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Senile Lentigo – Cosmetic or Medical Issue of the Elderly Population

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A B S T R A C T

Senile lentigo or age spots are hyperpigmented macules of skin that occur in irregular shapes, appearing most commonly in the sun- exposed areas of the skin such as on the face and back of the hands. Senile lentigo is a common component of photoaged skin and is seen most commonly after the age of 50. There are many disscusions on whether senile lentigo represents a melanoma precursor, namely lentigo maligna melanoma and, if there is a need for a regular follow up in cases of multiple lesions. Clinical opservations sometimes report that in the location of the newly diagnosed melanoma, such lesion preexsisted. On contrary, some authors believe that senile lentigo represents a precursor of seborrheic keratosis, which does not require a serious medical treatment. However, the opservation of the possible association of senile lentigo with the melanoma development makes us cautious in the assessment of this lesion. Histologically, there are elongated rete ridges with increased melanin at the tips, and the number of melanocytes is not increased. The dermatoscopic features are also distinctive. If the lesion becomes inflammed it may evolve into benign lichenoid keratosis. Cryotherapy and laser treatment are common therapeutic approaches. Sun protection creams may be useful in early lesions.

Key words: *senile lentigo, UV radiation, photoimmunology, oncogene*

Introduction

Lentigo senilis (synonyms: lentigo solaris, liver spot, old age spot, senile freckle) is well-circumscribed, round, oval or irregularly shaped macule that vary in color from light brown to dark brown or black which usually develops on chronically photoexposed areas in the elderly people, predominantly on the face, the dorsal aspects of hands, extensor forearms, the upper chest and back[1]. More than one half of all patients over age 64 will have at least one senile lentigo, and most patients have more than one. Senile lentigines are found in 90% of the Caucasian poplulation older than 60 years, and according to published epidemiological data their incidence increase with advancing age and cumulative ultraviolet (UV) light exposure [2,3]. With respect to increased incidence of this common skin lesion, senile lentigo has become a significant cosmetic and medical issue. The incidence rates of lentigines have increased worldwide over the past several decades. The similar trend has been observed in Croatia. The exact incidence rate is unknown since they are considered benign lesions and not routinely added into National Register[4].

The most significant environmental factor for the development of senile lentigo is cumulative UV radiation, particularly solar UVB radiation[5]. During the past century, changes in clothing styles, recreational activities, chronic occupational solar exposure, longevity, and other aspects of lifestyle have resulted in increased exposure to sunlight. Although most UV radiation comes from the sun, the use of sunbeds as arteficial sunlight has resulted in a rising incidence of UV-induced lentigines. The most important defense mechanisms in the protection of human skin against UV radiation involve melanin synthesis and active repair mechanisms. Low pigmentation capacity in Caucasians and rare genodermatosis Xeroderma pigmentosum lead to multiple senile lentigines associated with multiple skin cancers. Inherited patterned lentiginosis favors more lightly pigmented African-Americans[6].

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Despite their benign nature, lentigines can cause substantial cosmetic issue, with strong impact on health care budgets due to their extraordinary high incidence.

UV Radiation and Senile Lentigo

UV radiation is well-known, potent, environmental agent closly associated with the development of senile lentigo in fair-skinned, elderly individuals. The concept of UV radiation as the significant etiologic factor in the pathogenesis of senile lentigo originates from the beginning of the twentieth century followed by astute observations of clinicians who noted that senile lentigo frequently appeared on the sun-damaged skin of fair-skinned individuals who pursued outdoor occupations.

Within the UV radiation spectrum, the UVA (wavelengths between 320 and 400 nm), and particularly UVB (wavelengths between 290 and 320 nm) are the most significant. Besides occupational UV exposure, UV phototherapy has been associated with senile lentigo.

PUVA (psoralen+ UVA) lentigo is a well- circumscribed hyperpigmented macule that commonly develops in individuals undergoing long-term PUVA chemotherapy. About 50% of PUVA-treated patients develop PUVA lentigines after average of 5 to 7 years of photochemotherapy. The frequency and severity of the lesions are positively correlated with greater number of treatments, age of starting therapy, and male sex. There is a negative association wih skin phototypes V and VI. In contrast to typical senile lentigines, PUVA lentigines usually exhibit darker pigmentation and more of a stellate appearance. Histologically, the PUVA-induced lesions display lentiginous hyperplasia of larger melanocytes that often exhibit mild cytologic atypia. Patients treated with PUVA should also be monitored for the development of melanoma[2,7].

Numerous studies have supported the notion that UV radiation causes significant damage to keratinocytes and melanocytes[8]. A case-controlled study in France found that multiple senile lentigines on the upper back and shoulders of adults may serve as clinical markers of past severe sunburn and may be used to identify a population at higher risk of developing cutaneous melanoma[9]. The researchers suggested that senile lentigo may be induced by the mutagenic effect of repeated past UV light exposures, leading to characteristic enhancement of melanin production[10].

Little is known about the genetic basis of human senile lentigines, which were analyzed for potential fibroblast growth factor receptor 3 (FGFR3) and phosphatidylinositol 3 CA-kinases (PIK3CA) mutations. A recent study (Hafner et al.) investigated environmental and genetic risk factors for senile lentigo. FGFR3 and PIK3CA regulate several important cellular processes, including regulation of cell growth and division. The FGFR3 gene is located on the short (p) arm of at position 16.3 and PIK3CA gene is located on the long (q) arm of at position 26.3. The FGFR3 gene mutations were detected in 17% of senile lentigines, and PIK3CA gene mutations were detected in 7% of senile lentigines, suggesting that FGFR3 and PIK3CA mutations are involved in their pathogenesis and further substantiating previous speculations that UV exposure may be a causative factor for FGFR3 and PIK3CA mutations in human skin[11].

Furthermore, UV radiation induces the release of prostaglandins and cytokines by the keratinocytes. Among the mediators released by keratinocytes in response to UV radiation, there is a small peptide endothelin-1 (ET-1), a ligand for the endothelin-B (ET_B) receptor expressed on melanocytes, which can lead to an increase in tyrosinase activity followed by an increase in melanin production. A recent report (Kadono et al.) demonstrates focal epidermal ET-1 hypersecretion and endothelin-B (ET_B) overexpression in human skin samples from lentigo senilis[12].

The activation of the ET-1/ET_B pathway downregulates E-cadherin and associated catenin proteins in human melanocytes and melanoma cells. E-cadherin is an established suppressor of melanoma cell invasion *in vitro* and *in vivo*. Downregulation of E-cadherin, cellular adhesion molecule, by ET-1/ET_B receptor involves the downstream activation of caspase-8 but not of distal, executioner caspases, and does not lead to apoptosis[13].

Interactions between keratinocytes and melanocytes including ET-1 and ET_B receptor as well as stem cell factor (SCF) and c-KIT receptor expressed on melanocytes are responsible cytokine networks for senile lentigo and UVB-melanosis[14]. Disturbed keratinocytes-melanocytes interactions during melanosome transfer and skin melanosome distribution patterns could be related to senile lentigo formation. Melanocytes located in the basal layer of epidermis produce melanin-loaded melanosomes, which are distributed to neighboring keratinocytes. Chronic UV radiation lead to an accumulation of melanosomes in melanocytes and also increase the phagocytose of melanosomes by keratinocytes[15].

Affymetrix gene-expression analysis (Goyarts et al.) was performed on mRNAs from involved and uninvolved skin biopsies from volunteers with lentigo senilis. In this study serine peptidase gene was downregulated in keeping with the suggestion that lentigo senilis is associated with impaired melanin degradation. The antiapoptotic genes were downregulated, and six genes associated with transmembrane transport of melanosomes were upregulated[16].

Production of the growth factors, can also lead to an increase in the pigment content within melanocytes in senile lentigo. There is also increasing evidence that UV radiation can affect receptors, kinases, phosphatases and transcription factors.

The most important defense mechanisms in the photoprotection involve melanin synthesis and active repair mechanisms. Low pigmentation capacity in Caucasians and rare genodermatosis Xeroderma pigmentosum are mainly responsible for protection failures.

Clinical, Histological and Dermatoscopic Features of Senile Lentigo

Clinical appearance and histologic features of lentigo senilis have been well documented. Senile lentigines are well-circumscribed, round or oval macules that vary in color from yellow, light brown to dark brown or black. More lightly pigmented lesions are usually homogeneous, whereas darker ones tend to have a mottled appearance. The lesions increase in number and in size gradually. They usually vary from about 3 mm to 2 cm in diameter and demonstrate a tendency towards confluence. Larger and older lesions are often irregular in shape and are often dark brown or brownish-black in color. Senile lentigines occur on sun-exposed areas, predominantly the dorsal aspects of hands, extensor forearms, the face, the upper chest and back of fair-skinned, elderly individuals[1].

Differential diagnosis of senile lentigo includes a wide range of benign and malignant lesions, such as early stage of seborrheic keratosis and lentigo maligna. Dermatoscopy as new, noninvasive diagnostic technique may be helpful in diagnosis of senile lentigo, since senile lentigo may mimic early stage of seborrheic keratosis, solitary lichen planus-like keratosis (SLPLK) or lentigo maligna.

Major dermatoscopic features of senile lentigo are: a diffuse light brown structureless area, sharply demarcated and/or moth-eaten borders, fingerprinting, and a reticular pattern with thin lines that are occasionally short and interrupted[17].

According to Nouveau et al. dermatoscopic pictures of senile lentigo have shown that the observed structures can be vary different within a given lesion, suggesting that different areas of a senile lentigo could be in different grades of severity, which proves the heterogeneity of senile lentigo architecture[18]. There is clinical and histologic evidence of close relationship between lentigo senilis, SLPLK, and reticulated form of seborrheic keratosis. In the histologic study performed by Mehregan histologic transformation was found from lentigo senilis into central SLPLK.

It was concluded that SLPLK is an inflammatory variant of lentigo senilis with irritation, trauma, or other yet unknown factors leading to basal cell damage, liquefaction degeneration, and incontinentia of pigment followed by induction of an inflammatory cell reaction in a fashion similar to that which recently has been postulated to occur in lichen planus. The same study also has shown histologic transformation from lentigo senilis into reticulated seborrheic keratosis. Fully developed reticulated seborrheic keratosis shows a more complicated network pattern of pigmented basaloid cell and areas of keratin cyst formation. Intention of the study performed by Mehregan was to evaluate the possibility of relationship between lentigo senilis and lentigo maligna. The light--brown area of lentigo maligna exhibits diffuse proliferation of anaplastic clear cells at the dermoepidermal junction. There is no evidence of basaloid cell proliferation or budding and no resemblance to lentigo senilis[19].

The development of melanocyte cytologic atypia in senile lentigines on occasion suggests a relationship of solar lentigines to lentigo maligna, but clear progression to lentigo maligna has not been established[20]. Senile lentigines have been shown to be an independent risk factor for the development of melanoma.Senile lentigines are phenotypic manifestation of sun exposure. They are associated with a two-to threefold relative risk for the development of melanoma[4,20]. In a study of 513 melanoma patients these lesions were identified with increasing age[21].

A biopsy is mandatory for any lesion that develops an irregular border and color, particularly very dark brown or black hues. The biopsy findings in solar lentigo are characterized by proliferation of basaloid cells forming buds and strands that contain increased amounts of melanin. In some cases, the melanocytes are increased in number at the dermoepidermal junction. There is no junctional activity. Melanocytes in dopa-stained sections of solar lentigines exhibit increased melanogenesis, and these cells have more numerous as well as longer and thicker dendritic processes than the melanocytes of normal skin. In the superficial dermis there is the constant finding of actinic elastosis and dermis often contains melanophages and occasionally a mild perivascular infiltrate of lymphocytes. Electron microscopic studies reveal abbundant melanosome complexes in keratinocytes which appear to be larger than in normal surrounding skin[2,22].

Treatment of Senile Lentigo

Cryotherapy and laser surgery have been shown to be equally effective, but caution must be used to prevent post-treatment dyspigmentation. Senile lentigines may be removed with various types of chemical peels, 2% mequinol/0,01% tretinoin, or special lasers[23]. They may also be temporarily bleached with 3-4% concentration hydroquinone creams which are used as cytotoxic effects to melanocytes and tyrosinase inhibitors. Another depigmenting agent kojic acid interrupts intermediates in melanin synthesis[24].

Primary prevention of senile lentigo is appropriately focused on the avoidance of excessive sun exposure of the skin. Photoprotection is one of the fundamental prevention of BCC. Dermatologists should educate their patients in the use of sunscreen. The use of a highly effective broad-spectrum UVA and UVB sunscreen have been shown to influence the development of nevi in children, suggesting that they should play a role in preventing senile lentigines if used correctly and consistently. Combination of UVA and UVB filters may offer a powerful protection against UV-induced effects in the use of suncare products[25].

Conclusion

Senile lentigo is an entity with distinct histologic features characterized by proliferation and downward budding of basaloid cells accumulating melanin pigment. There is no significant degree of proliferation of melanocytes and in this respect lentigo senilis is a proliferative epidermal disorder rather than a disease of the melanocytic system. There is no histologic evidence to incriminate lentigo senilis as an early or precursor stage of the precancerous melanosis. However, It is crucial to recognize its role as an indication of chronic UV damage which dictates monitoring of the patient for non-melanoma skin cancer and melanoma.

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LENTIGO SENILIS- KOZMETSKI ILI MEDICINSKI PROBLEM TREĆE DOBI

SAŽETAK

Lentigo senilis (senilne pjege) podrazumijeva promjene na koži koje se klinički očituju kao hiperpigmentirane makule koje se najčešće pojavljuju na fotoeksponiranim područjima kao što su lice i dorzumi šaka. Senilni lentigo spada u uobičajene komponente tzv. fotostarenja kože i najčešće se vidi u osoba starijih od 50 godina. Često se vode rasprave je li lentigo senilis preteča melanoma, i to lentigo maligna melanoma te treba li osobe koje imaju multiple promjene redovito kontrolirati. U kliničkim iskustvima ponekad se dobije podatak da je melanomu prethodila upravo takva lezija. Također, neki autori smatraju, suprotno prethodnome, da je lentigo senilis preteča seborejičke keratoze, a koja ne zahtjeva ozbiljan medicinski tretman. No, ipak nas opservacije o poveznici senilnog lentiga s mogućim nastankom melanoma čine opreznijim u opserviranju ove lezije. Histološki, kod senilnog lentiga vide se produljene epidermalne prečke s povećanom količinom melanina u vršcima, dok broj melanocita nije povećan. Dermatoskopska slika je također karakteristična. Uslijed inflamatornog procesa solarni lentigo može prijeći u dobroćudnu lihenoidnu keratozu. Krioterapija i laserski tretman danas su najčešće primjenjivane metode u uklanjanju senilnih pjega, a kod početnih promjena primjena krema s UV filtrima može biti učinkovita.