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ORALNA LEUKOPLAKIJA: PREGLED KLINIČKIH KARAKTERISTIKA I TRENDOVA U LEČENJU

ORAL LEUKOPLAKIA: A REVIEW OF CLINICAL FEATURES AND TRENDS IN MANAGEMENT

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Sažetak

Uvod: *Oralni, potencijalno maligni poremećaji (OPMD) čine grupu bolesti od velike važnosti za stomatologa. Oralna leukoplakija (OL) dugo je bila predmet debate brojnih istraživača. Uobičajeni etiološki faktor je duvan, koji je povezan sa karcinomom usne šupljine.*
Cilj studije *je ukazati na ozbiljnost lezije, najčešću kliničku sliku i lokalizaciju. Prevalencija leukoplakije u svetu je 2,6% sa stopom maligne konverzije u rasponu od 0,1% do 17,5%. Nalazi u literaturi o prevalenci i godišnjoj stopi maligne transformacije od približno 2%, ukazuju da ove promene traba ozbiljno shvatiti i redovno pratiti*
Zaključak: *Umeće postavljanja tačne dijagnoze pruža ključ za sprečavanje progresije premaligne ka malignoj transformaciji. Opisani su različiti medicinski i hirurški modaliteti lečenja ove lezije. Ovaj članak naglašava različite trendove u dijagnostici i lečenju oralne leukoplakije.*

Ključne reči: *potencijalno maligni poremećaj, leukoplakija, maligna transformacija*

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Abstract

Introduction: *Oral potentially malignant disorders (OPMD)conisit of the group of diseases of great importance for dentists. Oral leukoplakia (OL) has long been the subject of debate by numerous researchers. A common etiologic factor is tobacco, which is associated with oral cancer.*
The aim *of the study is to indicate the severity of the lesion, the most common clinical characreistics and localization. The prevalence of leukoplakia in the world is 2.6% with a rate of malignant conversion ranging from 0.1% to 17.5%. Literature data about the prevalence and annual rate of malignant transformation, approximately 2%, indicate that these changes should be taken seriously and regularymonitored*
Conclusion: *Occurate diagnosis provides the key to preventing to malignant transformation. Various medical and surgical treatment modalities for this lesion have been described. This article highlights various trends in the diagnosis and treatment of oral leukoplakia.*

Key words: *potentially malignant disorder, leukoplakia, malignant transformation*

Uvod

Termin leukoplakija prvi je upotrebio Švimer 1877. godine[1]. Termin leukoplakija izveden je od grčke reči leucos što znači belo i plakija što znači fleka[2]. Butlin je 1885. godine povezao ove lezije sa pušenjem i smatrao je da je ova promena kod pušača rana faza naprednije lezije belog tumefakta, koji je nazvao leukom[3]. Akell je 1996. godine definisao leukoplakiju kao belu mrlju od 5 mm ili više, koja se ne može otkinuti i ne može se pripisati nijednoj drugoj dijagnostikovanoj bolesti[4]. Leukoplakija predstavlja oblik hiperkeratoze oralnog epitela. Faktor rizika za ovu bolest je duvan, kako u vidu cigareta, sa dimom, tako i u formama bez dima. Drugi faktori koji doprinose razvoju leukoplakije su alkohol, hronična iritacija sluzokože, oralna kandidijaza, nedostaci u ishrani, polno prenosive lezije, kao što je sifilis i izlaganje ultraljubičastom zračenju[5]. Predloženi su različiti načini prevencije, sa ciljem sprečavanja napredovanja leukoplakije u oralni karcinom skvamoznih ćelija. U ovom radu opisani su različiti klinički tipovi, dijagnostičke metode i strategije lečenja leukoplakije.

Definicija oralne leukoplakije

Tokom godina, predložene su različite definicije oralne leukoplakije. Na prvoj međunarodnoj konferenciji o oralnoj leukoplakiji (Malme, Švedska, 1984. godina), definisana je leukoplakija kao „bela mrlja ili plak koji se ne može klinički ili patološki okarakterisati kao bilo koja druga bolest i nije povezana ni sa jednim fizičkim ili hemijskim uzročnikom osim sa upotrebom duvana"[6]. Ovo je pojednostavljeno 1994. godine kao „pretežno bela lezija oralne sluzokože, koja se ne može okarakterisati kao bilo koja druga lezija, koja se može definisati"[7]. Akell i sar.[4] definisali su 1996. godine leukoplakiju kao „belu mrlju veličine 5 mm ili više, koja se ne može ostrugati i ne može se pripisati nijednoj drugoj bolesti". Svetska zdravstvena organizacija (SZO) je 1997. godine modifikovala definiciju kao „pretežno belu leziju oralne sluzokože, koja se ne može okarakterisati kao bilo koja druga definisana lezija"[7,8]. SZO je 2005. godine definisala leukoplakiju kao „beli plak sumnjivog rizika, koji je isključio (druge) poznate bolesti ili poremećaje, koji ne nose povećan rizik od raka"[9]. Varnakulasuriia i sar. 2007. godine[10] predložili su sledeću definiciju: „beli plak sumnjivog rizika, koji je isključio druge poznate bolesti ili poremećaje, koji ne nose povećan rizik od raka".

Introduction

The term leukoplakia was first coined by Schwimmer in 1877[1]. Leukoplakia is derived from the Greek word Leucos which means white and plakia which means a patch[2]. In 1885, Butlin related these lesions to smoking and considered smokers patch to be an early stage of a more advanced white raised lesion that he termed leukoma[3]. In 1996, Axell defined leukoplakia as a white patch measuring 5 mm or more which cannot be scrapped off and cannot be attributed to any other diagnostic disease[4]. It represents a form of hyperkeratosis of the oral epithelium. The risk factors for this disease include tobacco, both in smoked and smokeless form. Other contributing factors include alcohol, chronic mucosal irritation, oral candidiasis, nutritional deficiencies, sexually transmitted lesions like syphilis and exposure to ultraviolet light[5]. Various management strategies have been proposed to halt the progress of leukoplakia into oral squamous cell carcinoma. The present review describes the various clinical types, diagnostic methods and management strategies of leukoplakia.

Definitions of oral leukoplakia

Various definitions for oral leukoplakia have been proposed over the years. The first International Conference on Oral Leukoplakia, Malmo, Sweden, 1984, defined leukoplakia as "A white patch or plaque that cannot be characterized clinically or pathologically as any other disease and is not associated with any physical or chemical causative agent except the use of tobacco"[6]. This was simplified in 1994 as "A pre-dominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion"[7]. In 1996, Axell et al.[4] defined leukoplakia as "A white patch measuring 5 mm or more, which cannot be scraped off and cannot be attributed to any other diagnostic disease". In 1997, the WHO modified the definition as "A predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion"[7,8]. In 2005, WHO defined leukoplakia as "a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer"[9]. Warnakulasuriya et al. in 2007[10] proposed the following definition "A white plaque of questionable risk having excluded other known diseases or disorders that carry no increased risk of cancer".

Epidemiologija

Prevalencija leukoplakije u svetu je 2,6%, sa stopom maligne konverzije u rasponu od 0,1% do 17,5%[11]. U Indiji, prevalencija leukoplakije je između 0,2% i 5,2%, sa stopom maligne transformacije od 0,13% do 17,5%[5,12]. U studiji koju su sproveli Martorell-Calataiud i sar.[13], utvrđeno je da je prevalencija leukoplakije u rasponu od 0,4% do 0,7%[13]. Gopinath D i sar.[12] pronašli su žarište oralnih karcinoma kod 11,9% biopsiranih oralnih leukoplakija. Feller i sar.[14] pokazali su to da se stopa prevalencije leukoplakije kreće od 0,5% do 3,46%. Takođe, pokazali su to da se stopa maligne transformacije leukoplakije kretala od 0,7% do 2,9%. Brouns i sar.[15] izvestili su o prevalenciji i godišnjoj stopi maligne transformacije od približno 2% i 1%.

Starost i pol

Leukoplakija se obično javlja kod osoba srednjih godina i starijih osoba, pretežno kod muškaraca[16]. Manje od 1% slučajeva leukoplakije javlja se kod muškaraca mlađih od 30 godina[11]. Espinoza i sar.[17] pokazali su to da leukoplakiju u svim starosnim grupama sa višom stopom prevalencije kod starije populacije, u rasponu od 0,35% do 18,6%. Bokor-Bratiket i sar.[18] pokazali su to da se oralna leukoplakija javlja u vidu crvenila kod muškaraca preko 40 godina i kod žena preko 50 godina. Leukoplakija je češća kod muškog pola, verovatno zbog povećane prevalencije navika konzumiranja duvana i alkohola u poređenju sa ženama[19].

Lokalitet leukoplakije

Leukoplakija se može videti na bukalnoj sluzokoži, labijalnoj sluzokoži, podu usta, gingivi i jeziku. Ramia i sar.[20] izvestili su o tome da je bukalna sluzokoža najčešće mesto za leukoplakiju. Na mesto leukoplakije utiče povezana navika. Pušači beedi cigareta imaju veću incidenciju leukoplakije u prednjoj bukalnoj sluzokoži, pri čemu je, kao i kod žvakanja duvana, veća verovatnoća da će se leukoplakija pojaviti u zadnjoj bukalnoj sluzokoži[21].

Klasifikacija

Mnogi autori predložili su različite klasifikacije leukoplakije. Leukoplakija se uglavnom klasifikuje kao homogena i nehomogena, gde je homogena leukoplakija uniformno bela mrlja, koja se ne može strugati, dok se nehomogena leukoplakija sastoji od mešanih crvenih i belih područja i uključuje pegastu, nodularnu i verukoznu leukoplakiju[22,23].

Epidemiology

The prevalence of leukoplakia worldwide is 2.6% with a malignant conversion rate ranging from 0.1% to 17.5%[11]. In India, the prevalence rate of leukoplakia is between 0.2% and 5.2% with a malignant transformation rate from 0.13% to 17.5%[5,12]. In a study done by Martorell-Calatayud et al.[13] the prevalence of leukoplakia was found to be in the range from 0.4% to 0.7%[13]. Gopinath D et al.[12] found oral foci of carcinoma in 11.9% of biopsied oral leukoplakias. Feller et al.[14] showed that the prevalence rate of leukoplakia was found to be ranging from 0.5% to 3.46% in his study. He also showed that the malignant transformation rate of leukoplakia ranged from 0.7% to 2.9%. Brounset al.[15] reported a prevalence and annual malignant transformation rate of approximately 2% and 1%, respectively.

Age and gender

Leukoplakia commonly occurs in middle aged and older individuals predominantly in males[16]. Fewer than 1% cases of leukoplakia occur in males less than 30 years of age[11]. Espinoza et al.[17] showed leukoplakia in all age groups with a higher prevalence rate in the elderly population, ranging from 0.35% to 18.6%. Bokor-Bratić et al.[18] showed that oral leukoplakia occur red in men over 40 years and in women over 50 years of age. Leukoplakia is more prevalent in male gender probably due to the increased prevalence of habits in males when compared to females[19].

Site of Leukoplakia

Leukoplakia can be seen in the buccal mucosa, labial mucosa, floor of the mouth , gingiva, and the tongue. Ramya et al.[20] reported that the buccal mucosa was the most common site for leukoplakia. The site of leukoplakia is affected by the associated habit. Beedi smokers have greater incidence of leukoplakia in the anterior buccal mucosa, where as in tobacco chewing, leukoplakia is more likely to occur in the posterior buccal mucosa[21].

Classification

Various classifications have been suggested by many authors. Leukoplakia is mainly classified as homogenous and non-homogenous where homogenous leukoplakia is uniformly white non scrapable patch while non-homogenous leukoplakia consists of mixed red and white areas and includes speckled, nodular and verrucous leukoplakia[22,23].

Leukoplakija se takođe može klasifikovati kao tanka, glatka leukoplakija, debela, fisurna leukoplakija, granularna, veruciformna leukoplakija i eritro-leukoplakija[24]. U daljoj modifikaciji 2002. godine, SZO podelila je leukoplakiju u četiri faze: faza I koja se sastoji od tanke, glatke leukoplakije; faza II kao gusta, pukotinasta leukoplakija; faza III kao proliferativna verukozna leukoplakija (PVL) i faza IV kao eritroleukoplakija[21]. Proliferativna verukozna leukoplakija (PVL) je podtip verukozne leukoplakije sa ekstenzivnim širenjem, otpornošću na terapiju i visokim stepenom maligne transformacije. PVL je klasifikovana kao oblik nehomogene leukoplakije[25]. Nasuprot tome, van der Vaal pominje to da sve ekstenzivne leukoplakije imaju povećan potencijal za malignu transformaciju, te PVL ne treba klasifikovati kao poseban entitet. Dalje, PVL se može smatrati vrstom homogene leukoplakije, jer je pretežno bele boje[23].

Histopatološka klasifikacija

Histopatološka klasifikacija zasniva se na stepenu epitelne displazije u leukoplakiji. Tri glavne klasifikacije uključuju klasifikaciju SZO, binarni sistem klasifikacije i Brothvellovu klasifikaciju[26]. Klasifikacija SZO koristi citološke i ćelijske arhitektonske promene, kako bi podelila leukoplakiju na blagu, umerenu ili tešku epitelnu displaziju. „Blagu displaziju“ karakterišu ćelije koje pokazuju nuklearni hiperhromatizam i pleomorfizam bazalnih i parabazalnih epitelnih regiona. „Umerena displazija“ karakteriše se ćelijama sa nuklearnim hiperhromatizmom i pleomorfizmom u bazalnom, parabazalnom i spinoznom sloju. Lezije „teške displazije“ karakterišu lukovičasti zaravnjeni procesi sa hiperhromatskim jedrima i pleomorfizmom po celoj debljini epitela[26]. Brothvellov sistem sličan je klasifikaciji SZO, sa dodatnim nivoom „karcinoma in situ“, koji karakterišu displastične promene u celom epitelu, koje sugerišu na invaziju u osnovno tkivo, ali bez dokaza o istom[27]. Binarni sistem kategoriše lezije kao visokorizične i niskorizične[28].

Etiologija

Duvan: Oralna leukoplakija ima multifaktorsku etiologiju, ali najčešće impliciran uzročnik je upotreba duvana u vidu cigareta za pušenje ili bez dima. Duvan oslobađa karcinogene, koji se vezuju za DNK, izazivajući mutaciju. Oni, takođe, mogu dovesti do stvaranja visokoreaktivnih slobodnih radikala, koji uzrokuju oštećenje ćelijske membrane i DNK[25].

Leukoplakia can also be classified as thin, smooth leukoplakia, thick, fissured leukoplakia, granular, verruciform leukoplakia and erythro leukoplakia[24].

In a further modification in 2002, the WHO categorised leukoplakia into Phase I consisting of thin, smooth leukoplakia; Phase II as thick, fissured leukoplakia; Phase III as proliferative verrucous leukoplakia (PVL) and Phase IV as erythro leukoplakia[21].

Proliferative verrucous leukoplakia (PVL) is a subtype of verrucous leukoplakia with extensive involvement, resistance to therapy and high degree of malignant transformation. PVL has been classified as a form of non-homogenous leukoplakia[25]. In contrast, van der Waal mentions that since all extensive leukoplakias have increased potential for malignant transformation, PVL need not be classified as a separate entity. Further, PVL could be considered as a type of homogenous leukoplakia since it is predominantly white[23].

Histopathologic classification

Histopathologic classification is based on the degree of epithelial dysplasia in the leukoplakia. The three main classification include WHO classification, Binary classification system and Brothwell's classification[26].

WHO classification uses cytological and cellular architectural changes to classify leukoplakia as having mild, moderate or severe epithelial dysplasia.

"Mild dysplasia" is characterized by cells showing nuclear hyperchromatism and pleomorphism in the basal and parabasal epithelial regions; "Moderate dysplasia": is characterised by cells with nuclear hyperchromatism and pleomorphism in the basal, parabasal, and spinous layers; while "Severe dysplasia"lesions are characterized by bulbous straight processes with nuclear hyperchromatism and pleomorphism throughout the epithelial thickness[26].

Brothwell's system is similar to WHO classification with an additional 'carcinoma in situ' level characterised by dysplastic changes throughout the epithelium suggestive of invasion into underlying tissue but without evidence of the same[27]. The binary system categorises lesions as high risk and low risk[28].

Etiology

Tobacco: Oral leukoplakia has a multifactorial etiologybut the most commonly implicated agent is the use of tobacco in either smoking or smokeless form.

Toplota od pušenja i iritacija trenjem od duvanskih proizvoda za žvakanje mogu izazvati stimulaciju keratinocita i hiperkeratinizaciju. Bezdimni duvan može se udisati, žvakati ili pušiti. U južnoj Aziji često se meša sa arekanom, listom betela, gašenim krečom i začinima[25].

Postupci transplantiranja

Alkohol: Alkohol deluje kao ko kancerogen i ima sinergistički efekat sa duvanom u razvoju leukoplakije[29]. Alkohol ima dehidrirajući efekat na oralnu sluzokožu, čineći je podložnijom dejstvu duvana[30]. Pored gore navedenih etioloških agensa, ulogu u nastanku ove lezije imaju mehaničke traume usled loših protetskih nadoknada i oštrih zuba, kao i virusi poput humanog papiloma virusa i Epstein Barr virusa[29].

Leukoplakija povezana sa kandidom: Kandida oslobađa nitrozamine koji mogu da konvertuju etanol u acetaldehid kod konzumenata alkohola i izazivaju leukoplakiju povezanu sa duvanom. Nutritivni faktori kao što su nedostatak gvožđa, folne kiseline, vitamina A, B_1 i B_2 mogu imati ulogu u njegovoj etiologiji. Displazija je 4 – 5 puta veća kod leukoplakije povezane sa kandidom[31,32].

Viadent leukoplakija: Sangvinarna leukoplakija povezana je sa leukoplakijom u predelu vestibuluma maksile i alveolarnoj sluzokoži i uzrokovana je biljnim ekstraktom prisutnim u viadent pastama za zube i rastovrima za ispiranje usta[19,30,33].

Nutritivni faktori

Smanjeni nivoi vitamina A, B_{12}, C, beta karotena i folne kiseline u serumu primećeni su kod subjekata sa oralnom leukoplakijom[34]. Pretpostavlja se da atrofija epitela povezana sa ovim nedostacima u ishrani, kao kod nedostatka gvožđa, može povećati osetljivost na razvoj leukoplakije[35].

Dijagnoza

Dijagnoza leukoplakije može se postaviti na osnovu kliničkih nalaza i dopunskih ispitivanja. Leukoplakija se može definitivno dijagnostikovati na osnovu istorije bolesti, kliničkih karakteristika i histopatološke procene. Suština dijagnostike je isključiti leukoplakiju . Leukoplakija je klinički termin tako da je neophodna patohistološka dijagnoza, kako bi isključili druge bele lezije[25].

Uobičajena karakteristika leukoplakije je prisustvo bele mrlje koja se ne može skinuti, što je generalno povezano sa konzumiranjem duvana[36].

Tobacco releases carcinogens that bind to DNA causing mutation. They may also lead to the formation of highly reactive free radicals causing cell membrane and DNA damage[25]. The heat from smoking and the frictional irritation from chewing tobacco products may cause keratinocyte stimulation and hyper-keratinisation. Smokeless tobacco can be inhaled, chewed, or smoked. In South Asia, it is often mixed with arecanut, betel leaf, slaked lime, and spices[25].

Transplatation protocol

Alcohol: Alcohol acts as a co-carcinogen and has synergistic effect with tobacco in the development of leukoplakia[29]. Alcohol has a dehydrating effect on the oral mucosa rendering it more susceptible to the effects of tobacco[30].

In addition to the above etiological agents, mechanical trauma from ill-fitting dentures and sharp teeth as well as viruses like human papilloma virus and Epstein Barr virus has been implicated[29].

Candida-associated leukoplakia: *Candida* releases nitrosamines which can convert ethanol into acetaldehyde in alcohol consumers and cause leukoplakia in association with tobacco. Nutritional factors such as deficiency of iron, folic acid, vitamins A, B_1, and B_2 may have a role in its etiology. Dysplasia is 4-5-fold higher in candida-associated leukoplakia[31,32].

Viadent leukoplakia: Sanguinaria-associated leukoplakia Sanguinaria has been associated with leukoplakia in maxillary vestibule and alveolar mucosa and is caused by aherbal extract present in toothpastes and mouth rinses[19,30,33].

Nutritional factors

Decreased serum levels of vitamin A, B_{12}, C, beta carotene, and folic acid have been noted in subjects with oral leukoplakia[34]. It is hypothesized that the epithelial atrophy associated with these nutritional deficiencies, as in iron deficiency and OSMF, can increase susceptibility to the development of leukoplakia[35].

Diagnosis

The diagnosis of leukoplakia can be done on the basis of clinical findings and chair side investigations. Leukoplakia can be definitively diagnosed based on subject history, clinical features and histopathologic evaluation. It is essentially a diagnosis of exclusion. Leukoplakia is a clinical term; a biopsy is essential to confirm the diagnosis and to rule out other white lesions[25].

Homogena leukoplakija je bela mrlja koja može biti naborana (poput peščane plaže) sa finim linijama poznatim kao kriste ili naborana forma, koja se obično opisuje kao izgled suvog, ispucanog blata[36]. Nehomogena leukoplakija može biti nodularna ili pegasta. To su keratotični čvorići ili mrlje prisutne na eritematoznoj bazi sluzokože[36]. Verukozni oblik leukoplakije ima gusto keratinizovane projekcije površine sluzokože[36]. Proliferativnu verukoleukoplakiju karakteriše prisustvo egzofitnih i proliferativnih keratotskih plakova koji nisu mnogo povezani sa upotrebom duvana[37]. Ima najveći potencijal za malignu transformaciju među leukoplakijama[16,25,37]. Uobičajena mesta za oralnu leukoplakiju su dno usta, jezik, bukalna sluzokoža, usne gingive, nepce i crna ivica usne. Kada lezija zahvata dno usta i jezika, veća je verovatnoća da će doživeti malignu transformaciju[38].

Ispitivanje

Vitalno bojenje

Vitalno bojenje je postupak prikom koga žive ćelije preuzimaju određene boje, koje ih selektivno boje. Upotreba vitalnog bojenja toluidin plavim ili jodom može ocrtati prisustvo displazije i identifikovati mesto biopsije u velikim lezijama[16]. Toluidin plavo boji nukleohistone u DNK[39]. Njegova upotreba *in vivo* zasniva se na činjenici da displastične i anaplastične ćelije sadrže kvantitativno više nukleinskih kiselina nego normalna tkiva, pokazuju gubitak ćelijske kohezije i povećanu mitozu. Lugolov jod boji glikogen citoplazme. Pošto displastične i maligne ćelije imaju manje glikogena, a normalna tkiva više, on selektivno boji normalna tkiva braon u crno[39,40,41].

Optičke tehnike: Optičke tehnike zasnivaju se na sposobnosti tkiva da fluoresciraju. Vizilit je hemiluminiscentna metoda koja se koristi za otkrivanje displastičnih područja oralne sluzokože. Kada se koristi u kombinaciji sa toluidin plavim, efikasan je u identifikaciji područja displazije za biopsiju[42]. Velscope koristi sposobnost autofluorescencije, dajući fluorescentnu boju normalnim tkivima i boju od tamno zelene do crne boje abnormalnim tkivima[43,44].

Glavni nedostatak navedenih metoda je učestalost lažno pozitivnih i lažno negativnih rezultata[16,33].

Ostalo: fluorescentno endoskopsko snimanje posredovano 5-aminolevulinskom

A common feature in leukoplakia is the presence of a non-scrapable white patch, generally associated with tobacco consumption[36]. Homogeneous leukoplakia is a white patch which can be either corrugated (like a beach with ebbing tide) with fine lines known as cristae or a wrinkled form, which is commonly described as dry, cracked mud appearance[36]. Non-homogeneous leukoplakia may be nodular or speckled. These are keratotic nodules or specks present on an erythematous base of mucosa[36]. Verrucous form of leukoplakia has densely keratinized projections of the mucosal surface[36].

Proliferative verrucous leukoplakia is characterized by the presence of exophytic and proliferative keratotic plaques which are not much associated with the use of tobacco[37]. It has the highest potential for malignant transformation among the leukoplakias[16,25,37].

Common sites for oral leukoplakia are the floor of the mouth, tongue, buccal mucosa, gingiva lips, palate, and vermilion border of the lip. When the lesion involves floor of mouth and tongue, it is more likely that it will undergo malignant transformation[38].

Investigations

Vital Staining

Vital staining is a procedure where living cells take up certain dyes, which selectively stains them. Use of vital staining with toluidine blue or lugol's iodine can delineate the presence of dysplasia and identify the site of biopsy in large lesions[16]. Toluidene blue stains the nucleohistones in DNA[39]. Its use *in vivo* is based on the fact that dysplastic and anaplastic cells contain quantitatively more nucleic acids than normal tissues, show loss of cell cohesion and increased mitosis. Lugol's iodine stains the glycogen of the cytoplasm. Since dysplastic and malignant cells have less glycogen and normal tissues have more, it selectively stains the normal tissues brown to black[39,40,41].

Optical techniques: These are based on the ability of the tissues to fluoresce. Vizilite is a chemiluminescent method used to detect dysplastic areas of the oral mucosa.

When used in combination with toluidine blue, it is effective in identifying areas of dysplasia for biopsy[42]. Velscope utilises the ability of autofluorescence giving fluorescent colour to normal tissues and dark green to black colour to abnormal tissues[43,44].

kiselinom (ALA), digitalizovano fluorescentno endoskopsko snimanje posredovano ALA i autofluorescentna spektroskopija koriste se za usmeravanje biopsija i otkrivanje margina za hirurško resekciju[16].

Histopatološke metode

Histopatološke metode uključuju eksfolijativnu citologiju, biopsiju četkicom i biopsiju. Eksfoliativna citologija je histopatološka studija eksfolijiranih ćelija za određivanje karakteristika displazije. Suština metode je da displastične ćelije u dubljim epitelnim slojevima, postaju labavije u malignim stanjima i sidaju se zajedno sa ćelijama površnog sloja[45]. Nedostaci su lažno pozitivni i lažno negativni rezultati[45].

Biopsija četkicom, takođe poznata kao oralna CDk biopsija ili transepitelna biopsija, prikuplja ćelije iz svih slojeva oralnog epitela i smatra se reprezentativnijom od eksfoliativne citologije. Rezultati se procenjuju korišćenjem kompjuterske analize[16,46]. Biopsija može biti inciziona ili eksciziona. Inciziona biopsija savetuje se za lezije manje od 1 cm, dok se kod većih lezija biopsira reprezentativno područje. Odabir ovog područja može se izvršiti nakon bojenja toluidin plavim, kako bi se identifikovala područja displazije[42].

Histološke karakteristike

Kod leukoplakije, epitelna displazija može biti prisutna u rasponu od blage do teške. Displastične promene kod leukoplakije uključuju ćelijski pleomorfizam, nuklearni hiperhromatizam, povećan nuklearno-citoplazmatski odnos, uvećane nukleole, smanjenje ćelijske kohezije, keratinizaciju jedne ćelije, gubitak polariteta bazalnih ćelija, rete pege u obliku kapi, povećan broj mitotičkih figura, prisustvo mitotičke figure, i prisustvo više od jednog sloja ćelija koje izgledaju kao ćelije bazalnog sloja (VHO, 1978)[47]. Molekularni markeri Mib-l, Ciclin Dl i CENP-F i eksprimirani su u bazalnim suprabazalnim i površinskim slojevima oralne sluzokože sa leukoplakijom[48]. Markeri proliferacije i kontrole ćelijskog ciklusa koriste se za određivanje malignog potencijala lezije.

Određivanje malignog potencijala lezije uključuje Ki-67, ciklin D1 i proteine kao što su p53, p16 i pRb[26]. Prekomerna ekspresija p53 i smanjeni p16 smatraju se najranijim markerima maligne

The main disadvantage of the above methods is the incidence of false positive and false negative results[16,33].

Others: 5-Aminolevulinic acid (ALA) mediated fluorescence endoscopic imaging, ALA mediated digitized fluorescence endoscopic imaging and autofluorescence spectroscopy are used to direct biopsies and detect the margins for surgical resection[16].

Histopathological Methods

These include exfoliative cytology, brush biopsy and biopsy.

Exfoliative cytology is the histopathologic study of exfoliated cells for features of dysplasia. The rationale is that dysplastic cells in the deeper epithelial layers become loose in malignant conditions and are shed along with superficial cells[45]. Disadvantages are false positive and false negative results[45].

Brush biopsy, also known as oral CDx biopsy or transepithelial biopsy, collects cells from all layers of the oral epithelium and is considered more representative than an exfoliative cytology. Results are evaluated using computer analysis[16,46].

Biopsy can be incisional or excisional. Incisional biopsy is advised for lesions less than 1 cm in size while in larger lesions a representative area is biopsied. Selection of this area can be done following a toluidine blue staining to identify areas of dysplasia[42].

Histological features

In leukoplakia, epithelial dysplasia may be present ranging from mild to severe. Dysplastic changes in leukoplakia include cellular pleomorphism, nuclear hyper-chromatism, increased nuclear- cytoplasmic ratio, enlarged nucleoli, reduction of cellular cohesion, single cell keratinization, loss of basal cell polarity, drop shaped rete pegs, increased number of mitotic figures, presence of mitotic figures, drop shaped rete pegs and presence of more than one layer of cell having basaloid appearance (WHO, 1978)[47].

Molecular markers

Mib-l, Cyclin Dl, and CENP-F i are expressed in basal suprabasal and superficial layers of oral mucosa with leukoplakia[48].

Markers of proliferation and cell cycle control are used to determine malignant potential of a lesion.

transformacije. Ovo je posebno relevantno kod nedisplastične leukoplakije, prilikom koje promene p53, Ki-67 i p16 ukazuju na progresiju u malignitet[22,26].

Morfometrijska analiza uz pomoć kompjutera ispituje ćelijski i nuklearni perimetar korišćenjem kompjuterskih slika histoloških preseka. Primećeno je to se veličina ćelije i jedra progresivno povećavaju od normalne sluzokože prema leukoplakiji do oralnog skvamoznog karcinoma[22].

AgNOR tehnika: Ova tehnika detektuje proteine povezane sa transkripcionom aktivnošću nukleolarnih organizacionih regiona (NOR) kroz impregnaciju koloidnog srebra, nazvane AgNOR proteini. NOR se mogu vizualizovati pod mikroskopom kao male, dobro definisane tamne mrlje unutar ćelijskog jezgra[26]. AgNOR se smatraju markerima proliferacije epitela i pretpostavlja se da se njihov broj povećava sa malignitetom. Međutim, autori nisu uspeli da pokažu definitivnu vezu između AgNOR-a i maligne transformacije[26,49,50].

Diferencijalna dijagnoza

Diferencijalna dijagnoza leukoplakije uključuje lichen planus, leukoedem, amelanotični nevus, sifilitičnu sluzokožu, eritematozni lupus discoideus, bradavice, hemijsku opekotinu i hroničnu mehaničku povredu usled ujeda obraza[29]. Asimetrična bela mrlja koja se ne može skinuti, odsustvo Vikamovih strija bez okolne upale pomaže u postavljanju kliničke dijagnoze leukoplakije[51]. PVL, posebno nehomogeni tip, može se pomešati sa lichen planusom zbog njegovog multifokalnog i bilateralnog širenja[25].

Stopa maligne transformacije i prognostički indikatori

Globalna stopa maligne transformacije leukoplakije kreće se od 0,7% do 2,9% 12. Poznato je da se leukoplakija javlja 5 godina pre početka oralnog karcinoma skvamoznih ćelija[32]. Postoje različiti faktori koji povećavaju sklonost leukoplakije ka malignoj transformaciji. To su: ženski pol, dugo perzistentna lezija koja ne reaguje na terapiju, I lokalizacija visoko rizičnim mestima kao što su dno usta, ventrolateralna strana jezika i meko nepce, prisustvo lezije kod nepušača ili idiopatska leukoplakija.

Veću tendenciju maligne transformacije imaju nehomogena leukoplakija egzofitnog i verukoznog izgleda i leukoplakija sa epitelnom displazijom[52].

These include Ki-67, cyclin D1 and proteins such as p53, p16 and pRb[26]. Overexpression of p53 and decreased p16 are considered as the earliest markers of malignant transformation. This is especially relevant in non-dysplastic leukoplakia where p53, Ki-67, and p16 alteration are suggestive of progression to malignancy[22,26].

Computer-assisted morphometric analysis: analyses cell and nuclear perimeter using computer images of histologic sections. The cell and nuclear size was observed to increase progressively from normal mucosa to leukoplakia to oral squamous cell carcinoma[22].

AgNOR technique: This technique detects proteins associated with the transcriptional activity of nucleolar organizing regions (NORs) through colloidal silver impregnation, named AgNOR proteins. NORs can be visualized under the microscope as small, well-defined dark spots within the cell nucleus[26].

AgNORs are considered as markers of epithelial proliferation and their numbers are hypothesized to increase with malignancy. However, authors have failed to show a definite relation between AgNORs and malignant transformation[26,49,50].

Differential diagnosis

Differential diagnosis of leukoplakia includes lichen planus, leukoedema, white sponge nevus, syphilitic mucous patch, discoid lupus erythematosus, verruca vulgaris, chemical burn, and chronic cheek bite[29]. Asymmetric, non-scrapable white patch, absence of Wickham's striae without surrounding inflammation helps establish a clinical diagnosis of leukoplakia[51]. PVL, especially the non-homogenous type, may be confused with lichen planus due to its multifocal and bilateral involvement[25].

Malignant transformation rate and prognostic indicators

Global rates of malignant transformation of Leukoplakia range from 0.7% to 2.9%[12]. Leukoplakia has been known to occur 5 years prior to the onset of oral squamous cell carcinoma[32].

There are various factors that increase the tendency of aleukoplakia to turn malignant.

This includes female gender, leukoplakias persisting over prolonged periods and resistant to treatment, OL in high risk sites such as the floor of the mouth, ventrolateral tongue and soft palate, OL among non-smokers or idiopathic leukoplakia.

Homogena leukoplakija ima najmanji potencijal za malignu transformaciju, dok PVL ima najveći maligni potencijal od oko 70-80%[29]. Prema Varnakulasuria i sar[10], ženski pol, dugotrajna leukoplakija, leukoplakija kod nepušača (idiopatska leukoplakija), lokalizacija na jeziku ili dnu usta, veličina veća od 200 mm2, nehomogena leukoplakija, prisustvo kandide i prisustvo epitelne displazije imaju povećanu tendenciju maligne transformacije. Displastični epitel ima stopu maligne transformacije od oko 41% dok nedisplastični epitel ima potencijal maligniteta od samo oko 9,5%[53,54]. Molekularni markeri kao što su Ki-67, bromodeoksiuridin i kombinacija hromozomske polisomije, gubitak heterozigotnosti i p5 veruje se da tačno predviđaju potencijal maligne transformacije[53]. Subjekti sa višestrukim područjima leukoplakije skloniji su malignoj transformaciji od onih sa pojedinačnim lezijama[53]. Leukoplakija sa gubitkom heterozigotnosti (LOH) na 3p14 i/ili 9p[21] bila je povezana sa većim rizikom od razvoja invazivnog karcinoma[33]. Gopinath i sar.[12] su izvestili da korisnici duvana imaju četiri puta veći rizik od maligne transformacije u poređenju sa onima koji ne koriste duvan.

Režim praćenja: Potreba za praćenjem određena je stepenom displazije i mestom leukoplakije. Šestomesečno praćenje preporučuje se za lezije bez displazije, tromesečno za blagu/umerenu displaziju, a mesečno za tešku displaziju / karcinom *in situ*[33,55].

Lečenje

Prvi cilj u lečenju leukoplakije je prevencija maligne transformacije56. Lečenje leukoplakije može se podeliti na konzervativno, medicinsko i hirurško lečenje. Pre nego što se odluči o lečenju, mora se proceniti stepen epitelne displazije. Hirurško lečenje poželjnije je kod umerene do teške displazije, dok u slučajevima sa blagom displazijom, odluke o upravljanju treba da se procene u kontekstu drugih karakteristika kao što su mesto, veličina, prestanak upotrebe duvana, itd[22].

Konzervativno lečenje

Prvi korak u lečenju oralne leukoplakije je uklanjanje etioloških faktora kao što su duvan, alkohol i žvakanje betel kuida.

Ovo se može uraditi kroz savetovanje o navikama. Oko 60% leukoplakije može regresirati ako se prestane sa pušenjem. Pokazalo se da redovno savetovanje povećava

Non homogenous leukoplakia with exophytic and verrucous appearance and leukoplakia with epithelial dysplasia have a higher tendency for malignant transformation[52]. Homogenous leukoplakia has the least potential for malignant transformation while PVL has the highest malignant potential of around 70-80%[29].

According to Warnakulasuriya et al[10], female gender, long term leukoplakia, leukoplakia in non-smokers (idiopathic leukoplakia), location in the tongue or the floor of the mouth, size greater than 200 mm^2, non homogenousleukoplakia, presence of *Candida Albicans and* presence of epithelial dysplasia have increased tendency for malignant transformation. Dysplastic epithelium has a malignant transformation rate of around 41% while non-dysplastic epithelium has a malignancy potential of only around 9.5%[53, 54]. Molecular markers such as Ki-67, bromodeoxyuridine and a combination of chromosomal polysomy, loss of heterozygosity and p53 are believed to accurately predict the potential for malignant transformation[53]. Subjects with multiple areas of leukoplakia are more prone to malignant transformation than those with single lesions[53]. Leukoplakia with loss of heterezygosity (LOH) at 3p14 and/ or 9p[21] was associated with more risk of developing invasive cancer[33]. Gopinath et al[12] reported that tobacco users had four fold increased risk of malignant transformation when compared to non-users.

Follow up Regimen: The need for follow-up is determined by the degree of dysplasia and the site of leukoplakia. Six-monthly follow up is recommended for lesions without dysplasia, three-monthly for mild/moderate dysplasia, and monthly for severe dysplasia/carcinoma *in situ*[33,55].

Management

The first aim in the management of leukoplakia is the prevention of malignant transformation[56]. Management of leukoplakia can be divided into conservative, medical and surgical management. Prior to deciding the treatment, the degree of epithelial dysplasia must be assessed. Surgical management is preferred in moderate to severe dysplasia while in cases with mild dysplasia, management decisions need to be evaluated in the context of other features like site, size, discontinuation of tobacco use, etc[22].

Conservative Management

The first step in the management of oral leukoplakia is the removal of etiological-factors such as tobacco, alcohol and betel quid chewing.

stopu odvikavanja od duvana[22,53]. Martin i sar. prijavili su regresiju leukoplakije nakon prestanka navike žvakanja duvana[57]. Enameloplastika oštrih zuba i zamena neispravnih nadoknada predstavljaju početni tretman u slučajevima sa hroničnom iritacijom izazvanom leukoplakijom. Upotreba lekova protiv gljivica korisna je u slučajevima leukoplakije povezane sa kandidom. Preporučuje se prekid konzumacije alkohola i uvođenje zdrave ishrane i dobre oralne higijene. Drugi pristup je metoda „čekaj i vidi" po kojoj se pacijenti redovno prate kako bi se otkrili početni znaci maligne transformacije, kada se može uvesti odgovarajući tretman[22].

Medicinski tretman

Medicinski tretman poželjniji je kod pacijenata sa osnovnim zdravstvenim stanjima koja predstavljaju rizik za hirurške procedure. Prednosti ove metode su minimalni neželjeni efekti, niska cena i jednostavnost. Ovo je preporučeni metod u slučajvima u kojima je lezija široko rasprostranjena ili u slučajevima u kojima je lezijom zahvaćeno više mesta [52]. Hemoprevencija je metoda upotrebe hemijskih agenasa za preokretanje, suzbijanje ili sprečavanje razvoja maligniteta. Neke od metoda medicinskih tretmana su:

Beta karoten: je prekursor vitamina A. Njegov način delovanja je uklanjanje slobodnih radikala. Kombinuje se sa reaktivnim vrstama kiseonika i deluje kao antioksidans smanjujući šanse da lezija postane maligna. Prijavljeno je da je beta karoten efikasniji kod pušača koji imaju nizak nivo vitamina C i beta karotena. Doziranje varira u različitim studijama u rasponu od 20-90 mg/dan tokom 3 do 12 meseci. Studije su prijavile minimalne neželjene efekte kao što su bol u mišićima i glavobolja. Regresija leukoplakičnih lezija je zabeležena kod 4-54% ispitanika nakon tretmana. Međutim, određene studije pominju recidiv i malignu transformaciju nakon prestanka uzimanja leka[52,53].

Likopen: Likopen je karotenoid koji se nalazi u zrelom paradajzu. To je efikasan antioksidans koji neutrališe slobodne radikale i veruje se da štiti ćelije od progresije u displaziju inhibiranjem proliferacije tumorskih ćelija[52].

Singh M i sar.[58] procenili su efikasnost likopena kod leukoplakije i otkrili da je 8 mg/dan bolje od 4 mg/dan u lečenju leukoplakije. Patel JS i sar.[59] su otkrili da je likopen zajedno sa vitaminom E i selenom pokazao kliničko i histološko poboljšanje u poređenju sa placebom.

This can be done through habit counselling. Around 60% of leukoplakia can regress if tobacco habits are stopped. Use of habit counselling also increases tobacco quit rates[22,53]. Martin et al. reported regression of leukoplakia after stopping ~~the~~tobacco chewing habit[57]. Enameloplasty for sharp teeth and replacement of faulty restorations form the initial management in cases with chronic irritation induced leukoplakia. Use of anti-fungal medication is useful in cases of Candida associated leukoplakia. Stoppage of alcohol and institution of a healthy diet and good oral hygiene is recommended.

Another approach is the 'wait and see' method where patients are kept onregular follow up to detect initial signs of malignant transformation, at which time, appropriate treatment can be instituted[22].

Medical Management

Medical management is preferred in patients with underlying medical conditions which pose a risk for surgical procedures. The advantages of this method are minimal adverse effects, low costand ease of use. It is the recommended method in widespread cases or cases with multiple sites of involvement[52].

Chemoprevention is the method of using chemical agents to reverse, suppress, or prevent development of malignancy. Some of the methods of medical management include:

Beta Carotene: is a precursor of Vitamin A. It's mode of action is through scavenging of free radicals. It combines with reactive oxygen species and acts as an antioxidant decreasing the chances of the lesion turning malignant. Beta carotene has been reported to be more effective in smokers who have inherently low levels of vitamin C and beta carotene. The dosage varies in different studies ranging from 20-90 mg/day for 3 to 12 months. Studies have reported minimal side effects such as muscle pain and headaches. Regression of OL lesions has been noted in 4-54% subjects after treatment. However, certain studies mention recurrence and malignant transformation after stoppage of the medication[52,53].

Lycopene: Lycopene is a carotenoid found in ripe tomatoes. It is an effective antioxidant which neutralises free radicals and is believed to protect cells from progression into dysplasia by inhibiting tumour cell proliferation[52].

Terapija vitaminom A (retinoična kiselina):

Vitamin A je potreban za normalnu diferencijaciju epitelnih ćelija i formiranje keratina. Retinoidi deluju svojim delovanjem na proizvodnju keratina, rast ćelija, diferencijaciju ćelija i gubitak ćelija. Nedostatak je povezan sa malignitetima epitela[53]. Kod oralne leukoplakije preporučuje se retinoid 13-cis-retinoična kiselina (13-cRA, izotretinoin). Lokalni 0,1% izotretinoin gel je pokušavan za oralnu leukoplakiju tokom 4 meseca, pri čemu je jedna trećina ispitanika pokazala potpunu regresiju leukoplakije. Studije sa sistemskom primenom pokazale su različite rezultate. Sistemska 13-cis retinoična kiselina (1-2 mg/kg dnevno) tokom perioda od 3 meseca bila je povezana sa smanjenjem veličine lezije u 67% slučajeva[60]. Glavni nedostatak terapije izotretinoinom je ponavljanje lezije nakon prestanka uzimanja leka. Neželjeni efekti kao što su glavobolja, bol u mišićima, primećeni su uz delimično ili potpuno povlačenje lezija. Ostali prijavljeni neželjeni efekti su hipervitaminoza, teratogenost i promene u različitim organskim sistemima. Fenretinid je analog vitamina A sa manje toksičnosti i testiran je sa različitim rezultatima kod OL-a i oralnog lihen planusa (OLP). Lokalna primena dva puta dnevno tokom jednog meseca ili sistemska primena od 200 mg/dan tokom 3 meseca dala je prihvatljive rezultate u OL i OLP[53,61].

Vitamin C i vitamin E su testirani zbog njihovog antioksidativnog dejstva sa nekoliko studija koje su pokazale delimičnu ili potpunu regresiju leukoplakije[61].

Topikalni bleomicin: Studija je koristila 1% topikalni bleomicin tokom 14 uzastopnih dana nakon čega je usledila biopsija odmah nakon tretmana. Rezolucija displazije je zabeležena kod 75% pacijenata uz poboljšanje od najmanje dva stepena displazije. Zaključili su da bleomicin može usporiti napredovanje displazije u malignitet[62]. Bleomicin se takođe može koristiti kod ekstenzivnih leukoplakija da bi se smanjila veličina lezije nakon čega sledi hirurška ekscizija[63].

Antifungalna terapija: savetuje se 2-4 nedelje antifungalne terapije kod mogućih leukoplakijskih lezija, uz uklanjanje mogućih uzročnika kao što je pušenje kako bi se procenila regresija lezije.

Vizhi i sar.[64] su prijavili konverziju 14% slučajeva nehomogene leukoplakije u homogenu leukoplakiju nakon tretmana sa 1% topikalnog klotrimazola tri puta dnevno tokom 3 nedelje. Takođe je primećeno smanjenje veličine lezije i poboljšanje kliničkog stadija, čime se smanjuju šanse za malignu transformaciju[64].

Singh M[58] et al evaluated the efficacy of lycopene in leukoplakia and found that 8 mg/day was better than 4 mg/day in management of leukoplakia. Patel JS et al[59] found that lycopene along with Vitamin E and selenium showed clinical and histologic improvement when compared with placebo.

Vitamin A (Retinoic acid) therapy: Vitamin A is needed for normal epithelial cell differentiation and keratin formation. Retinoids act through their action on keratin production, cell growth, cell differentiation and cell loss. Deficiency has been associated with epithelial malignancies[53]. In oral leukoplakia, the retinoid 13-cis-retinoic acid (13-cRA, isotretinoin) is recommended. Topical 0.1% isotretinoin gel was tried for oral leukoplakia for 4 months with one-third of subjects showing complete regression of leukoplakia. Studies with systemic administration have shown varied results. Systemic 13-cis retinoic acid (1–2 mg/kg per day) for a period of 3 months was associated with decreased lesion size in 67% cases[60]. The main drawback of isotretinoin therapy is the recurrence of the lesion after the medication is stopped. Side effects such as headaches, muscle pain, were noted with partial or complete resolution of lesions. Other reported side effects are hypervitaminosis, teratogenicity and alterations in various organic systems. Fenretinide is a Vitamin A analogue with less toxicity and has been tried with varied results in OL and oral lichen planus(OLP). Topical application twice daily for one month or systemic use of 200 mg/day for 3 months gave acceptable results in OL and OLP[53,61].

Vitamin C and Vitamin E have been tried for their antioxidant effect with few studies showing partial or complete regression of leukoplakia[61].

Topical bleomycin: A study used 1% topical bleomycin for 14 consecutive days followed by immediate post treatment biopsy. Resolution of dysplasia was noted in 75% patients with improvement of at least two grades of dysplasia. They concluded that bleomycin may retard the progression of dysplasia into malignancy[62]. Bleomycin can also be used in extensive leukoplakias to decrease the size of the lesion followed by surgical excision[63].

Antifungal therapy: A 2-4 week course of antifungal therapy is advised in possible leukoplakia lesions along with removal of possible of causative agents like smoking in order to evaluate for lesion regression.

Fotodinamička terapija (PDT): je neinvazivna metoda lečenja OL. Daje dobre kozmetičke rezultate, dobro se podnosi; može se koristiti kod osoba kod kojih nije preporučljivo hirurško lečenje, kao što su osobe sa pejsmejkerima ili sklonostima krvarenju. PDT deluje tako što proizvodi reaktivne vrste kiseonika koje mogu da ubiju displastične ćelije direktnim dejstvom, oštećenjem vaskulature ili imunološkom aktivacijom. Selvam i sar.[65] su koristili 10% ALA emulziju kao afotosenzibilizator u slučajevima OL nakon čega je usledila primena svetlosti pomoću ksenonske lampe tokom 1000 sekundi. Ova terapija je nastavljena tokom 6-8 sesija sa intervalom od 1 nedelje između sesija. Od 5 ispitanika u studiji, potpuna i delimična rezolucija OL-a zabeležena je kod po 2 subjekta. Neželjeni efekti su uključivali prolazni osećaj pečenja[65].

Hirurške opcije

Hirurško lečenje se savetuje u prisustvu umerene do teške epitelne displazije. U slučajevima niskog do umerenog rizika, potrebno je proceniti druge faktore pacijenta, kao što je prestanak navika. Kriohirurgija: Ovo je metoda izlaganja tkiva ekstremnoj hladnoj temperaturi. Ćelijska smrt se javlja na -20 stepeni Celzijusa. Koristi se krio sonda hlađena tečnim azotom. Zamrzavanje se vrši 1 minut, a zatim odmrzavanje od 5 minuta. Ova procedura se ponavlja 2-3 puta da bi se postiglo maksimalno uništenje tkiva[66].

Elektrohirurgija: Ova tehnika koristi struju visokog napona koja se kontroliše pomoću pokretne elektrode. Izaziva destru-kciju tkiva uz laku kontrolu krvarenja[67]. Laseri su povezani sa smanjenim intraoperativnim krvarenjem, smanjenim edemom lica i smanjenim ožiljcima tkiva. Međutim, otkriveno je da su post-hirurški bol i otok slični kod ekscizije skalpelom[68].

Karbonski laser: Sadrži ugljen-dioksid, azot i helijum. Ima dubinu prodiranja u tkiva od 0,2 do 0,3 mm i talasnu dužinu od 10.600 nm u infracrvenom spektru. Kod laserske ablacije postiže se površinska dubina vaporizacije od 0,5 mm, što obično rezultira dobrom sekundarnom reepitelizacijom[69,70].

Kalijum-titanil fosfatni (KTP) laseri: Imaju talasnu dužinu od 532 nm i proizvode se propuštanjem Nd: IAG laserskog zraka (1064 nm) kroz KTP kristal, čime se njegova talasna dužina prepolovi do 532 nm. Ima sposobnost ablacije krvnih sudova hraneći leziju uz očuvanje biološke obloge sluznice koja se nalazi iznad[69].

Vizhi et al[64] reported conversion of 14% cases of non-homogenous leukoplakia into homogenous leukoplakia after treatment with 1% topical clotrimazole thrice daily for 3 weeks. Decreased lesion size and improvement in clinical staging thereby reducing the chances of malignant transformation[64].

Photodynamic therapy (PDT): is a non-invasive method of OL management. It produces good cosmetic results it is tolerated well; can be used in subjects where surgical management is not advisable such as subjects with pacemakers or bleeding tendencies. PDT acts by production of reactive oxygen species which can kill dysplastic cells through direct effect, damage to vasculature or through immune activation. Selvam et al[65] used 10% ALA emulsion as aphotosensitizer in OL cases followed by light application using a xenon lamp for 1000 sec. This therapy was continued for 6-8 sessions with interval of 1 week between sessions. Out of 5 subjects in the study, complete and partial resolution of OL was noted in 2 subjects each. Side effects included transient burning sensation[65].

Surgical options

Surgical management is advised in the presence of moderate to severe epithelial dysplasia. In cases of low to moderate risk, other patient factors need to be assessed such as habit cessation.

Cryosurgery: Here tissue is exposed to extreme cold temperature. Cell death occurs at -20 degree Celsius. Cryo probe refrigerated by liquid nitrogen is used. Freezing is done for 1 minute, followed by a thaw of 5 minutes. This procedure is repeated 2-3 times to achieve maximum tissue destruction[66].

Electrosurgery: This technique employs high voltage current that is controlled by a movable electrode. It causes tissue destruction with easy control of haemorrhage[67].

Lasers are associated with decreased intraoperative bleeding, decreased facial edema and decreased scarring of tissue. Post-surgical pain and swelling, however were found to be similar in scalpel and laser excision[68].

Carbon dioxide LASER: It contains carbon dioxide, nitrogen and helium. It has a tissue depth of 0.2 to 0.3 mm and 10.600 nm wavelength in the infrared spectrum. In laser ablation a surface vaporization depth of 0.5 mm is achieved which normally results in good secondary re-epithelization[69,70].

Menadžment PVL

Najveće poteškoće/prepreke u zbrinjavanju nastaju zbog pojave recidiva nakon lečenja i toksičnosti na propisane lekove. Kod PVL, laserska ablacija i topikalna fotodinamička terapija daju bolje rezultate od ostalih tradicionalnih metoda. Međutim, potpuna ekscizija sa marginama bez bolesti u kombinaciji sa dugotrajnim praćenjem čini oslonac lečenja u PVL[37]. Ponavljanje OL nakon hirurškog lečenja prijavljeno je u 10–35% slučajeva[52,71]. Različite studije su pokazale da se čak i nakon hirurškog lečenja leukoplakija može ponoviti u 13-42% slučajeva, a maligna transformacija može doći u 3-11% slučajeva na mestu ekscizije[70]. Još jedan važan nalaz je da recidiv leukoplakije nije bio povezan sa korišćenim protokolom lečenja[71]. Sundberg i sar.[71] sproveli su prospektivnu studiju kako bi procenili karakteristike pacijenata i metode lečenja leukoplakije sa stopama recidiva. Otkrili su ukupan recidiv od 42% nakon hirurškog uklanjanja. Glavni faktori koji su doveli do recidiva bili su nehomogena leukoplakija i upotreba burmuta. Utvrđeno je da savetovanje o prestanku pušenja pomaže ljudima da ostave pušenje i povezano je sa smanjenim recidivom. Takođe su otkrili da se 9% slučajeva rekurentne leukoplakije transformiše u karcinom skvamoznih ćelija[71]. Ovo implicira da je rekurentna OL povezana sa većim rizikom od maligne transformacije. Moguće objašnjenje za recidiv leukoplakije može se naći u konceptu kancerizacije polja gde je genomska nestabilnost prisutna u celoj sluzokoži što dovodi do generalizovanog povećanog rizika od maligne transformacije. Kuribajashi i sar.[72] su pronašli stopu recidiva od 15.1% i stopu maligne transformacije od 1.9% nakon hirurške ekscizije. Stepen displazije nije bio u korelaciji sa malignom transformacijom[72].

Drugi agensi za hemoprevenciju

Agensi uključuju inhibitore ciklo-oksigenaze-2 (COKS2) poput celekoksiba i ketorolaka[73,74]; polifenoli zelenog čaja poput epigalokatehin-3-galata (EGCG)75; p53-ciljani agensi koji koriste modifikovani adenovirus[76]; tiazolidindioni kao što je pioglitazon[77] i inhibitori EGFR koji su pokazali promenljive rezultate[33].

Potassium-Titanyl phosphate (KTP) lasers: It has a wavelength of 532 nm and is produced by passing a Nd: YAG laser beam (1064 nm) through a KTP crystal, thus halving its wavelength to 532 nm.

It has the ability to ablate the underlying vasculature feeding the lesion while preserving a biological dressing of overlying mucosa[69].

Management of PVL

The major difficulties/ hurdles in the management are due to recurrence after treatment and toxicity to the prescribed medications. In PVL, laser ablation and topical photodynamic therapy have given better results than the other traditional methods. However, total excision with disease free margins combined with long term follow up forms the mainstay of treatment in PVL[37]. Recurrence of OL after surgical treatment has been reported in 10%–35% of cases[52,71]. Various studies have shown that even after surgical management leukoplakia can recur in 13-42% of cases and malignant transformation can occur in 3–11% of cases at the excision site[70]. Another important finding is that leukoplakia recurrence was not related to the treatment protocol used[71].

Sundberg et al.[71] carried out a prospective study in order to evaluate patient characteristics and leukoplakia management methods with recurrence rates. They found an overall recurrence of 42% after surgical removal. The major factors promoting recurrence were nonhomogenous leukoplakia and the use of snuff. Tobacco cessation counselling was found to help people quit smoking and associated with decreased recurrence. They also foundthat 9% of cases of recurrent leukoplakia transformed into squamous cell carcinoma[71]. This implies that recurrent OL is associated with higher risk of malignant transformation.

A possible explanation for leukoplakia recurrence could be found in the concept of field cancerisation where genomic instability is present throughout the mucosa leading to a generalised increased risk of malignant transformation. Kuribayashi et al[72] found a recurrence rate of 15.1% and a malignant transformation rate of 1.9% after surgical excision. The degree of dysplasia was not correlated to malignant transformation[72].

Izazovi u lečenju leukoplakije

Jedan od glavnih faktora koji utiču na lečenje leukoplakije je nedostatak znanja o prirodnoj istoriji bolesti uprkos ogromnoj količini objavljenih podataka. Neke leukoplakije će ostati statične godinama, neke će se povući nakon prestanka navika, dok će se neke od nedisplastičnih leukoplakija transformisati u maligne lezije[33]. Drugi izazov je koncept „kancerizacije polja" koji podrazumeva da zdrava sluzokoža kod pacijenata sa potencijalno malignim i malignim lezijama takođe može imati displastične promene. Upotreba vitalnog bojenja može pomoći u identifikaciji takvih područja[33].

Zaključak

Leukoplakija je oralna potencijalno maligna lezija koju treba pravilno pregledati jer ima velike šanse za malignu transformaciju. Lekar bi trebalo da ima temeljno znanje o kliničkoj dijagnozi, različitim metodama ispitivanja i terapijskim protokolima koji će obezbediti lečenje lezije, koja bi trebalo da se završi obnavljanjem normalne zdrave sluzokože. Prestanak štetnih navika putem savetovanje važan je deo lečenja leukoplakije. Dugotrajno praćenje neophodno je u svim slučajevima oralne leukoplakije, čak i nakon hirurške ekscizije.

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Other chemoprevention agents

These include cyclooxygenase-2 (COX2) inhibitors like celecoxib and ketorolac[73,74]; green tea polyphenols like epigallocatevhin-3-gallate (EGCG)[75]; p53-targeted agents using modified adenovirus[76]; thiazolidinediones such as pioglitazone[77], and EGFR inhibitors with variable results[33].

Challenges in the management of leukoplakia

One of the major factors affecting the management of leukoplakia is the absence of knowledge regarding the natural history of the disease despite the huge amount of published data. Some leukoplakias will remain static for years, few will regress after stoppage of habit while few non-dysplastic leukoplakias will transform into malignant lesions[33]. Another challenge is the concept of 'field cancerisation' which implies that healthy-appearing mucosa in patients with potentially malignant and malignant lesions, may also present with dysplastic changes. The use of vital staining, can help identify such areas[33].

Conclusion

Leukoplakia is an oral potentially malignant lesionwhich should be screened properly as it has a high chance of malignant transformation. The clinician should have a thorough knowledge about the clinical diagnosis, the various investigativeand managementprotocols which will ensure the resolution of lesion followed by the restoration of normal healthy mucosa. Cessation of adverse habits through habit counselling is an important part of the management in leukoplakia. Long-term follow up is essential in all cases of oral leukoplakia even after surgical excision.

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