposed that the immunosuppression triggered by chronic inflammation enhances carcinogenesis in OSCC, instead of initiating it [24]. So, inflammatory cellular infiltration in oral tissues was reported as a strong risk factor for oral cancer by many studies [22,23].

Interestingly, atrophic and erosive OLP lesions were reported to have a higher rate of MT (3.5% - 4.0%) than non-atrophic and non-erosive lesions (0.5%) under the same follow-up period [25]. Canto, et al. showed the greater incidence of MT in OLP was detected in the atrophic, ulcerated and erosive types and the most common site was tongue [26]. Moreover, Agha-Hosseini, et al. found that the highest rate of malignancy was observed in atrophic and erosive lesions [27]. Most recently, Gonzalez-Moles, et al. reported that the high MT of OLP was detected in erosive and atrophic lesions while reticular lesions have no risk of MT. Thus, the authors recommended follow up of OLP patients should focus on atrophic-erosive rather than the reticular ones [4].

Additionally, Mignogna, et al. suggested that the OLP-related Inflammation may not only be able to initiate MT in normal oral mucosa, but also it may act as a co-factor toward the molecular changes caused by environmental carcinogens, as alcohol and tobacco [22]. Furthermore, the cell cycle may be affected by certain proteins generated by inflammatory cells resulting in mutagenesis and tumor formation [28].

Chronic inflammation can enhance MT of OLP through oxidative stresses and also it can lead to the release of inflammatory cytokines, which then activate transcription factors in premalignant cells [13,29]. Considering OLP as a pure inflammatory disorder necessitates OLP patients to be meticulously controlled over time in order to allow the chance for the early detection of a possible malignancy.

Human papilloma viruses

Human papilloma viruses (HPVs) are circular double-stranded DNA viruses. About 170 subtypes of HPV were detected in oral mucosa as well as other sites [30].

HPV16 and 18 were found to be strongly associated with oral premalignant lesions, especially OLP [31,32]. Pol, et al. reported that OLP lesions have a higher percentage of HPV16 and HPV18 in comparison to the normal population. In addition, they found that about 70% of OLP patients showed HPV16 positivity while all the controls were negative [31].
Candida albicans (C. albicans), candida tropicalis (C.tropicalis), and the combination of Calbicans & C.tropicalis were detected in OLP. [37,38]. Furthermore, Calbicans was detected in premalignant lesions as well as OSCCs [37,39]. Sing, et al. detected Calbicans in about 83.3% of OLP patients [37]. Kragelund, et al. reported the presence of Candida SPs in 16 of 30 patients with OLP [40]. Others reported that there was no significant difference regarding the colonization of Calbicans between reticular, atrophic and erosive forms of OLP [41].

In combination with other risk factors such as smoking and alcohol, candida was reported to have a synergistic impact. [21]. Candida Infection can induce inflammatory changes in the oral epithelium that may result in dysplastic changes [42]. Researchers’ attention has been drawn to the possible association between candida species (SPs) and oral cancer. However, no enough studies were published that could support or disapprove this hypothesis.

Various biological theories were reported to favor that correlation. Candida can easily colonize and penetrate the oral mucosa and induce chronic inflammation that predisposes to neoplastic evolution [42]. The induction of carcinogenic changes by candida was reported in animal models [43]. Researchers should put into consideration if candida over infected OLP after or before OLP treatment as immunosuppressive therapy can induce candida overgrowth [44]. In addition, types of candida and resistance of candida to drugs should be reported [45].

Initial colonization of Candida SPs is in yeast form. After that, epithelium may undergo some changes due to trauma, immunosuppression or other factors resulting in more invasion of Candida into underlying connective tissue with changing into hyphae forms that produce intra-mucosal hydrolytic enzymes [46]. It was assumed that Calbicans may play a direct role in MT of OLP due to the yeast forms which are capable of producing carcinogenic enzyme N-nitrosobenzylmethyamine [47].

Recently, the authors found that C. albicans was able to activate the TLR2/MyD88/NF-KB signaling pathway in OLP epithelial cells with increasing the expression of cytokines and decreasing keratinocyte apoptosis. The later are the two principal pathogenic factors in MT of OLP namely increased inflammation and decreased apoptosis [48].

In addition, some authors found that there was a higher correlation between the number of candida colonies and the severity of epithelial dysplasia [49]. Werneck, et al. reported that in OLP cases, nine cases had epithelial dysplasia. Cytological examination showed an association with candidiasis in 8 of the 21 cases [50]. Based on the previous studies, it is reasonable to suggest further studies on the role of Candida SPs in MT of OLP based on a biochemical basis through which the production of carcinogenic enzymes can be detected.

**Immunosuppressive therapy**

It is conceivable that, systemic immune defects may be involved in developing carcinoma in OLP patients [51]. Corticosteroids act as an immune-modulating agent which often are utilized to reduce the inflammatory response in OLP and OLLs [52]. There is still debate regarding whether utilization of corticosteroids is contraindicated in OLP and OLLs or not, as this treatment could depress local cell mediated immunity and may enhance the progression of neoplastic transformation [53].

Corticosteroids have been suggested to increase the susceptibility of patients to MT [51]. Immunosuppressive treatment may act as a cofactor to smoking and alcohol in producing oral cancer. Duffey et al reported that 5 cases of OLP patients who received topical and systemic steroid treatment developed OSCC later. Two of those patients were smokers and alcohol consumers. The authors recommended that possible avoidance of topical steroids could decrease the future incidence of OSCCs in OLP lesions [51]. Furthermore, Laeijendecker, et al. detected OSCC in three patients who had OLP and were treated with immunosuppressive drugs. One of those patients received systemic immunosuppressive medication (corticosteroids and cyclosporine) over a period of about 2 years. The authors reported that therapy could have increased the chance of developing OSCC in OLP lesions [54].

Treatment of lichenoid lesions with topical steroids
increased the risk of HPV infection from 16% to 21%. These findings could be attributed to the chronic use of topical steroids that may be associated with reactivation of the latent HPV or may promote its overexpression and may induce malignant changes [55,56].

On the other hand, other studies suggested that, immunosuppressive treatment does not increase the risk of MT of OLP [57,58] and may reduce it. Otero-rey, et al. reported that, low dose maintenance therapy of topical corticosteroids could inhibit the progression of OLP to OSCC as it may prevent the persistence of chronic inflammation and so inhibit MT [59]. It has been suggested that, the elevation of proinflammatory cytokines may enhance the neoplastic transformation and the use of a more aggressive immunosuppressive therapy against the associated inflammatory reaction in OLP might restore normal immunosurveillance and interfere with neoplastic progression [11].

Topical tacrolimus which is an immunosuppressive drug used for the treatment of OLP was implicated in developing oral cancer. Mattsson, et al. reported that five years after diagnosis of a patient with OLP and treatment with topical tacrolimus, the patient developed a SCC in the region where tacrolimus had been applied [60] (Figure 1). Tacrolimus was reported to induce MT by affecting cancer signaling pathway as the mitogen-activated protein kinase (MAPK) pathway and PS3 [61]. Becker, et al. reported another case of recalcitrant OLP which received maintained dose of topical tacrolimus for 3 years and developed OSCC at the lateral border of the tongue [61]. Morita, et al. reported a case of OLP who applied tacrolimus ointment to the lower lip after being diagnosed with OLP in 2008, and whose lesion developed a SCC in 2010 [62]. Despite the correlation between topical tacrolimus treatment and cancer development has been documented in only a few cases, still the number of available cases and follow-up period has been insufficient to draw any firm conclusions. However, the clinician must be careful in choosing tacrolimus as a second-line treatment for OLP.

**Hepatitis c virus**

Hepatitis c virus (HCV) was reported to elevate the chance of MT [63] and HCV replication was detected in samples taken from patients having oral cancer [64]. Positive HCV serology was reported in about 12.8% of patients with head and neck cancer [63]. A population-based cohort study performed in Taiwan reported that HCV infection alone is a risk factor for oral cancer [65]. Despite many studies reported the correlation between OSCCs and HCV detection, this association remains controversial and it would be difficult to present unequivocal or definitive conclusions [66].

Studies point out that the HCV viral capsid protein is characterized by oncogenic potential being able to act through different mechanisms such as cellular proliferation and death or chronic inflammation. In addition, HCV can induce the production of free radicals [67]. The mechanism of inducing tumorigenesis by HCV infection may involve either direct or indirect actions. The direct action is by deregulation of the cell cycle, while the indirect action is by producing cirrhosis [68]. Some HCV proteins, namely the core and the non-structural protein may deregulate the cell cycle in vitro.

Nagao, et al. studied the relation between HCV and OLP and showed that occurrence of OLP in HCV infected patients is not only related directly to the virus itself, but also to other host factors such as immunity, genetics and insulin resistance [69]. Lodi, et al. studied the correlation between OLP and HCV infection. They reported that HCV infection presented in up to 20% of OLP patients. These findings may encourage including HCV serology in evaluation and treatment plan of OLP [70].

Hepatitis c virus (HCV) infection is one of the risk factors involved in MT of OLP [51].

Gandolfo, et al. studied the role of HCV infection as a risk factor in the neoplastic transformation of OLP. They found that 44% of OLP patients who developed carcinomas were HCV positive. In addition, they reported that the relative risk of MT of OLP cases infected with HCV in comparison with HCV negative patients was 3.16 (0.8–12.5). The authors concluded that the risk of development of oral cancer in OLP patients is increased with HCV infection [57]. Nagao, et al. reported a high rate for MT of OLP in HCV endemic areas, HCV-RNA strands were found in OLP tissues [64]. Another study reported that the percentage of HCV-positive OLP patients who developed an oral carcinoma are higher in comparison with HCV negative patients [71].

While the risk of MT in HCV positive OLP patients is indefinite, screening of all OLP patients for detection of HCV became a controversial matter [72,73]. Generally, we believe that HCV screening is recommended in countries with a high...
prevalence of HCV among the general population. In addition, the treatment intervention for HCV infection could reduce the consequences of hepatocellular carcinoma and OSCC.

**Conclusion**

The most critical variables in the estimation of carcinoma development in OLP are the initial diagnosis of OLP and the time between initial diagnosis and MT Symptoms aggravation and homogeneity loss of OLP lesions should be evaluated during the patients follow up visits. If those signs detected, more frequent follow up and further biopsy should be performed for early detection and monitoring of malignant changes in OLP lesions.

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