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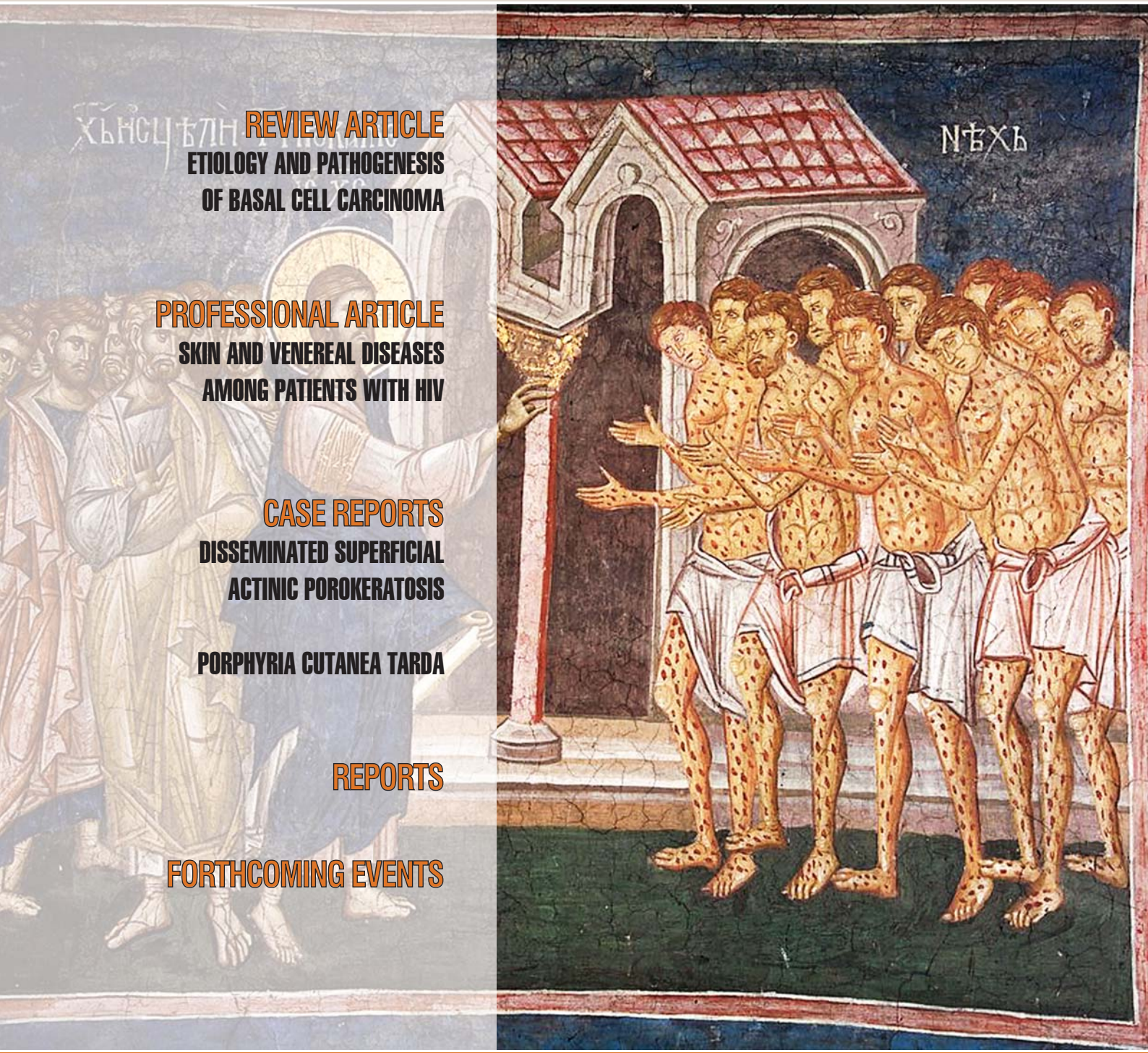

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ETIOLOGY AND PATHOGENESIS OF BASAL CELL CARCINOMA

PROFESSIONAL ARTICLE
SKIN AND VENEREAL DISEASES AMONG PATIENTS WITH HIV

CASE REPORTS
DISSEMINATED SUPERFICIAL ACTINIC POROKERATOSIS

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REPORTS

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CONTENTS

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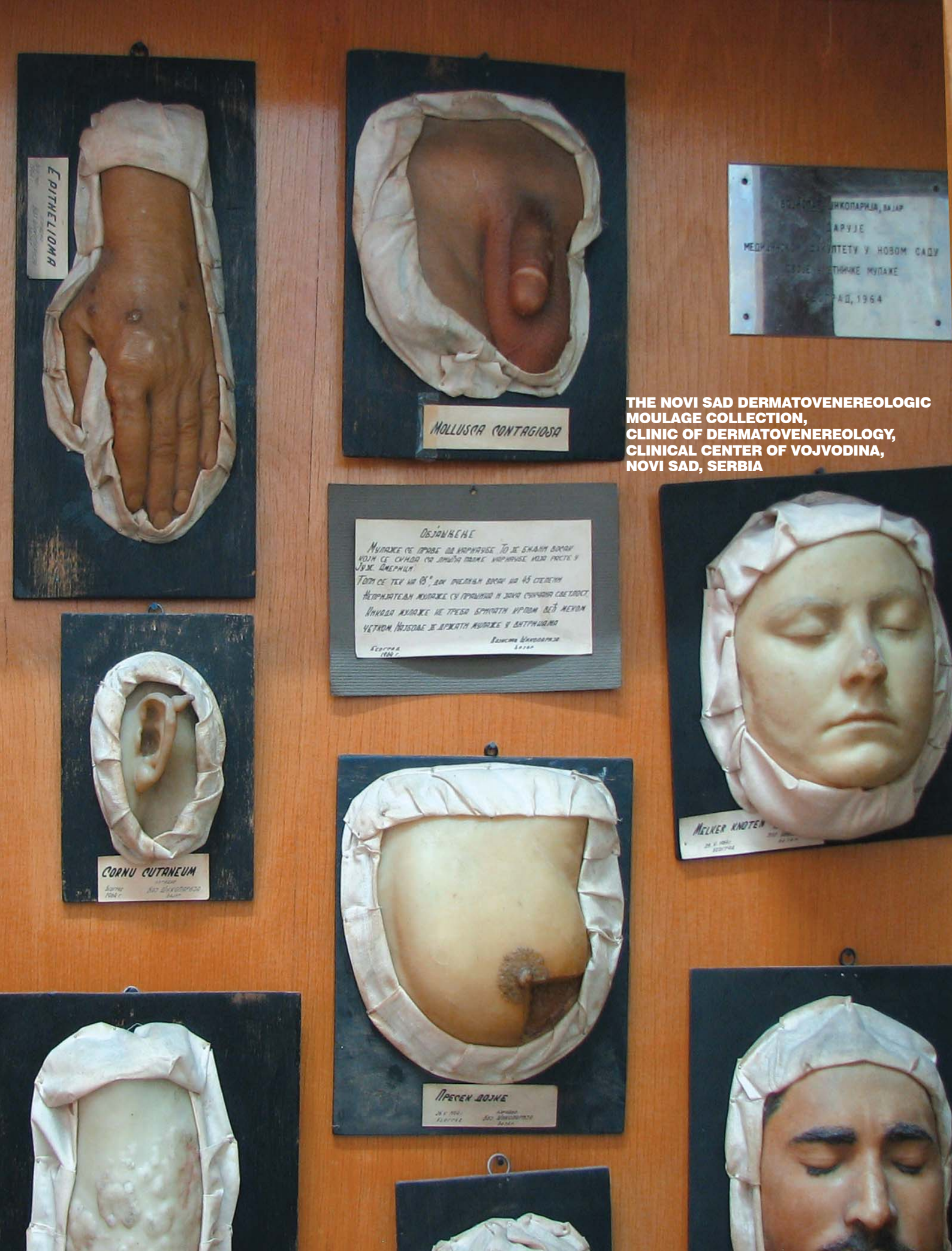

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Etiology and pathogenesis of basal cell carcinoma

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Abstract

Basal cell carcinoma (BCC) is the most common cancer among Caucasians. It generally occurs on sun-exposed areas of the body, mostly on the head and neck (80%), trunk (15%), rarely on arms and legs. Basal cell carcinoma is a good example of a disease caused by a combination of genetic and environmental factors. Ultraviolet (UV) radiation plays a dual role in the development of BCC: it causes DNA damage and immunosuppression. UVA and UVB rays damage the DNA via various mechanisms. UVB radiation directly damages DNA within skin cells, causing cytosine → thymine mutations at dipyrimidine sites, whereas UVA radiation is 10.000 times less mutagenic, but it is significantly more present in the natural UV radiation. Also, UVA photons have lower energy than UVB photons and do not induce mutations. UV radiation exerts immune suppression by decreasing the antigen presenting cells ability and by producing immunosuppressive cytokines, such as interleukin-10 (IL-10) and tumor necrosis factor alpha (TNF-α). Mediators of UV-induced immunosuppression are DNA and cis-urocanic acid. Several studies showed a significant association between the development of BCC and sun-exposure during childhood and adolescence, and a strong relation with family history of skin cancer.

Exposure to ionizing radiation increases the risk of nonmelanoma skin cancers by three times, while the risk is proportional to the radiation dose.

Chemical carcinogens, such as arsenic, tar, psoralen, and pesticides, increase risks for nonmelanoma skin cancers, predominantly for squamous cell carcinoma (SCC).

Regarding genetic predisposition, there is glutathione S-transferase (GST) as an important part of cellular defense against endogenous and exogenous chemicals. Several polymorphisms in GST family members have been associated with impaired detoxification, thus influencing the risk for some cancers, including nonmelanoma skin cancers. Cytochrome P450 enzymes are involved in detoxification of photosensitizing agents, and thus involved in BCC carcinogenesis. PTCH is a tumor suppressor gene first identified in patients with Gorlin syndrome. Abnormal activation of this gene and its pathways result in various types of tumorigenesis. BCC is associated with homozygous PTCH gene deletion.

With regard to acquired genetic mutations, it was found that aggressive BCCs are significantly associated with increased p53 protein expression, probably representing the mutated form, although that assertion could not be established with certainty. Considering the apparently limited contribution of DNA damage and chromosome instability to the expression of BCC phenotype, the relevance of p53 mutations for BCC growth remains to be demonstrated. Data on the role of Bcl-2 gene family in the development of BCC are scarce. It is unclear whether Bcl-2 has a functional role in the development of BCC, or it only indicates the level of gene expression in tumor stem cells. Activation of Ras gene may play an important role during early stages in the development of nonmelanoma skin cancers, and it is often found on UV-exposed skin in BCC, actinic keratosis and SCC.

Concerning immunologic factors, studies have shown that tumor necrosis factor-α (TNF-α) is the critical mast cell product involved in ultraviolet-induced immunosuppression: mast cells contain high quantities of TNF-α which is released after activation; the level of TNF-α is increased in the skin exposed to UV radiation disrupting the morphology and function of Langerhans cells, the principal antigen-presenting cells of the skin. An animal study suggests that the degree of susceptibility to ultraviolet-B-induced local immunosuppression depends on TNF-α level within the epidermis after UVB. It has been established that mast cell-derived histamine stimulates prostaglandin E2 (PGE2) production from keratinocytes. PGE2 alters the cytokine balance in favor of the immunosuppressive interleukin-10 (IL-10) against the immunostimulatory IL-12; histamine also increases suppressor T-cell function by binding to the H2 receptors, which in turn release higher levels of immune suppressive cytokines including IL-10 and induce apoptosis of antigen-presenting cells. All this results in a shift of the immune response from T helper 1 (Th1) cytokine profile to T helper 2 (Th2) cytokine profile, inhibiting antigen-presenting cells to induce antitumor activity.

Key words

Carcinoma, Basal Cell + etiology + pathology + genetics; Immunosuppression; Ultraviolet Rays; Risk Factors; Genes, Tumor Suppressor; Genes, p53; Genes, bcl-2

Basal cell carcinoma (BCC) is the most common type of skin cancer in Caucasians. It mostly occurs in areas that are often exposed to the sun and is most frequently manifested on the head and neck (80%), the trunk (15%) and rarely on upper and lower extremities. Also, very rarely, BCC affects the skin on axillary and perineal region, the hands and soles and genital region (1,2,3). Skin phototypes 1 and 2, male sex, old age and history of previous sun burns are all considered significant risk factors in developing BCC (1).

Also, simultaneous appearance of BCC and other cutaneous lesions, that come as a direct consequence of exposure to UV radiation and skin phototype, such as solar lentigo and actinic keratosis, has also been proven. Apart from standard sun-ptrotection, chemopreventive agents such as retinoids offer the possibility of effective non-melanoma skin cancer prevention (4).

Basal cell carcinoma is a good example of a disease caused by interaction of genetic and site-specific factors. However, BCC remains a frequent challenge for dermatologists (5). The following text will explain factors that influence its development and pathogenesis.

Ultraviolet Radiation

Ultraviolet (UV) radiation plays two key roles in the development of BCC: it causes DNA damage and immunosuppression (6). UVA and UVB rays damage DNA by different mechanisms. UVB rays harm the DNA directly by causing constitutional cythosine à thymine (C à T) mutations at dyprimidine sites, as well as CC à TT, while UVA rays have 10.000 times lower mutagenic effect but are significantly more present in natural UV radiation (7). Also, UVA radiation photons are lower in energy compared to UVB radiation photons and have no mutagenic effect.

UVB radiation induces cutaneous ornithine-decarboxylase, the first enzyme in polyamine-biosynthesis pathway, which plays an important role in proliferation and monoclonal expansion of initially mutated cells leading to cancerogenesis. Grossman and Leffell demonstrated the association between exposure to UVB rays and skin cancer development (6). UV radiation induces immunosuppression by reducing antigen-presenting ability, as well as immunosuppressive cytokine production, such as interleukin-10 (IL-10) and tumor necrosis factor alpha (TNF-a) (1). Mediators of immunosuppression induced by UV radiation are DNA and cis-urocanic acid.

UV radiation-induced mutations of the human patched gene (PTCH) were found in several sporadic cases of BCC, approximately 30-41% (8). However, this type of DNA damage has been recorded in 79% of patients suffering from BCC and xeroderma pigmentosum (9). Half of these cases had both PTCH and p53 mutations, as well as a large number of UV specific alterations (10). These results strongly suggest the existence of other causes of mutation, in adition to UV radiation, which can cause inactivation of PTCH and initiate tumorigenesis. This hypothesis is supported by results of epidemiological studies showing low correlation between the dose of UVB radiation and occurrence of BCC, as opposed to higher correlation between UVB radiation and squamous cell carcinoma (SCC) (11). Vitasa et al. demonstrated that the cumulative dose of ultraviolet radiation is in direct correlation with occurrence of SCC, but not with occurrence of BCC (12). Considering the fact that BCC develops from cells found in deeper skin layers than SCC, it can be assumed that these two tumors need different doses and wavelenghts of UV rays in order to occur. Several studies indicate that short-term intermitent exposure to UV rays during vacations can pose a higher risk of skin cancer compared to the amount of sun exposure that outdoor workers get (13). Corona et al. noted a significant association between occurrence of BCC and sun exposure during childhood and adolescence, as well as its high correlation with family history of skin cancer (14). Ramani and Bennett reported a significantly higher incidence of BCC in Second World War soldiers based in the Pacific as opposed to those who were stationed in Europe (15). These data show that intense UV exposure in periods ranging from a few months to several years can have long-term harmful effects. In adition, latitude plays no important role in development of BCC, which is not the case with SCC (16). Regular use of sunscreens before the age of eighteen, reduces the risk of nonmelanoma skin cancers by up to 78% (17).

Several studies show an increased risk of BCC and SCC in people who are exposed to artificial sources of

UV radiation (18,19). Thus, when it comes to BCC, Boyd et al. determined that female patients with BCC visited solariums twice as much than patients in the contol group (20). However, a significant number of BCC cases develop on skin that has not been exposed to UV rays, e.g., recently Popadić et al. reported a patient who exhibited superficial BCC on the penis (3), suggesting the existence of other risk factors that contribute to the occurrence of BCC.

Ionizing Radiation

Exposure to ionizing radiation increases the risk of nonmelanoma skin cancers by three times (17). The risk is proportional to the amount of recieved radiation. It is generally believed that high single doses of radiation (> 12–15 Gy) are required for the tumor to develop, which means the risk caused by ionizing radiation can be reduced if the total radiation sum is fractioned into smaller individual doses (21). Most SCC and BCC cases that occur due to ionizing radiation have a long latency period, lasting up to a few decades. Before the discovery of effective antifungal medications, treatment of fungal scalp infections was associated with the development of multiple BCCs. In a study including 2.224 Caucasian children treated with X-rays, the relative risk of developing BCC on the head and neck proved to be higher [RR 3.6 (95% CI, 2.3-5.9)], compared to the control group of 1.380 children treated only with topical therapy (22). Cases of BCC on skin within the radiation field after therapy for port wine stain vascular malformation, Hodgkin disease, as well as after accidental radiation, have all been documented (23).

Chemical Carcinogens

Chemical carcinogens, such as arsenic, tar, psoralens and pesticides increase the risk of nonmelanoma skin cancers, predominantly SCC. Lesions are mainly localized on the hands and are usually multiple (24). The period from exposure to chemical carcinogens and the occurrence of tumors lasts from 20 to 40 years (25). Exposure to psoralen combined with UVA radiation (PUVA), used in the treatment of patients with psoriasis, increases the risk of BCC and SCC. However, some studies show no increased risk of BCC in patients undergoing PUVA therapy (26). Considering all facts, it can be concluded that agents causing DNA damage more often lead to the development of SCC than BCC. This observation is consistent with the fact that in congenital diseases, caused by defects in DNA reparation process, the above mentioned defects are more often manifested with SCC than with BCC.

Viruses

Some authors point to the connection of oncogenic types of human papillomaviruses (HPV) and the development of BCC (27, 28). HPV-DNA has been detected in BCC related lesions, indicating a possible role of HPV infections in the development of BCC (27, 28). It is generally assumed that carcinogenesis is associated with apoptosis inhibition, by blocking the effects of Bcl-2 homologous antagonist killer protein by the HPV E6 protein. However, a strong correlation between HPV and BCC has not yet been established, and there is a reasonable doubt that this correlation will ever be confirmed (29).

Genetic Predisposition

Glutathion S-transferase

Glutathion S-transferase (GST) is part of the cellular defense mechanism against chemicals, endogenous or exogenous: UV radiation causes oxidative stress in skin cells, leading to lipid peroxidation and DNA damage via hydrogen formation. GST is responsible for removing these potential mutagens. Seven distinct gene families are responsible for coding human soluble GST synthesis. Most of the genes belonging to these families are polymorphic, but researchers most frequently concentrate on *mi*, *theta* and *pi* gene families. *Alpha, mi* and *pi* classes counteract potentially dangerous *a*-β-unsaturated carbonyl compounds, such as acrolein found in cigarette smoke, 4-hydroxynonenal, adenine- and thymine-propene caused by the oxidative DNA damage, and aminochrome, dopachrome and noradrenochrome which are derived from catecholamine (30). *Zeta* class enzymes degrade dichloroacetic acid, a common contaminant in chlorinated drinking water (30). Unlike other classes, *theta* class enzymes catalyze a number of important small dihaloalkanes, such as dichloromethane used in chemical synthesis of plastic and drug manufacturing (30). In addition, *theta* class enzymes metabolize: monochlorometane, ethylene

oxid present in cigarette smoke, and polycyclic aromatic hydrocarbon epoxides (30). GST activity is mostly expressed in sebaceous glands and outer hair follicle sheath. Insufficient detoxification of some polymorphic GST family members increases the risk of cancer, including nonmelanoma skin cancers. GSTT1 null genotype is associated with high sensitivity to UV radiation. GSTM1 null genotype is also associated with predisposition to BCC, most probably due to its role in defense mechanisms against UV-induced oxidative stress (29, 31). It has been proved that GSTM3 polymorphism also increases the risk in BCC occurrence (32).

Cytochrome P450

Cytochrome P450 enzymes (CYP) are a superfamily of monooxygenases that catalyze the oxidation of various organic substances. These enzymes are part of the detoxification process of photosensitive agents, and therefore are also included in BCC carcinogenesis: genetic polymorphism CYP2D6 (cytochrome P450 encoding gene) correlates with an elevated number of BCC (33). In addition, certain CYP2D6 allelic variants are in direct correlation with the occurrence of multiple BCCs. Patients who carry them have an elevated risk of developing BCC in the future (34).

DNA Repair

It has been observed, in 1973, that patients suffering from xeroderma pigmentosum are prone to SCC, BCC and melanoma (29, 35). Segerbäck et al. demonstrated that BCC patients have a less efficient DNA repair mechanism compared to healthy individuals (36). Werner and Bloom syndrome are hereditary diseases associated with DNA helix defects and a high tendency to develop skin cancer, but not BCC (37, 38). Contrary to these, patients with Rothmund-Thomson syndrome do develop BCC, considering that DNA helix defects are present only in some cases. Diseases identified with chromosome instability, such as ataxia-telangiectasia syndrome and Nijmegen breakage syndrome, do not carry an increased risk of BCC. The same goes for Li-Fraumeni syndrome, which may be caused by p53 gene mutations, and dyskeratosis congenital, associated with defect in telomere maintenance (29, 39, 40). The reason for which various forms of genetic instability are not associated with the development of BCC is unknown. Biological differences between BCC and other malignancies may be one explanation: primarily due to the fact that most tumors, sooner or later, show chromosomal instability, which does not seem to be the case with BCC (29).

Patched Gene

The patched gene (PTCH) is a tumour-suppressor gene first discovered in patients suffering from Gorlin syndrome. PTCH inactivation in people with Gorlin syndrome raised suspicion that PTCH mutations can also contribute to the pathogenesis of sporadic BCC. Alternations in PTCH have been detected in 30-40% of sporadic BCC cases, 41% of which carry specific UV-signature mutations: C-T, CC-TT substitutions at dypirimidine sites, suggesting that UVB rays play a role in their development. All BCC lesions carrying this type of mutation occur on skin that has been exposed to UV radiation, which further confirms these claims (41). The gen is located in the 9q22.3 chromosome and regulates the process of gene expression, thus controlling embryonic cell development, growth and differentiation processes, such as Hedgehog signaling pathway. Abnormalities in the activation of PTCH and its signaling pathways lead to various types of carcinogenesis: homozygous deletion of the patched gene is necessary for the formation of BCC. Earlier studies demonstrate the occurrence of BCC in patched heterozygous mutant mice, but for the occurrence of these tumors UV or ionizing radiation is necessary and, in some cases, p53 mutations as well (42). The PTCH gene is responsible for coding the synthesis of a large transmembrane glycoprotein that, combined with a transmembrane glycoprotein coded by the Smo gene (smoothened gene), forms a part of the receptor complex. This protein complex is the principal receptor for the hedgehog extracellular signaling molecule. The patched gene protein acts as a Smo inhibitor. Abnormal activation of the Smo protein leads to continuous uncontrolled signal transmission to the nucleus, resulting in the transcription activation controlled by the so called Gli transcription factors. PTCH mutations cause inactivation of the suppression function and lead to uncontrolled cell proliferation, resulting in tumor formation. PTCH damage causes not only changes in the hedgehog signaling pathway

but also in downstream events. This mainly refers to the Wnt gene and its protein product. Certain genetic polymorphisms are associated with certain phenotypic characteristics of BCC. PTCH mutations are found in all types of BCC, but their expression levels do not correlate with different types of tumors (43).

In addition to PTCH mutations, sporadic BCC cases also contain Smo gene mutations (6-20%) as well as PTCH2 mutations. The highest percentage of Smo gene mutations were detected in BCC lesions in patients with xeroderma pigmentosum. All this points to the fact that mutations in one (or more) signaling pathway components inevitably lead to uncontrolled cell proliferation, which ultimately results in tumor occurrence.

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)

A good example of the importance of embryonic developmental pathway in occurrence of BCC is the discovery that deficiency in nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), one of the signal pathway components, can also cause BCC (29).

The activation of NF-kB depends on phosphorylation and subsequent degradation of NF-kB inhibitor proteins (IkB) via IkB kinase complex (100). The NEMO gene (nuclear factor B essential modulator) mutation which causes incontinentia pigmenti, is part of the IkB kinase complex. In adition, cylindromatosis (CYLD) gene intarracts with the NEMO gene, and these mutations were found with the familiar trichoepithelioma (44, 45). These findings suggest that the NF-kB singnaling pathway, involved in inflammatory processes and embryogenesis of skin adnexal epithelium, may also affect the development of BCC (29).

Acquired Genetic Mutations

p53 gene

Most common genetic aberrations in skin carcinomas, as well as their precursor lesions, are found in the p53 gene (46). The p53 gene is responsible for coding the synthesis of phosphoprotein and is part of the cell cycle system and enables chromosome stability. In case of cellular stress, i.e. DNA damage, p53 is activated by phosphorylation. The level of p53 protein in the cell determines the cellular reaction to existing DNA damage: in case of low or medium p53 expression, the cell will allow DNA repair, but high p53 levels result in cellular apoptosis (47). The so called wild type p53 is not detectable in healthy skin, but becomes visible two hours after sun exposure. Its levels peak after 24 hours, only to become undetectable 36 hours after radiation exposure (48). Mutated p53 gene is known to accumulate inside the cell, and these mutations have been detected in approximately half of all BCC patients (49). Also, it has been suggested that more aggressive types of BCC go hand in hand with elevated p53 expression, probably in its mutated form, but this claim has not been proven yet (29). Consequently, it seems reasonable to assume that p53 mutations are secondary events in BCC pathogenesis occurring after tumor initiation. The vast majority of p53 mutations in sporadic BCCs are missense mutations, frequently displaying UV-signature. In patients with Gorlin syndrome, p53 gene mutations are different, showing single nucleotide deletions, previously undetected in sporadic BCC, SCC or actinic keratosis, as well as rare double substitution of base pairs. One possible explanation could be that patients with Gorlin syndrome avoid solar radiation due to propensity for skin cancer, and that several mutations are secondary to other mutagenic events such as oxidative stress.

A study including BCC patients, compared those who used sunscreens and those who did not, showed a significantly lower level of p53 gene mutations in patients using UV protection, which supports the assumption that mutations of p53 gene are secondary events that may not contribute considerably to tumorigenesis (50). Other studies showed that p53 mutations were detected in 33% of BCCs found in Korean patients compared to 50% of BCCs in Caucasian patients (49, 51). These findings suggest that ethnic factors play an important role in the development of BCC, as well as life-style habits related to UV exposure. Due to the limited role of DNA damage and chromosomal instability in the development of BCC, the role of p53 gene mutations in BCC remains unclarified (29).

Finally, in the absence of genetic damage, p53 activation will not occur. Moreover, one of the hallmarks of p53 dysfunction, aberrant mitosis, perhaps as a consequence of centrosome amplification, has never been observed in BCC (52).

p63 gene

The p63 gene, a p53 homologue and a member of the p53 family of proto-oncogenes, is located on chromosome 3q27 and encodes at least six different protein isoforms. The p63 is restricted to cells with a high proliferative potential, and is absent in cells undergoing terminal differentiation. The p63 gene is rarely mutated in BCC. It was shown that aberrant expression of p63 altered the UVB-induced apoptotic pathway, suggesting that down-regulation of this protein in response to UV radiation is important in epidermal apoptosis (53).

Bcl-2 gene

The Bcl-2 gene encodes synthesis of Bcl-2 protein expressing 24 kDa anti-apoptotic protein previously identified in human B-cell lymphoma. The cytoarchitectural distribution of Bcl-2 protein in normal skin includes basal keratinocytes, the dermal papillae of the hair follicle, the keratinized Huxley's and Henle's layers, and the keratinized outer root sheath cells of the isthmus and infundibulum of the hair follicle. Bcl-2 expression is negative in suprabasal keratinocytes (54). Most BCCs, if not all, express high levels of Bcl-2 protein, whereas SCCs typically exhibit no detectable BCL-2 protein (55, 56). In comparison with invasive BCCs, high level of Bcl-2 was found in less aggressive types of BCCs. There are some studies which stated that Bcl-2 diffusely stains the tumor nests in BCCs, while it stains the outermost cell layers in trichoepithelioma (56).

Another member of Bcl-2 family, the so-called BAX gene, encodes the synthesis of BAX protein with pro-apoptotic properties which is not elevated in BCC (57). Data on the role of other Bcl-2 family members in the development of BCC are scarce. It is an interesting paradox that BCC, with high level of apoptosis, expresses anti-apoptotic proteins (42). In the end, it is unclear whether Bcl-2 has a functional role in the development of BCC, or it only indicates the level of gene expression in tumor stem cells.

Ras genes

Ras genes are important constituents of mitogenic signaling pathways, and when activated, they contribute to deregulated cellular growth. The activated Ras genes can play an important role during early stages in the development of nonmelanoma skin cancers, and it is often found on UV exposed skin in BCC, actinic keratosis and SCC. The activation of Ras genes is a result of aberrant repair of UV-induced pyramidine dimers.

Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are a family of zinc dependent endopeptidases that degrade the extracellular matrix. Matrix metalloproteinases are produced by cells such as fibroblasts, keratinocytes, macrophages, endothelial cells, mast cells, and eosinophils. The activity of MMPs is inhibited by tissue inhibitors of metalloproteinases binding with active MMPs. Most MMPs are not expressed in normal intact skin, but they may temporarily be induced as a response to exogenous signals such as UV radiation. Aggressive types of BCCs express MMPs.

Immunologic factors

Immunosuppression

Organ transplant recipients are at higher risk for developing cancer because they often require life-long immunosuppressive therapy. Malignancies occur in at least 20% of transplant recipients within 20 years after grafting. Among them, skin carcinomas account for up to 50% (58). SCC of the skin is the most common malignancy occurring in the setting of solid-organ transplantation and immunosuppression, and its incidence increases substantially with extended survival after transplantation. Increased incidence of BCC has not been described in organ recipients, so it seems clear that immunosuppressive therapy after organ transplantation does not increase the risk of developing BCC (29). In a study involving South Australian and Danish subjects, patients with a history of basal cell carcinoma and melanoma are found to have a significantly higher, genetically predetermined density of dermal mast cells (59, 60). It is suggested that a higher density of dermal mast cells is a predisposing factor for the development of BCC and melanoma, and predisposes an individual to ultraviolet-B-induced immunosuppression. However, a similar correlation has not been found for patients with SCC, probably because development of SCC is caused by other immunomodulatory mechanisms (61).

Tumor necrosis factor-α (TNF-α) is the critical mast cell product involved in ultraviolet-

induced immunosuppression: mast cells contain high quantities of TNF-α which is released after activation; the level of TNF-α is increased in the skin exposed to UV radiation disrupting the morphology and function of Langerhans cells, the principal antigen-presenting cells of the skin. An animal study suggests that the degree of susceptibility to ultraviolet-B-induced local immunosuppression depends on TNF-α levels within the epidermis after UVB (62). Mast cell-derived histamine stimulates prostaglandin E2 (PGE2) production from keratinocytes. PGE2 alters the cytokine balance in favor of the immune suppressant interleukin-10 (IL-10) against the immunostimulatory IL-12 (63); histamine also increases suppressor T-cell function by binding to the H2 receptors, which in turn release higher levels of immune suppressive cytokines including IL-10 and induce apoptosis of antigen-presenting cells (64).

Several studies have shown that the level of immunosuppression is dose-dependent on UV irradiation, whereas immunosuppression is mediated by T-lymphocytes (65, 66). The mechanism of immunosuppression is based on two chromophores: DNA and urocanic acid, both altering expression of the following cytokines: TNF-α, IL-1α/β, IL-3, IL-6, IL-8, IL-10, granulocyte-macrophage colony stimulating factor (GM-CSF) and nerve growth factor (NGF) (67). All this results in a shift of the immune response from T helper 1 (Th1) cytokine profile to T helper 2 (Th2) cytokine profile, inhibiting antigen-presenting cells to induce antitumor activity (67, 68). It is assumed that production of IL-10 by keratinocytes or tumor cells induces immunosuppression and anti-inflammatory effects providing tumor cells to avoid immune response. It has been observed that most patients with solid tumors have increased levels of IL-10 (69). All these data show that UV radiation compromises the immune system of patients with cutaneous tumors (68).

Human Immunodeficiency Virus

Seemingly in contradiction to the lack of an increase in the incidence of BCC in organ recipients, people suffering from acquired immune deficiency syndrome (AIDS) have shown an elevated risk for developing BCC (70). There have also been some reports of BCCs metastasizing in people suffering from AIDS, suggesting that immune surveillance is one of the factors determining the normally nonmetastatic nature of the BCC (71). Why immunosuppression by HIV increases the risk of BCC, whereas pharmaceutical immunosuppression in transplant recipients does not, is not clear.

Human Leukocyte Antigen (HLA)

The major histocompatibility complex (MHC) genes code for membrane proteins that play important roles in controlling immune responses. While normal skin lesions show high levels of class I molecules (MHC I), BCC shows either complete absence or heterogeneous expression (72). All class I-negative tumors were histologically proven to be aggressive, whereas all non-aggressive BCCs were class I-positive. Low levels or absence of expression of class I antigens may result in escape from regulation by cytotoxic T cells, which then facilitates tumor growth (73). Evidence for the involvement of HLA genes in the development of skin cancers was provided by Bouwes Bavinck et al. These authors showed that the presence of HLA-DR7 and a decrease of HLA-DR4 are significantly associated with BCC (74). This corroborates the previous finding of Rompel et al. that HLA-DR4 is decreased in BCC, especially in patients with multiple BCCs located on the trunk. The authors suggested a protective role for HLA-DR4 against the development of BCC (75, 76). Czarnecki and associates showed that HLA-DR1 antigen is weakly associated with the development of multiple BCCs at an early age (77).

Cancer Stem Cells

The cellular origin of BCC is considerably less defined than in SCC. Several cell types have been suggested to be the precursor cells or stem cells for BCC: interfollicular basal keratinocytes, basal keratinocytes from hair follicles or sebaceous gland cells (78, 79). In general, stem cells have a relatively undifferentiated and slow-cycling phenotype, but can be stimulated to proliferate and give rise to transient amplifying cells which have a limited proliferative potential (80). Stem cells may be the target of carcinogens and as such play an important role in tumorigenesis. As first suggested, stem cells in the skin are in the bulge region of the outer root sheath (81). In support of this hypothesis, chemically-induced BCCs in rats arise from hair follicles, but it is not known whether this is also the case in humans. As a result, hair

follicles are likely to play an important role in skin homeostasis, wound healing and tumorigenesis (80). Histologically, BCC may resemble hair follicles, and may show characteristics from both bulge region stem cells and transient amplifying cells (82). In particular, BCC can histologically resemble trichoepithelioma, a benign hair follicle tumor (83). The suprabulbar region of the outer root sheath of the hair follicle has an immunohistochemical profile that is almost indistinguishable from that of a BCC (84). The hair follicle hypothesis is further supported by the fact that when a carcinogen is added in the anagen phase, in which the hair follicle bulge region cells undergo transient amplification, BCCs are generated more frequently (85). Furthermore, BCCs seldom occur on non-hairy skin, whereas expression of the basal cell adhesion molecule (B-CAM) occurs both in normal and diseased skin (82, 86). This cell-surface protein is preferentially expressed in suprabasal cell layers and the outer root sheaths of the hair follicle. It also shows high levels of expression in BCCs, suggesting that BCCs originate from hair follicles rather than from basal keratinocytes, which are negative for B-CAM in normal skin (29). However, the lack of cytokeratin 15 expression in the tumor cells supports the hypothesis that BCCs do not differentiate towards a hair bulge cell fate (87).

Finally, in conclusion, results of previous studies indicate that the hair follicle stem cell is the progenitor cell of the BCC. It seems that BCC cell is a hair follicle stem cell in which the normal differentiation and anagen-initiation program has gone awry (29). Unfortunatelly, the biomolecular basis responsible for the different susceptibility of skin at different sites of the body to BCC development is still not known (88).

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Abbreviations

BCC - basal cell carcinoma
SCC - squamous cell carcinoma
DNA - deoxyribonucleic acid
UV - ultraviolet
C→T - cytosine→thymine
IL - interleukin
TNF-a - tumor necrosis factor alpha
PTCH - patched
Gy - Gray
HPV - human papillomavirus
Bak - Bcl-2 Antagonist/Killer
GST - glutathione S-transferase
CYP - cytochrome P450
Smo - smoothened
NF-κB - nuclear factor kappa-light-chain-enhancer of activated B cells
NEMO - nuclear factor B essential modulator
CYLD - cylindromatosis
Bcl - basall cell lymphoma

MMP - matrix metalloproteinase
GM-CSF - granulocyte-macrophage colony-stimulating factor
NGF – nerve grouth factor
AIDS - acquired immunodeficiency syndrome
HLA - human leukocyte antigen
MHC - major histocompatibility complex
B-CAM - basal cell adhesion molecule

Etiopatogeneza bazocelularnog karcinoma

Sažetak

Uvod: Bazocelularni karcinom (BCK) predstavlja najčešći karcinom kod pripadnika kavkaske rase. Uglavnom nastaje na koži koja je izložena sunčevim zracima i najčešće se manifestuje na glavi i vratu (80%), trupu (15%), a retko na rukama i nogama. Bazocelularni karcinom je dobar primer oboljenja koje nastaje uzajamnim delovanjem genetike i faktora okoline.

Ultravioletni zraci: Ultravioletno (UV) zračenje ima dve ključne uloge u razvoju BCK: izazivanje DNK oštećenja i imunosupresija. Različitim mehanizmima UVA i UVB zraci oštećuju DNK. Direktno UVB zraci oštećuju DNK praveći karakteristične citozin→timin, (C→T) mutacije na dipirimidinskim mestima i CC→TT, dok UVA zraci imaju 10 000 puta manje mutageno dejstvo, ali su značajno više prisutni u prirodnom UV zračenju. Takođe, fotoni UVA zračenja imaju manju energiju od UVB zračenja i nemaju mogućnost izazivanja mutacija. Imunosupresiju UV zračenje indukuje smanjenjem antigen-prezentujuće sposobnosti, kao i produkcijom imunosupresivnih citokina kao što su interleukin 10 (IL-10) i faktor nekroze tumora alfa (TNF-a). Medijatori imunosupresije indukovane UV zračenjem su DNK i cis-urokanična kiselina. Nekoliko studija pokazalo je značajnu udruženost između nastanka BCK i izlaganja suncu tokom detinjstva i adolescencije, kao i visoku povezanost s porodičnom anamnezom o prisustvu karcinoma kože.

Jonizujuće zračenje: Izlaganje jonizujućem zračenju tri puta povećava rizik za nastanak nemelanomskih karcinoma kože, a rizik je proporcionalan primljenoj dozi zračenja.

Hemijski karcinogeni – arsen, katran, psoralen, pesticidi – povećavaju rizik za nastanak nemelanomskih karcinoma kože, uglavnom skvamocelularnog karcinoma (SCK).

Genetska predispozicija: Glutation S-transferaza (GST) deo je ćelijskog odbrambenog sistema usmeren protiv hemijskih produkata, produkovanih endogeno ili delovanjem faktora spoljne sredine. Postoji nekoliko polimorfizama članova GST familije kod kojih je prisutna insuficijentna detoksifikacija, koja povećava rizik za nastanak karcinoma, uključujući i nemelanomske karcinome kože. Citohrom P450 enzimi uključeni su u proces detoksifikacije fotosenzitivnih agenasa, čime su uključeni i u proces karcinogeneze BCK.

PTCH je tumorski supresorski gen koji je prvi put otkriven kod pacijenata s Gorlin–Golcovim (Gorlin–Goltz) sindromom. Abnormalna aktivacija ovog gena i njegovog puta vode različitim tipovima tumorogeneze: za formiranje BCK neophodna je homozigotna delecija PTCH gena.

Pokazalo se da su agresivniji tipovi BCK udruženi s povećanom ekspresijom p53 proteina, koja verovatno predstavlja mutiranu formu, ali ova tvrdnja nije sa sigurnošću potvrđena.

Stečene genetske izmene: Imajući u vidu ograničenu ulogu koju imaju oštećenja DNK i hromozomska nestabilnost u nastanku BCK, značaj mutacija p53 gena u BCK ostaje i dalje nepotvrđen.

Podaci o ulozi ostalih članova Bcl-2 familije gena u nastanku BCK su oskudni, ostaje nejasno da li Bcl-2 ima funkcionalnu ulogu u nastanku BCK ili samo odražava nivo genske ekspresije u matičnim ćelijama tumora.

Aktivnost Ras gena može biti rani događaj u razvoju nemelanomskih karcinoma kože, a aktivacija se često može naći kod osoba obolelih od BCK, aktinične keratoze i SCK na koži koja je izložena UV zracima.

Imunski faktori: Ispitivanja su pokazala da faktor nekroze tumora – α (TNF-α) predstavlja glavni medijator u UV indukovanoj lokalnoj imunosupresiji: mast-ćelije sadrže velike količine TNF-α, koji se oslobađa posle aktivancije; nivo TNF-α povišen je

u koži izloženoj UV zracima, pri čemu on menja morfologiju i funkciju Langerhansovih ćelija, glavnih antigen- prezentujućih ćelija u koži. Na životinjskom modelu, pokazano je da stepen lokalne imunosupresije, izazvane UVB zračenjem, zavisi od nivoa TNF-α u epidermisu posle ozračivanja UVB zracima. Utvrđeno je da histamin poreklom iz mast-ćelija ostvaruje lokalni imunosupresivni efekat tako što: stimuliše produkciju prostaglandina E2 iz keratinocita koji menja citokinski balans, favorizujući u odnosu na imunostimulatorni IL-12, produkciju imunosupresivnog IL-10; histamin nakon vezivanja za H2 receptore povećava funkciju supresorskih T-limfocita koji oslobađaju velike količine IL-10 indukujući apoptozu antigen- prezentujućih ćelija. Sve ovo rezultuje zamenom imunskog odgovora zavisnog od T-helper 1 citokinskog profila u korist supresivnog imunskog odgovora zavisnog od T-helper 2 citokinskog profila, čime se inhibira sposobnost antigen-prezentujućih ćelija da indukuju antitumorsku aktivnost.

Ključne reči

Bazocelularni karcinom + etiologija + patologija + genetika; Imunosupresija; Ultravioletni zraci; Faktori rizika; Tumor supresorski geni; p53 geni; bcl-2 geni

Skin Diseases and Sexually Transmitted Infections among Patients with HIV infection/AIDS referred at the City Institute for Skin and Venereal Diseases in Belgrade: a Case Series of 38 Patients

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Abstract

Human immunodeficiency virus (HIV) infection may be associated with a wide spectrum of dermatological disorders. This study reports the prevalence of dermatologic diseases and sexually transmitted infections among 38 HIV-infected adults who consecutively sought treatment at the City Institute for Skin and Venereal Diseases in Belgrade. Patients were referred by their primary HIV providers between January 2011 and June 2012. More than 80% of patients were men who have sex with men. The most prevalent diseases were anogenital warts (36.8%) and syphilis (34.2%), followed by folliculitis and dermatophyte infections (7.9% each). Thirty-four patients (89.5%) were on highly active antiretroviral therapy (HAART) before the first visit to the dermatologist. Although, the pattern of skin disorders was consistent with literature data, high prevalence of sexually transmitted infections among our patients was rather peculiar. These facts point to the need for education of sexually active persons with HIV about the consequences of sexually transmitted infections, risks of transmission of drug resistant HIV strains, as well as safe sex practice and consistent condom use.

Key words

HIV; Skin Diseases; Sexually Transmitted Diseases; Risk Factors; Acquired Immunodeficiency Syndrome

Disorders of the skin occur throughout the course of HIV infection affecting more than 90% of HIV-infected patients at some time (1, 2). Even before the causative agent was identified, skin involvement in AIDS (eng. acquired immunodeficiency syndrome) has been appreciated in: establishing criteria for diagnosis and staging, as well as prognostic significance of some complications. As the infection progresses and diseases develop, the number of patients with mucocutaneous complications as well as the number of manifestations in any one patient increases (3). Dermatological manifestations in HIV patients are often more atypical than in HIV-negative patients (4). Not only the incidence, but also the severity of common dermatoses, for example, seborrhoeic dermatitis, herpes simplex, mollusca contagiosum, is increased correlating in many cases with the absolute numbers of CD4+ T cells (3, 5).

The administration of highly active antiretroviral therapy (HAART) has been highly beneficial to patients with HIV-associated skin diseases, but on the other side, in many instances the skin has been affected by side effects of these drugs and manifestations of the immune reconstitution inflammatory syndrome/immune reconstitution disease (IRIS/IRD). Thus, HAART has altered clinical presentations of many skin diseases (6). Moreover, since the introduction of HAART, sexually transmitted infections have been increasing among HIV-infected homosexual men (7, 8).

According to the available data and routine surveillance, HIV infection in the Republic of Serbia has been well controlled. In the period of 2010 - 2011, there were 275 newly diagnosed HIV cases, 103 AIDS cases and 57 AIDS-related deaths reported to the Institute of Public Health of Serbia (Figures 1, 2, 3) (9).

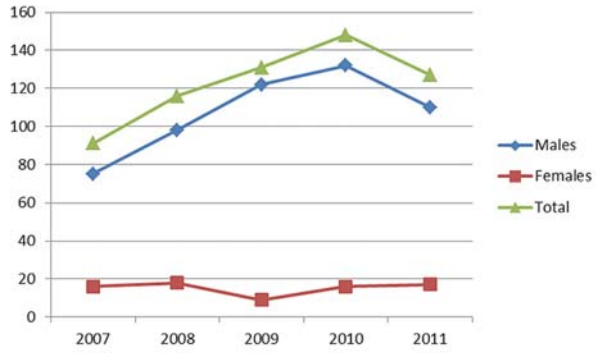

Figure 1. Number of newly diagnosed HIV cases, 2007 - 2011

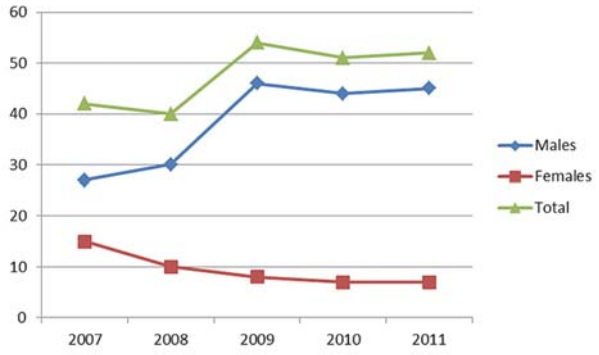

Figure 2. Number of AIDS cases, 2007 - 2011

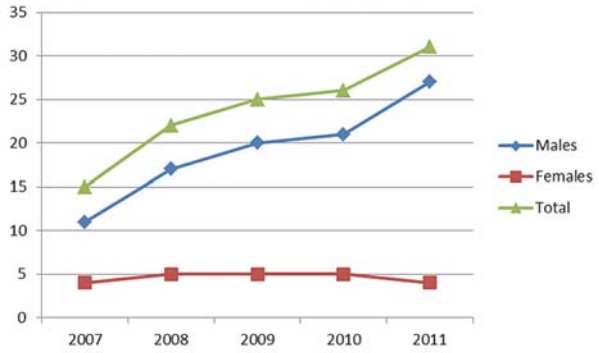

Figure 3. Number of AIDS-related deaths, 2007 - 2011

The purpose of this study was to investigate dermatologic diseases and sexually transmitted infections (STIs) among HIV-infected adults who sought treatment at the City Institute for Skin and Venereal Diseases in Belgrade.

Patients and Methods

The study included all patients referred to the City Institute for Skin and Venereal Diseases in Belgrade, by primary HIV providers, in the period between January 2011 and June 2012. One dermatologist examined and interviewed all HIV-infected patients. All diagnoses were based on patients' history and

Table 1. Demographic characteristics of 38 HIV-infected patients treated at the City Institute for Skin and Venereal Diseases in Belgrade

Patients	N	(%)
Age (years)		
21-30	9	23.7
31-40	19	50.0
41-50	4	10.5
51-60	6	15.8
Gender		
Male	34	89.5
Female	3	7.9
Transgender	1	2.6

N - number of patients

physical examination and confirmed by laboratory tests if necessary. Data on basic demographic characteristics, as well as laboratory and other clinical results were retrospectively collected from patients' records. Unfortunately, data on CD4 + T cell counts were not available.

Results

From January 2011 to June 2012, a total of 38 HIV-infected cases were referred to the City Institute for Skin and Venereal Diseases in Belgrade. Of 38 patients, there were 34 (89.5%) males, 3 (7.9%) females and one patient was transgender. Their average age was 37 years (range 22 - 59) (Table 1). Regarding sexual orientation, 31 (81.6%) patients were homosexual, two were bisexual and 5 were heterosexual (Table 2). Thirty-four patients (89.5%) were on HAART before the first visit to the dermatologist (Table 3).

All skin and venereal diseases diagnosed in our patients were ranked by prevalence (Table 4). The most prevalent diseases were anogenital warts (36.8%) and syphilis (34.2%). The next most common conditions were folliculitis (10.5%), common warts and dermatophyte infections (7.9%, each). The prevalence of molluscum contagiosum, seborrheic dermatitis, genital herpes, epidermoid cysts, gonorrhea and herpes zoster were 5.2%, each.

Discussion

Diseases of the skin and mucous membranes were among the first recognized clinical manifestations of AIDS. Mollusca contagiosum, oral hairy leukoplakia, oral candidiasis, chronic ulcerating herpes simplex and Kaposi's sarcoma are strongly associated with advanced immunodeficiency (2). Effects that HIV infection may have on some skin conditions, for

Table 2. Sexual orientation of 38 HIV-infected patients treated at the City Institute for Skin and Venereal Diseases in Belgrade

Patients	N	(%)
Homosexual	31	81.6
Bisexual	2	5.2
Heterosexual	5	13.2

N - number of patients

Table 3. Number of dermatovenereologic diagnoses per patient among 38 HIV-infected patients treated at the City Institute for Skin and Venereal Diseases in Belgrade

Patients	N	(%)
Initiated HAART	34	89.5
Number of diagnoses		
one	27	71.0
two	5	13.2
three	6	15.8

N - number of patients; HAART - highly active retroviral therapy

Table 4. The prevalence of dermatovenereologic diseases in 38 HIV-infected patients

Diseases	N	Prevalence (%)
Anogenital warts	14	36.8
Syphilis	13	34.2
Folliculitis	4	10.5
Common warts	3	7.9
Dermatophyte infections	3	7.9
Molluscum contagiosum	2	5.2
Seborrhoeic dermatitis	2	5.2
Genital Herpes	2	5.2
Epidermoid cyst	2	5.2
Gonorrhea	2	5.2
Herpes zoster	2	5.2
Erythrasma	1	2.6
Onychomycosis	1	2.6
Pityriasis versicolor	1	2.6
Alopecia areata	1	2.6
Androgenetic alopecia	1	2.6

N - number of patients

example, psoriasis and leprosy, are less clarified. Over the past decade, HAART has dramatically altered the natural history of HIV infection, induced immune recovery, and decreased cutaneous manifestations of HIV infection (6, 10, 11).

The majority of our patients have sought treatment for suspected STIs. The most prevalent were anogenital warts and syphilis, but gonorrhea and genital herpes were diagnosed as well. In this study more than 80% of patients were men who have sex with men (MSM). Moreover, in regard to HIV transmission among newly diagnosed HIV infected persons registered in Serbia in the period from 2002 - 2010, there was a clear increasing trend among MSM: 57% of all reported HIV cases in 2010 versus 26% in 2002 (9). Recent studies have shown an increase in sexually transmitted infections among HIV-positive homosexual men (7, 12). In an outbreak of early syphilis registered at the City Institute for Skin and Venereal Diseases in Belgrade during the period from 2010 to 2012, of all patients, 76.5% were men who have sex with men (13).

In this study, 38.6% of patients had anogenital warts. In the study of Zancarano et al., anogenital warts (condyloma acuminatum) were the second most common dermatological condition in HIV infected patients with a prevalence of 11.5% (6). Human papillomavirus (HPV) prevalence and symptoms tend to increase with disease progression, and anal cancer is associated with HPV infection and receptive anal intercourse. However, it is more common in HIV-positive than in HIV-negative homosexual men [14]. These facts point to the importance of preventive cytological screening for anal lesions to reduce the burden of morbidity and mortality from anal cancer.

Syphilis was diagnosed in 1/3 of our patients and all of them were homosexuals. Several worldwide studies have reported syphilis outbreaks among MSM (15, 16, 17). The patients in our study had atypical presentations with multiple ulcers that are usually associated with HIV coinfection (18). Although they were aware of infection, patients reported recent high-risk behavior. These data indicate that HIV-infected patients with syphilis may be among the most important transmitters of HIV infection due to biologic effects of genital ulcerations, and aggravation due to continued risky behavior. Folliculitis was the next most prevalent skin disorder (10.5%) in our patients, which is in accordance with other studies where the prevalence ranged between 8% and 18% (6, 19).

The most common skin diseases diagnosed in our patients were also reported in several other studies. According to Zancarano et al., the prevalence of dermatophyte infection of 7.1% was similar with our results, while prevalences of seborrheic dermatitis and skin xerosis were 10.6% and 9.7%, respectively (6). In the study conducted in Bangkok, among 120 patients infected with HIV, the most prevalent skin disorder was xerosis (73.3%), followed by oral candidiasis (54.2%) and seborrhoic dermatitis (46.7%) (20). In a study of Kumarasamy et al., the most frequent diagnoses in HIV infected patients were dermatophytosis, papular pruritic dermatitis, alopecia and herpes zoster (4).

Although the pattern of skin disorders was comparable to previous reports, there was a significantly higher prevalence of STIs in our patients. According to Kalichman et al, persons with HIV/AIDS report high rates of morbidity and symptoms of STIs (21). In Western Europe, STIs have been disproportionately diagnosed among HIV-positive MSM in the post-HAART era (12). It may be explained by an increase in high risk behavior due to treatment optimism, growing population of sexually active HIV-positive MSM and HIV-positive homosexual men unaware of their HIV status.

Our findings together with others, highlight the need for education of sexually active persons with HIV about consequences of STIs, as well as about risks of transmission of drug resistant HIV strains, safe sex practice and consistent condom use. Furthermore, routine testing for STIs and anal cytology screening should be encouraged and offered to HIV-positive MSM.

Acknowledgement

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Abbreviations

HIV - human immunodeficiency virus
AIDS - acquired immunodeficiency syndrome
HAART - highly active antiretroviral therapy
STIs - sexually transmitted infections
MSM - men who have sex with men

Dermatoze i seksualno prenosive infekcije kod pacijenata sa HIV invekcijom/AIDS koji su pregledani u Gradskom zavodu za kožne i venerične bolesti u Beogradu: serija od 38 pacijenata

Sažetak

Uvod: U toku infekcije virusom humane imunodeficijencije (HIV – eng. *human immunodeficiency virus*) i kod pacijenata sa sindromom stečene imunodeficijencije (AIDS – engl. *acquired immunodeficiency syndrome*), mogu se javiti različita dermatološka oboljenja.
Cilj: Cilj rada bio je da se utvrdi prevalencija i vrsta kožnih i polnih bolesti kod osoba sa HIV/AIDS-om.
Materijal i metode: Ispitivanje je obuhvatilo sve osobe inficirane HIV-om koje su se konsekutivno javile dermatovenerologu u Gradskom zavodu za kožne i venerične bolesti u Beogradu u periodu od januara 2011. do juna 2012. godine.
Rezultati: Preko 80% pacijenata bili su muškarci koji su imali seksualne odnose sa muškarcima. Najveća prevalencija zabeležena je za anogenitalne bradavice (36,8%) i sifilis (34,2%), a potom za folikulitis (7,9%) i dermatofitne infekcije (7,9%).
Diskusija i zaključak: Visoka prevalencija polno prenosivih infekcija kod pacijenata inficiranih HIV-om, ukazala je na značaj edukacije o bezbednim seksualnim tehnikama, stalnoj upotrebi kondoma, posledicama polnih bolesti i rizicima transmisije rezistentnih sojeva HIV-a u ovoj populaciji.

Ključne reči

HIV; Kožne bolesti; Seksualno prenosive bolesti; Sindom stečene imunodeficijencije; Faktori rizika

Progressive Disseminated Superficial Actinic Porokeratosis: a Case Report with a Family History in Three Generations

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Abstract

Disseminated superficial actinic porokeratosis is the most common form of porokeratosis in adults, which develops in the third or fourth decade of life, but may also occur later or earlier, more frequently in females, particularly in countries with high sun exposure. Lesions are numerous, uniform, superficial with central atrophy, demarcated by a distinct peripheral ridge, and usually found on sun exposed areas or elsewhere. The disease is inherited as an autosomal dominant condition.

We present a 57-year-old retired woman. Her initial skin changes, affecting the face, developed in her thirties, and they have not changed their features since. In the following years, changes developed on the extensor surface of her arms and legs, with more prominent erythema, and then also on other parts of the body, including palms and soles, presenting as dark brown pigmented patches. Her mother had similar changes, and her daughter, who lives abroad, also has them.

On examination, the patient presented with facial lesions, patches 2-3 mm wide, with peripheral hyperpigmentation and a pale center. There were multiple, 2-3 mm wide, dark brown lesions on the extremities and trunk. The lesions were either flat or with atrophic center with darker filiform corneal rim. Pathohistolgical examination revealed a "cornoid lamella", which is pathognomonic for the diagnosis of porokeratosis. Auxiliary diagnostic methods were also used – dermoscopy and Gentian violet staining.

The patient was advised to avoid sun exposure and to apply photoprotective sunscreens.

In conclusion, this is a case report of a disseminated superficial actinic porokeratosis that affected three generations of a family. Our patient developed lesions on palms and soles as well. A review of available world literature shows that this is the second case report of disseminated superficial actinic porokeratosis with palmoplantar involvement.

Key words

Porokeratosis + genetics; Keratosis, Actinic; Keratoderma, Palmoplantar; Disease Progression; Risk Factors

Porokeratosis (P) is a heterogeneous, genetically determined keratinization disorder, characterized by circular lesions with central atrophy and distinct peripheral ridges, on histology corresponding to a "cornoid lamella" (1). Depending on the size, localization and number of lesions, there are several subtypes of porokeratosis (2). Since 1893, when Mibelli described the "classic" type of porokeratosis, which was named porokeratosis of Mibelli after him (3), and Respighi described the disseminated superficial type of the disease, several new forms have been described (4-7). These are: 1) porokeratosis of Mibelli (PM); 2) linear porokeratosis (LP); 3) disseminated superficial porokeratosis (DSP); 4) disseminated superficial actinic porokeratosis (DSAP); 5) disseminated palmoplantar porokeratosis (DPPP); 6) punctate palmoplantar porokeratosis (PPPP) and 7) porokeratosis ptychotropica (8, 9).

Also, facial, giant, reticular, hypertrophic veruccous morphologial forms of porokeratosis have been distinguished (10). PM, LP, PPPP are localized, and DSAP, DSP and DPPP are disseminated types of porokeratosis.

The term DSAP was suggested by Chernosky and Freeman in 1967 (11). This is the most common type of porokeratosis, usually occurring in the third or fourth decade of life, but depending on the underlying cause, it may also occur later or earlier (12). It is more common in females, particularly in countries with long periods of sunshine. At least 50% of patients experience exacerbations after exposure to sun or artificial light. Although lesions affect sun exposed areas, only 15% of patients have facial lesions (10). However, lesions may also occur on parts of the body not exposed to light. The initial lesions are keratotic papules, while marked annular lesions with atrophic center and peripheral keratotic ridge, and "cornoid lamella" which is characteristic for all types of porokeratosis, develop later.

We report a case of a patient presenting with a severe DSAP, in whom initial skin changes developed 27 years earlier, and in 1990, her and her mother's case reports were presented at the Dermatological Days in Paris (13).

Case report

We present a 57-year-old female, a retired nurse who pursues farming, with a history of facial skin lesions which appeared at the age of thirty. One year later, after seaside sunbathing, lesions spread over the extensor sides of her forearms, upper arms, and on the legs below the knee. They were more palpable than visible at the time. In the years to come, new lesions developed, the size of about 2-5 mm. The patient did not suffer from any other diseases.

In 2001, she had hepatitis B. She also developed gonarthrosis, hypertension, as well as ptosis; she was regularly taking antihypertensive drugs. The patient's mother had the same skin condition, high blood pressure and coxarthrosis. Her daughter developed spot-like darker "stains" around the mouth, while her son was healthy.

Dermatological status

The skin condition in 1990: embarrassing lesions/blotches, 2-3 mm wide, hyperpigmented on the periphery and paler in the center appeared on the face (Figure 1); lesions on the trunk (Figures 2 and 3) and extremities (Figures 4 and 5) were rather inconspicuous, more palpable than visible, about 2-3 mm wide. Generally, all lesions were skin colored, flat or mildly depressed with filiform

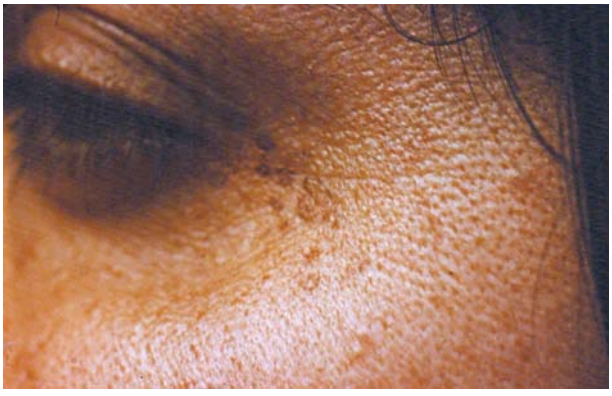

Figure 1. Facial lesions in 1990

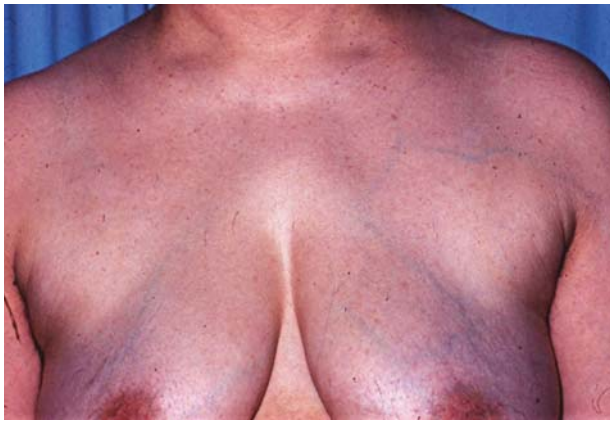

Figure 2. Lesions of the trunk in 1990

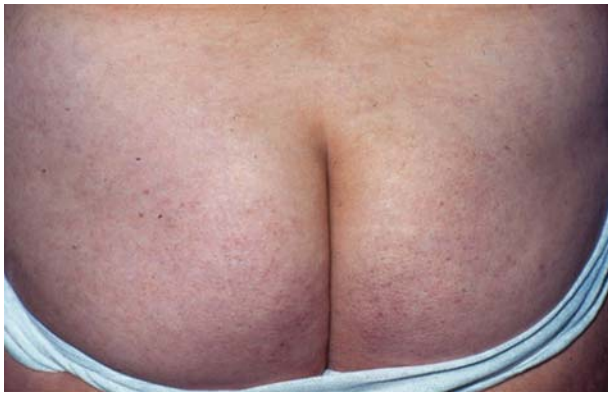

Figure 3. Lesions in the sacral region in 1990

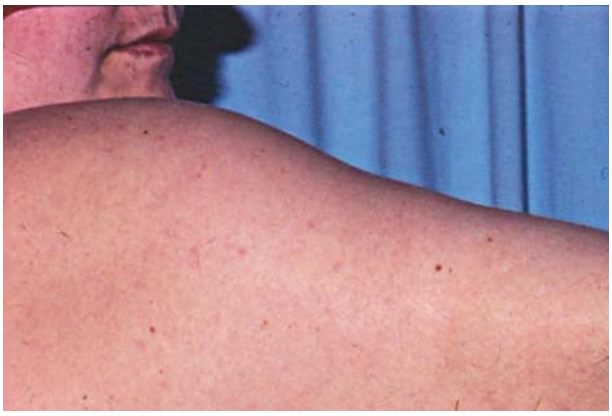

Figure 4. Lesions on the extensor surface of the upper arms in 1990

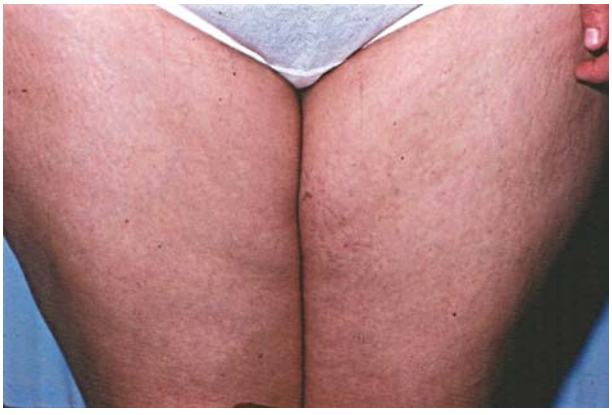

Figure 5. Lesions on the anterior thighs in 1990

cornoid lamella. No changes on the palms or soles were registered.

Current skin condition: dark pigmented circular lesions with atrophic center and keratotic ridge are present on the face (Figure 6) and the whole body (Figures 7 and 8); similar lesions affected the extremities (Figures 9 and 10), dorsal aspects of hands and both thenar and hypothenar sites as well. Hyperkeratosis, rhagades and erythema were present on palms and soles (Figures 11 and 12).

All relevant laboratory tests were within normal limits.

Histopathological analysis revealed features typical of porokeratosis, including cornoid lamella, irregular distribution of keratinocytes in the spinous layer, and lymphocyte perivascular infiltrates in the dermis (Figure 13).

Dermoscopy showed round structures in the form of a "white line" along the edge of each porokeratosis lesion, which is a characteristic

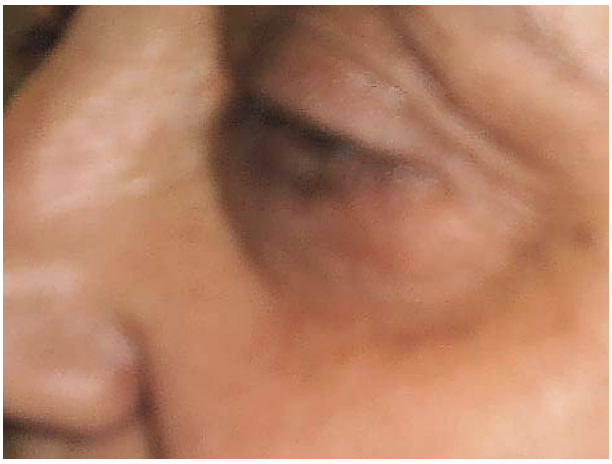

Figure 6. Facial lesions in 2013

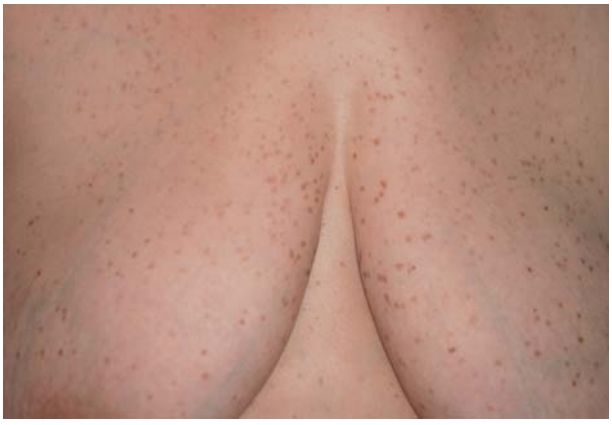

Figure 7. Lesions of the trunk in 2013

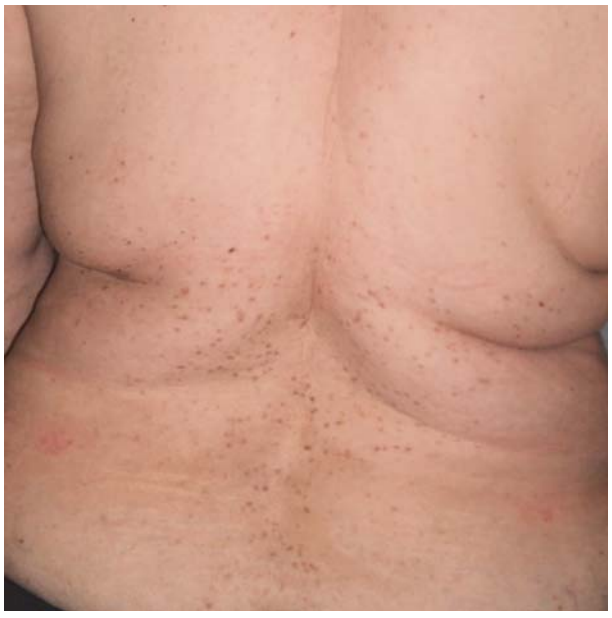

Figure 8. Lesions in the sacral region in 2013

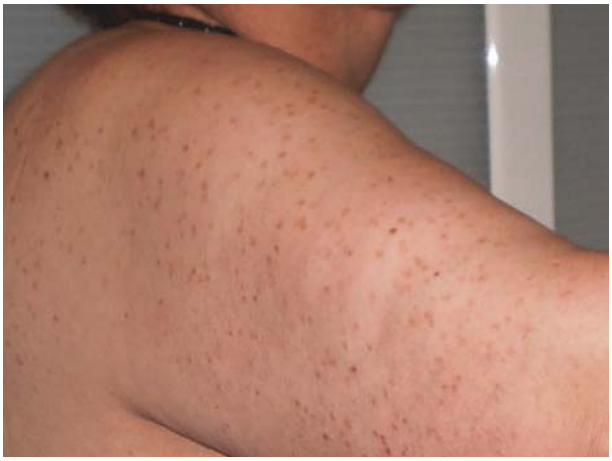

Figure 9. Lesions on the extensor surface of the upper arms in 2013

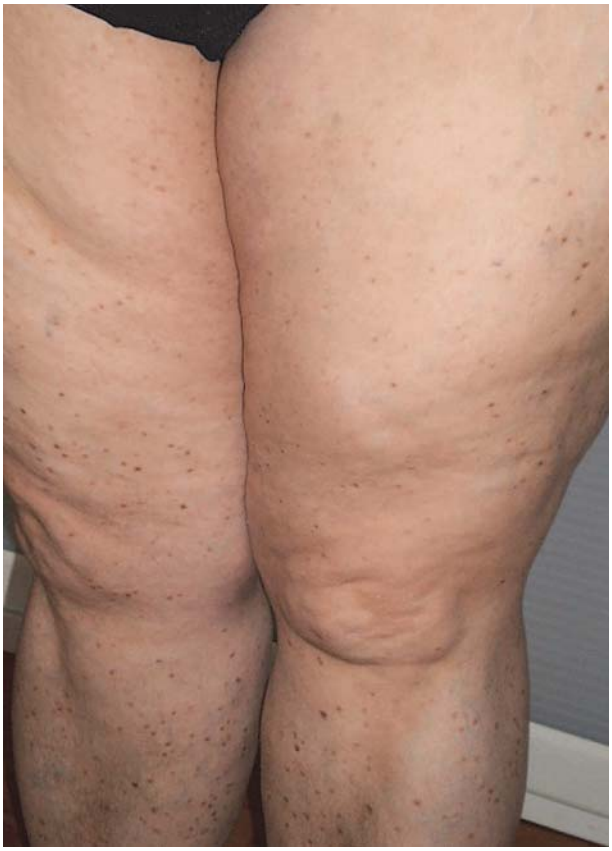

Figure 10. Lesions on the anterior thighs in 2013

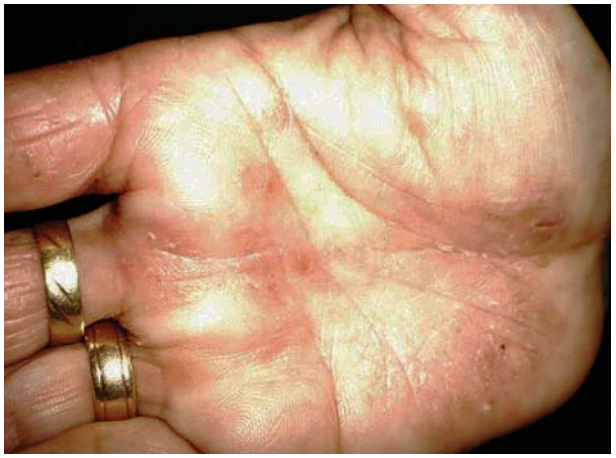

Figure 11. Palmar lesions in 2013

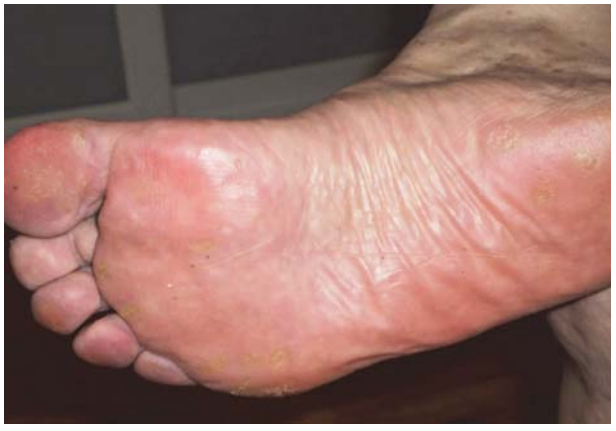

Figure 12. Plantar lesions in 2013

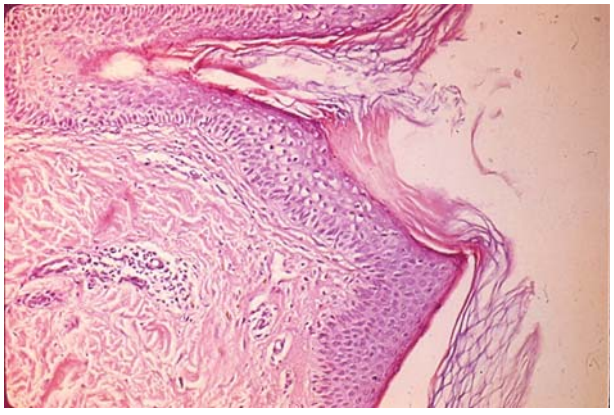

Figure 13. Histopathological findings

dermoscopy view of porokeratosis. They were identified at the periphery of the lesion along with brown pigmentation (globules and red spots) on the inside, and a double "white line" in some parts of the lesion. Structures of a single or double "white line" matched histologically the cornoid lamella and the red spots and globules the enlarged blood vessels (Figures 14 and 15).

Gentian violet staining was positive showing a marked violet staining of the edge of lesion (Figure 16).

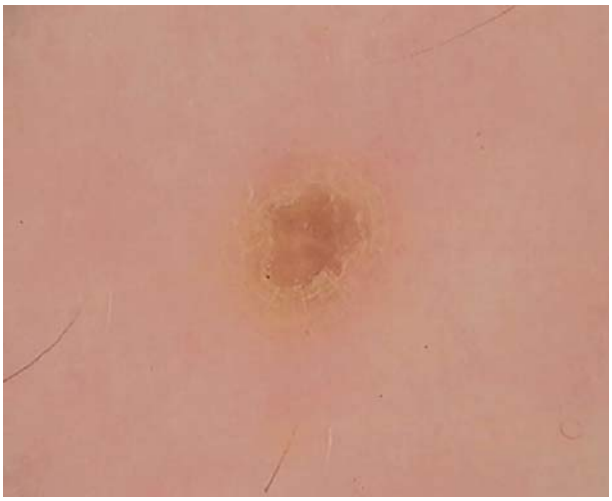

Figure 14. Dermoscopic finding

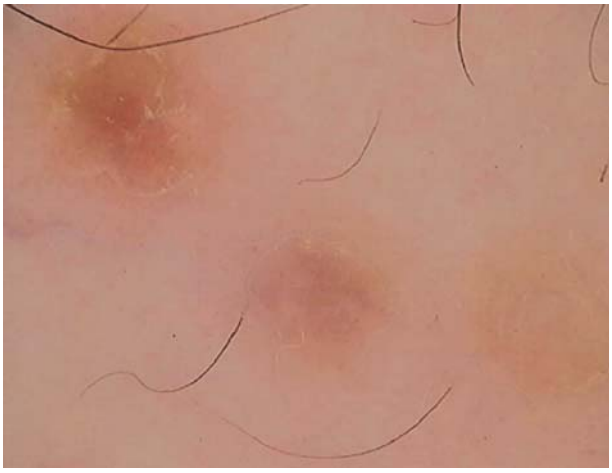

Figure 15. Dermoscopic findings

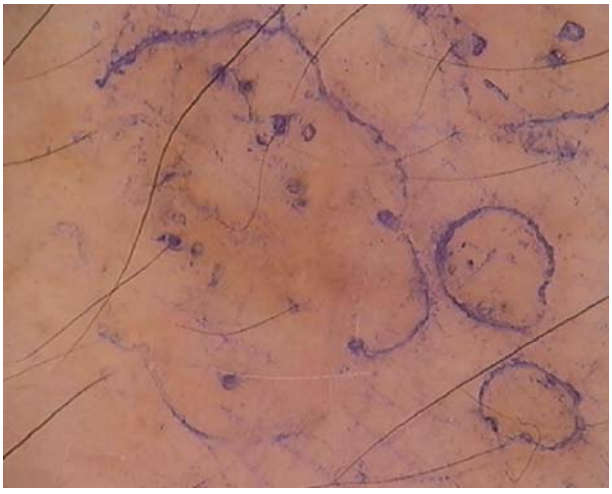

Figure 16. Gentian-violet staining

The patient had no complaints or any subjective symptoms, and she no longer worried about the lesions, not even for esthetic reasons. She was advised to avoid sun exposure, to use photoprotective sunscreens, and topical corticosteroids on the hands.

Discussion

The etiology and pathogenesis of porokeratosis have not been fully elucidated (14). An autosomal mode of inheritance with variable penetrance has been fairly well established for PM, DPPP, DSP and DSAP (15). Numerous genetic alterations have been indentified, and sometimes even p53 gene expression was altered (16). It is suggested that some clones of epidermal cells were inherited as mutants, the phenotype expression of which resulted from activation by exogenous trigger factors (14).

So far, 4 loci have been established for DSAP (DSAP1, DSAP2, DSAP3, DSAP4), one locus for PPPD and one for DSP (12, 17, 18), but a porokeratosis gene has not been identified (15). A pathological clone is present in a latent state, and some factors trigger its activation (18). Some predisposing and/or trigger factors have been identified for the development of porokeratosis: genetic predisposition, UV radiation, infectious agents, mechanical trauma and immunosuppression (due to therapy/transplantation) (10, 14, 19-24).

In the elderly (aged 70 to 90) the trigger factor, apart from UV radiation, can be age-related decreased immunocompetence (2). Diabetes mellitus may be associated with deterioration of immune competence of the elderly (18). It has even been suggested to classify porokeratosis as a subtype of DSAP in old population (2). In rare instances the following trigger factors have also been reported: anti-diabetic and antihypertensive medications, thiazides and antibiotics (2). Co-localization of P with other dermatoses, i.e. Lichen planus, is explained by isomorphic (Koebner) phenomenon, by some authors (25, 26).

Sporadic cases of DSAP (24) have been reported, as subsiding following topical application of 5% imiquimod or discontinuation of immunosuppressive medication.

DSAP is more or less frequently associated with other types of porokeratosis: DSAP with LP

and veruccous P (6); DSAP with warty P (29); DSAP with giant P (30), DSAP with LP and PP (31). Coexistence of LP and DSAP has also been reported (32-36). It has been suggested that simultaneous expression of two different genes due to loss of heterozygosity is responsible for coexsistence of various types of porokeratosis (37, 38). Squamous cell carcinoma may arise from lesions of porokeratosis; cases of basal cell carcinoma and Bowen's disease have also been described; malignant alterations have been reported in PM, LP, PPPP and DSP (39), and they are most common in LP. In patients with DSAP, squamous cell carcinoma is rare (40, 41). The prevalence of 19% and 3.4% has been reported in PL and DSAP, respectively (42). Porokeratosis is a genodermatosis with an increased malignant potential. The risk of malignant alterations is higher in wide, long-standing lesions and in elderly patients.

The diagnosis of DSAP is established based on clinical presentation, personal and family medical history, pathohistological findings, auxiliary methods such as dermoscopy (43, 44) and cornoid lamella staining with Gentian violet or toluidine blue to make it more visible (45, 46).

An important risk factor for the development of DSAP is chronic or occasional intensive sun exposure, or artificial UV irradiation (22). Our patient developed initial skin changes at the age of 30, on photo-exposed skin particularly the face, but later on, lesions progressed and affected non-exposed parts of the body, as well.

Her medical history revealed a significant deterioration after sunbathing and time spent at the seaside. The family history was, however, positive. DSAP occurred in three generations: herself, her mother and her daughter. The medical history of our patient suggests that DSAP occurred at the time when she was completely healthy, so effects of other triggers are ruled out.

Based on clinical examination and histopathological findings, differential diagnosis of porokeratosis included: actinic keratosis, psoriasis, lichen nitidus, hereditary punctate keratoderma, benign hamartoma of eccrine sudoriferous glands (10, 47).

In the available literature, we found only one report on palmar and plantar involvement in DSAP (31). In children's type of DSP, cases of DPPP have been reported. Can lesions on the hands and feet in our patient be explained as a pure coincidence of DSAP and PPPD, or can they be a part of DSAP?

DSAP usually has a poor therapeutic response to various treatment modalities (43). The course of the disease is progressive with potential malignant alterations. Topical treatment includes: salicylic acid, glycocorticoids, 5-fluorouracil, and retinoids for all types of the disease; 5% imiquimod cream is used in the treatment of PM, DPPP and genital P; vitamin D3 analogues for DSAP; and 3% diclofenac gel for DSAP and genital P. In systemic therapy, retinoids are highly recommended in the treatment of all types of P; photodynamic therapy in combination with CO2 laser for DSPA; surgical options include cryotherapy, electrocautery and curettage for small lesions; dermoabrasion for LP; ultrasound surgical aspiration for genital P; total excision for all types of P. Cryotherapy may yield positive results in localized forms such as LP (48). Sun protection is obligatory, as well as long follow-up of each patient in order to detect potential malignant alterations.

Conclusion

This is a case report of disseminated superficial actinic porokeratosis with a family history in three generations. The patient presented in this report developed lesions on palms and soles as well. As far as the available literature is concerned, this is the second case report of disseminated superficial actinic porokeratosis with palmoplatar involvement.

Abbreviations

DSAP - Disseminated superficial actinic porokeratosis
P - Porokeratosis
PM - Porokeratosis of Mibelli
LP – Linear porokeratosis
DSP - Disseminated superficial porokeratosis
DPPP - Disseminated palmoplantar porokeratosis
PPPP - Punctate palmoplantar porokeratosis
UV – Ultra violet
CO2 – Carbon dioxide

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Diseminovana superficijalna aktinička porokeratoza sa progresivnim tokom: prikaz slučaja u kome se bolest javila u tri generacije iste porodice

Sažetak

Uvod: Porokeratoza (P) jeste heterogena grupa genetski determinisanih poremećaja keratinizacije, koju karakterišu kružne lezije sa centralnom atrofijom i perifernim keratotičnim rubom koji histološki odgovara kornoidnoj lameli. Zavisno od veličine, lokalizacije i broja lezija, razlikuje se više podtipova P. Od 1893. godine, kada je Mibeli (Mibelli) opisao porokeratozu koja je po njemu dobila ime, registrovani su novi tipovi, to su: 1. Mibelijeva porokeratoza (Porokeratosis Mibelli – PM); 2. linearna porokeratoza (LP); 3. diseminovana superficijalna porokeratoza (DSP); 4. diseminovana superficijalna aktinička porokeratoza (DSAP); 5. diseminovana palmoplantarna porokeratoza (DPPP); 6. punktatna palmoplantarna porokeratoza (PPPP) i 7. ptihotropna prokeratoza. Takođe se govori o facijalnoj, džinovskoj, retikularnoj, hipertrofičnoj verukoznoj porokeratozi (10). PM, LP, PPPP su lokalizovane, a DSAP, DSP i DPPP su diseminovane porokeratoze.

Termin diseminovana superficijalna aktinična porokeratoza (DSAP) predložili su Černoski i Friman (Chernosky, Freeman) 1967. godine. To je najčešći oblik porokeratoze; obično se javlja u trećoj ili četvrtoj deceniji života ali, zavisno od uzroka, može nastati i ranije ili kasnije. Češća je kod žena, naročito u oblastima sa dugim periodima insolacije. Promene su lokalizovane na fotoeksponiranim regijama, ali na licu samo u 15% slučajeva. Mogu nastati i na fotoneeksponiranim delovima tela. Inicijalne lezije su keratotične papule, a kasnije nastaju naglašene anularne lezije sa atrofičnim centrom i keratotičnim rubom, kornoidnom lamelom koja je karakteristična za sve podtipove porokeratoze.

Prikazujemo slučaj bolesnice sa izraženom slikom

DSAP koja je prve promene na koži dobila pre 27 godina, a 1990. godine, slučaj ove bolesnice i njene majke prikazan je na Dermatološkim danima u Parizu.

Prikaz bolesnika: Bolesnica, 57 godina, medicinska sestra u penziji, bavi se i poljoprivredom.

Prve promene na koži lica javile su joj se u 30. godini života. Naredne godine, posle sunčanja i boravka na moru, promene su se javile na ekstenzornim stranama nadlaktica i podlakica i na potkolenicama. Tada su bile više palpabilne nego vidljive. Narednih godina javljale su se nove lezije veličine 2–5 mm. U to vreme nije bolovala od drugih bolesti. Tokom 2001. godine imala je hepatitis B, potom se kod nje razvila artroza oba zgloba kuka i dobila je povišen krvni pritisak. Majka je imala istu bolest kože, a ćerka tačkaste tamnije fleke oko usana.

U radu je uporedo prikazano stanje na koži 1990. i 2013. godine prilikom poslednjeg pregleda. Stanje na koži 1990. godine: promene na licu u vidu mrlja veličine 2-3 mm, hiperpigmentovane na periferiji i svetlije u centru, teško estetski prihvatljive; na trupu i ekstremitetima promene diskretne, više palpabilne nego vidljive 2-3 mm u prečniku, ravne ili lako deprimirane površine sa filiformnom kornoidnom ivicom klinički nepromenjene boje kože; promene na dlanovima i tabanima nisu registrovane.

Sadašnje stanje (2013. godina): na licu i čitavom telu tamnopigmentovane kružne lezije atrofičnog centra sa keratotičnom ivicom, promene istih osobina na ekstremitetima dorzumima šaka, tenaru i hipotenaru; na ostaloj koži šaka hiperkeratotične naslage, ragade i eritem; na tabanima blaga hiperkeratoza i eritem.

Svi rezultati osnovnih laboratorijskih analiza bili su u granicama referentnih vrednosti.

Patohistološka analiza bioptiranog uzorka promene na koži potvrdila je dijagnozu nalazom karakterističnim za porokeratozu, uključujući i kornoidnu lamelu, nepravilno raspoređene keratinocite u spinoznom sloju i limfocitni perivaskularni infiltrat u dermisu.

Dermoskopski pregled (struktura tzv. „belog traga“ prisutna na periferiji lezije sa braonkastom pigmentacijom prema centralnim delovima lezije i sa dvostrukom strukturom tipa „duplog belog traga“ na pojedinim delovima promene; crvene tačke i globule (krvni sudovi u centralnim delovima) i bojenje gencijanom violet (izrazita ljubičasta prebojenost rožaste ivice), kao pomoćne dijagnostičke metode, takođe su potvrdile dijagnozu porokeratoze.

U terapiji je savetovano izbegavanje izlaganja suncu i primena fotoprotektivnih krema, a za promene na koži naročito na šakama kortikosteridne masti.

Diskusija: Etiologija i patogeneza porokeratoze nisu potpuno razjašnjene. Autozomalni način nasleđivanja sa varijabilnom penetracijom je dosta dobro utvrđen za pojedine tipove porokeratoze : PM, DPP, DSP,DSAP. Pokazalo se da su neki klonovi epidermalnih ćelija nasleđeni kao mutant, čija je fenotipska ekspresija rezultat aktivacija egzogenih okidačkih faktora.

Značajan faktor za nastank DSAP je hronično ili povremeno intezivno izlaganje sunčevoj svetlosti ili veštačkim izvorima sunčevih zraka. Naša bolesnica je prve promene dobila na licu u 30. godini života, zatim na fotoeksponiranim, pa progresivno i na fotoneeksponiranim delovima tela. U anamnezi ima podatak o značajnom pogoršanju posle sunčanja i boravka na moru. DSAP može biti udružen sa ostalim tipovima: DSAP sa LP i verukoznom P; DSAP sa verukoznom P; DSAP sa gigantskom P, DSAP sa LP i PP. Koegzistencija LP i DSAP takođe je opisana.

Porokeratoza se smatra prekursorom za spinocelularni karcinom kože, a opisana je i pojava bazocelualrnog karcinoma i Bovenove (Bowen) bolesti. Kod bolesnika sa DSAP spinocelularni karcinom nastaje ređe u odnosu na LP (3,4 : 19%). Oboleli sa DSAP obično pokazuju slab terapijski odgovor na različite modalitete tretmana. Za topikalnu primenu koriste se salicilna kiselina, glikokortikoidi, 5-fluorouracil, analozi vitamina D3, diklofenak gel (3%); za sistemsku primenu koriste se retinoidi, a za fizikalnu fotodinamička terapija, eventualno CO_2 laser. Kod lokalizovanih formi, mogla bi se koristiti krioterapija koja je dala dobre rezultate kod linearne porokeratoze. Obavezno se savetuje zaštita od sunca i praćenje bolesnika, uz adekvatan tretman u slučaju eventualne maligne alteracije.

Zaključak: Prikazan je slučaj diseminovane superficijalne aktiničke porokeratoze s porodičnim

javljanjem u tri različite generacije. Kod obolele osobe prikazane u ovom radu, bolest je zahvatila i kožu šaka i stopala. Prema nama dostupnoj literaturi, ovo predstavlja drugi opisani slučaj diseminovane superficijalne aktiničke porokeratoze sa palmoplantarnim promenama.

Ključne reči

Porokeratoza + genetika; Aktinična keratoza; Palmoplantarna keratoderma; Tok bolesti; Faktori rizika

Porphyria Cutanea Tarda – a Case Report

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Abstract

Porphyria cutanea tarda is a metabolic disorder that results from a reduced enzymatic activity of uroporphyrinogen decarboxylase. It is the commonest chronic porphyria. Two types of this disease have been reported up to now: acquired (Type 1, 80%) and inherited (Type 2, 20%) an autosomal dominant pattern with low clinical penetrance. Both types are associated with haemochromatosis, alcohol abuse, estrogens, iron overload, hepatitis C virus infection, and halogenated aromatic hydrocarbons causing deficiency of the uroporphyrinogen decarboxylase enzyme in the liver.
In this case report we described a 23-year-old woman with increased hair growth on the face and neck, who visited an outpatient dermatology clinic for laser hair removal due to excessive hair growth on the face and neck during the last eight years (Figures 1, 2). Four laser treatments were carried out with incomplete effects. After the fourth laser hair removal treatment, a small sore on the tip of the nose was observed. The patient used oral contraceptive pills during the past 8 months. No additional medications were taken. The diagnosis of porphyria cutanea tarda was confirmed by specific biochemical analyses, since increased excretion of uroporphyrin and coproporphyrin were detected. After discontinuation of drospirenone and ethinyl estradiol (YazÒ tablets) a gradual clinical and laboratory improvement was noticed suggesting a causative role of this drug. There are many published reports discussing and describing estrogens as contraceptive agents, hormone supplements for postmenopausal replacement therapy in females, and adjunctive hormonal therapy in males with prostatic carcinoma, being the probable trigger of porphyria cutanea tarda. However, the mechanisms by which estrogens exert their effects on disease expression have not yet been fully clarified. Conclusion: this case report points to the importance of hypertrichosis as the first manifestation of porphyria cutanea tarda, since it may be a long lasting sign before the onset of other clinical symptoms of the disese.

Key words

Porphyrias; Estrogens + adverse effects; Hypertrichosis; Hair Removal; Antimalarials

Porphyrias are a group of clinically and genetically heterogeneous metabolic disorders that result from either an inherited or an acquired dysfunction of enzymes crucial for heme biosynthesis (1). Porphyria cutanea tarda (PCT) is the most common type of porphyria worldwide and its prevalence is estimated to be 1:10.000 with an equal sex ratio. Age of onset is usually around the ages of 30-40, not before puberty (2). There are at least two clinically similar forms that can currently be distinguished, both associated with decreased activity of uroporphyrinogen decarboxylase (UROD) enzyme in the liver: acquired-sporadic form (PCT type 1, 80%), and hereditary PCT (type 2, 20%), also referred to as familial form (3, 4). A high degree of molecular heterogeneity has been documented in familial PCT, since more than 105 different mutations in the UROD gene (mapped to chromosomal region 1p34) have been identified in patients with type 2 PCT (5). However, the rising incidence of PCT in females is probably due to

widespread use of estrogens in oral contraceptives as well as in other hormone supplements (6).

The disease was first recognized in the 1930s, by Waldenström, who identified a group of patients with excessive porphyrins in urine, skin lesions on sun exposed areas and a late ("tarda") onset in adulthood, so he named the disease "porphyria cutanea tarda" (7). The disease is characterized by skin photosensitivity with blistering on sun-exposed areas, skin fragility, hyperpigmentation or hypopigmentation and hypertrichosis (8).

Case report

We present a 23-year-old female patient who visited an outpatient dermatology clinic for laser hair removal due to excessive hair growth on the face and neck during the last eight years (Figures 1, 2). Four laser treatments were carried out with incomplete effects, and during the fifth visit, a sore was observed on the tip of the nose. After additional examination, the patient explained that she developed repeated blisters on the face and hands which healed spontaneously leaving scars at the age of 7 and 19, usually after prolonged sun exposure (Figures 3, 4). At the age of 15, she noticed excessive hair growth on the face and neck and darker urine. The patient was using combined oral contraceptives containing drospirenone and ethinyl estradiol (Yaz$^{©}$) during the last eight months before hospitalization. Also, during the last two years before admission to our clinic, the patient was observed by a gastroenterologist due to occasional dull pain in the upper abdomen and triple elevated serum transaminaze levels, higher urine and serum copper and ferritin levels. Abdominal

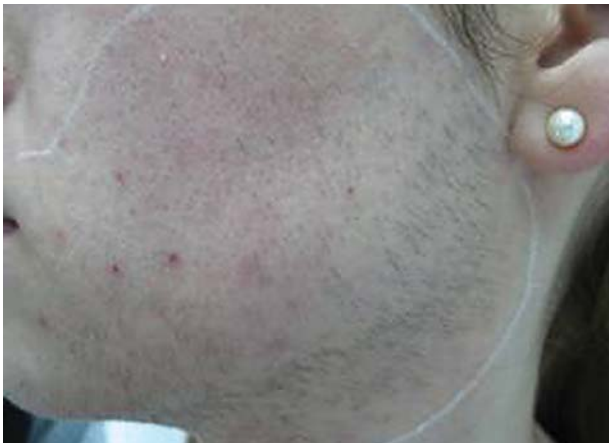

Figure 1. Hypertrichosis of the malar regions

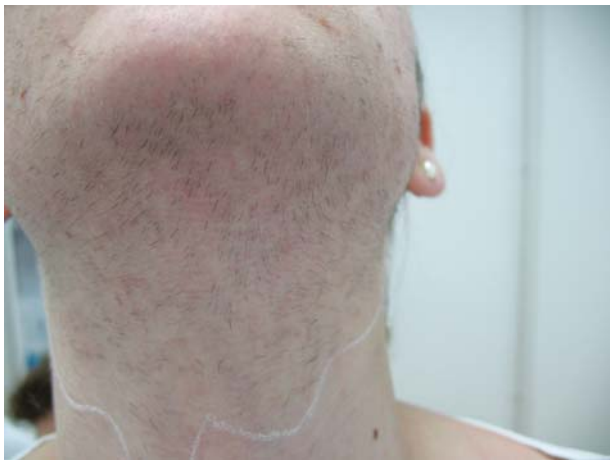

Figure 2. Hypertrichosis on the neck

ultrasound was within normal limits, except for two gallbladder concrements. There was no prior history of exposure to other drugs, alcohol, or viral hepatitis, and no evidence of porphyria or hypertrichosis in family members.

The laboratory analysis showed increased serum levels of aspartate aminotransferase (AST) 162 U/l (n.v. 0-34), alanine aminotransferase (ALT) 210 U/l (n.v. 7-49), and ferritin 470 mg/l (n.v. 20-280), as well as 24-urine copper 0.122 mg/24h (n.v. <0.05 mg/l). Urinary porphyrin excretion analysis revealed markedly elevated levels of total porphyrins up to 9023 μg/24 h (n.v. < 150). Full blood cell count, serum biochemistry studies, urea and creatinine, iron kinetics, ELISA- tests for hepatitis B surface antigen (HbsAg), anti-hepatitis C virus (HCV) antibodies, anti-human immunodeficiency virus-1 (HIV-1) and anti-HIV-2 antibodies, antimitochondrial, anti-smooth muscle and antinuclear antibodies, as well as abdominal ultrasound were negative or within normal limits. Direct immunofluorescence examination of the skin biopsy sample revealed deposition of fibrinogen at the dermo-epidermal junction and around blood vessels.

Histopathological examination of the skin lesion biopsy specimen from the hand showed typical early leasions in porphyria cutanea tarda (Figure 5), while histopathological examination of the liver biopsy revealed infiltration and mild periportal inflammation which was predominantly mononuclear. Also, iron deposits were present in periportal macrophage areas as well as in smaller groups of periportal hepatocytes (Figure 6).

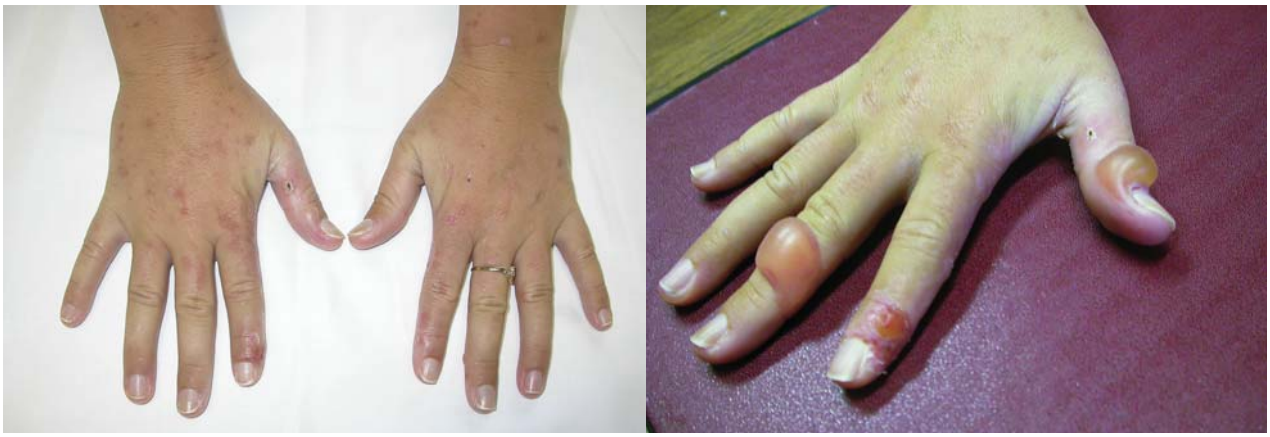

Figure 3. and Figure 4. Tense bullae on the dorsal side of the middle finger and thumb; erosion on the first finger

Clinical, histological, and laboratory findings were consistent with the diagnosis of PTC. Oral contraceptives were discontinued and treatment with hydroxichloroquine (200 mg 2x per week) and periodic phlebotomy of 300-500 ml with a consultation of a hematologist were initiated. Clinical improvement was apparent after four weeks, evidenced by the absence of new lesions. Four months later, the patient presented with a lighter urine color and reduction of uroporphyrin and coproporphyrin levels. After 3 years of follow up at our department there are no clinical or laboratory signs of PTC. Results of repeated laboratory tests are listed in Table 1.

Discussion

Porphyria cutanea tarda is the most common type of porphyria. It belongs to the group of chronic porphyrias and has four different forms: PCT,

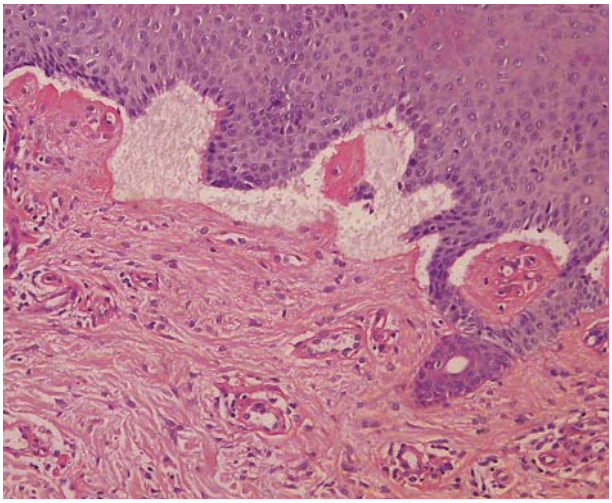

Figure 5. Separation of the epidermis from the dermis in a one segment with a lobular proliferation of capillaries in PAS positive upper dermis (PASx50)

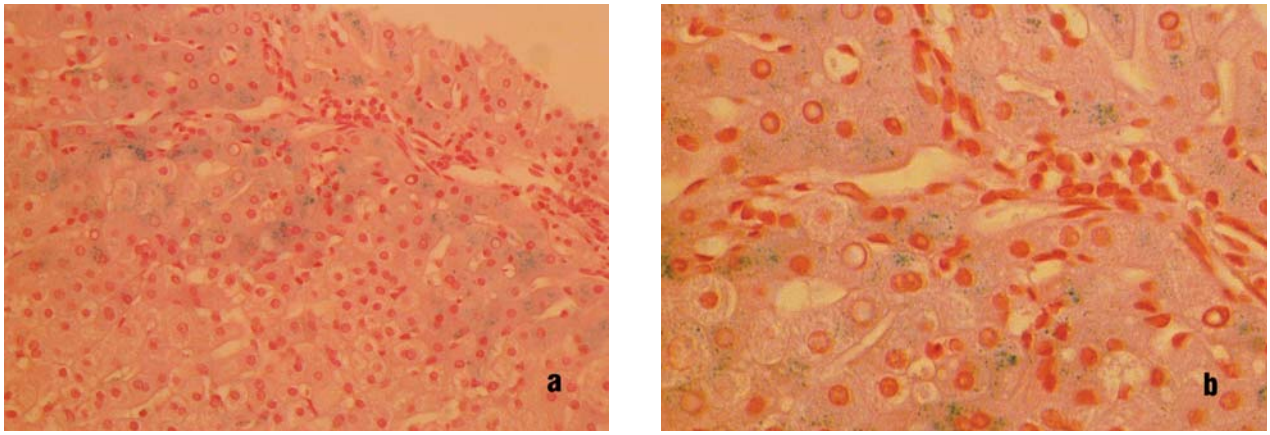

Figure 6. Iron deposits within macrophages and in small groups of periportal localized hepatocytes: a) Perl's iron stain x200; b) Perl's iron stain x400

Table 1. Laboratory test results during the follow-up

Follow-up period	Iron µmol/l (n.v. 9-31)	TIBC µmol/l (n.v. 48-80)	UIBC µmol/l (n.v. 48-80)	Ferritin µg/l (n.v. <280)	ALT U/l (n.v. 7-49)	AST U/l (n.v. 0- 34)	E x1012/L (n.v. 3.80-5.80)	Hgb g/L (n.v. 115-165)	URPOR µmol/24h (n.v <1.2)	COPOR µmol/24h (n.v <0.18)
After 3 months	18.1	54.5	36.4	55.9	42	33	4.49	161	8.8	0.5
After 6 months	6.9	75.1	68.2	7.1	27	33	3.94	118	0	0.1
After 9 months	12.1	60	47.9	6.8	29	33	4.50	120	0	0
After 12 months	12.5	ND	ND	9.4	35	36	4.86	134	0	0
After 24 months	18.7	53	34.2	33.3	16	20	4.63	137	ND	ND
After 36 months	9.6	ND	ND	5.1	18	23	4.33	117	0	0.08

TIBC - total iron bind capacity; UIBC - unsaturated iron bind capacity; ALT - alanine aminotransferase; AST - aspartate aminotransferase; E - eosinophils; Hgb - haemoglobin; URPOR - uroporphyrin; COPOR - coproporphyrin; n.v. - normal values; n – normally; ND - not done

hepatoerythropoietic porphyria (HEP), erythropoietic protoporphyria (EPP) and congenital erythropoietic porphyria (CEP) (4). PTC belongs to the group of cutaneous and chronic hepatic porphyrias (2).

This metabolic disorder results from a decreased catalytic activity of uroporphyrinogen decarboxylase (UROD) which is the fifth enzyme in heme biosynthesis (7, 9). In type 1 PCT, UROD deficiency is restricted to the liver. Opposite to this, in type 2 PCT, decreased levels of residual UROD activity, by approximately 50%, are found in all tissues, including red blood cells and skin fibroblasts (1b,1f).

Approximately 80% of all cases of porphyria cutanea tarda are acquired (4, 10, 11, 12), and type 2 PCT is known as familial (4, 13). However, not every PTC patient with positive family history will necessarily suffer from type 2 PTC, because the penetrance of this autosomal dominant form is less then 10%. Thus, type 3 PCT with normal erythrocyte UROD activities and familial occurrence has been suggested (2, 6). Biochemically, PTC is characterized by eleveted levels of porphyrins, principally by hepatic accumulation of uroporphyrin, oxidized substrate of UROD, which circulates in plazma and urine. When clinically manifested, the residual UROD activity in PTC is 25% of the normal level or less (6). The half-normal enzyme activity in patients with the type 2 PTC represents a significant predisposing factor, but is insufficient by itself to cause symptoms of PCT. Other genetic and environmental factors contribute to susceptibility in both types 1 and 2 PCT. Low level enzyme activity is caused by iron-dependent oxidation of uroporphyrinogen to uroporphomethene, which acts as a competitive inhibitor of UROD in the liver (2, 6). Thus, iron overload acts as a causative factor and as a therapeutic target. Serum iron and ferritin levels are elevated or in the upper normal range, but in clinically overt PCT, iron overload in the liver is present in basically all patients, like in our patient, while elevation of plasma iron is found only in up to one-half of affected individuals (2).

Numerous agents and conditions are known to contribute to the development of PTC: excess hepatic iron such as haemochromatosis - causing

polymorphisms in cytochromes (CYP1A2) and transferrin receptor 1 gene (TFRC) mutations, commonly present in patients with types 1 and 2 PCT; hepatitis C and HIV infections, as well as excessive alcohol intake; all the aforementioned may increase intestinal iron absorption by decreasing hepcidin production in hepatocytes; exposure to estrogens in women, and in men receiving adjunctive estrogen therapy in the treatment of prostate carcinoma; hexachlorbenzene and hemodialysis in patients with renal failure (4). The increased hepatic iron and oxidative stress leads to the formation of the enzyme inhibitor and oxidation of porphyrinogens to porphyrins (4). Histopathological examination of the liver biopsy revealed iron deposition in our patient.

Chronic porphyrias are characterized by the development of mild-to-severe chronic cutaneous lesions, usually after sun exposure. Uroporphyrin is responsible for the skin photosensitivity in the affected individuals. Other signs include skin fragility as well as blistering, erosions, crusts, milia and scar formation on sun-exposed areas on the trunk and extremities. Additionally, hyperpigmentation, hypertrichosis, sclerodermoid plaques, scarring alopecia and onycholysis may be observed (14). Generally, histopathologic skin examination does not contribute to confirming the presumptive diagnosis (2), but in our patient it pointed to the early lesions in porphyria cutanea tarda.

The diagnosis of PCT can be confirmed by specific biochemical analyses, since an increased excretion of uroporphyrin and coproporphyrin can be detected, like in our patient (2, 6). Measurement of erythrocyte UROD activity, as a screening technique to distinguish type 1 and type 2 PCT, apparently is not very reliable, because some patients with type 2 PCT may reveal residual UROD activities which may overlap with the lowest values found in patients with type 1 PCT (2). Additional molecular genetic analysis may be helpful not only in individuals with erythrocyte UROD activity in an intermediate range, but is also recommended for setting the diagnosis in patients with no family history, since they may have predisposing UROD mutations (3). Unfortunately, this genetic analysis was not available in our patient.

Classic PCT should be distinguished from epidermolysis bullosa acquisita, polymorphous light eruption, phototoxic and bullous drug eruptions (by measuring urinary and stool porphyrins), as well as other types of cutaneous porphyrias that manifest with blistering: variegate porphyria (acute course), hereditary coproporphyria (increased coproporphirins in urine and feces), mild variants of HEP (onset in early childhood), CEP (fluorescent erythrocytes), EPP (porphyrins increased in fesec but not in urine) and pseudoporphyria cutanea tarda (2, 4). The latter is associated with the use of specific drugs: non-steroidal antiinflammatory drugs (e.g. naproxen, nabumetone, and ketoprofen), furosemide, antibiotics (e.g. tetracyclines and nalidixic acid) and retinoids (6).

In our case, we considered oral contraceptive pills to be the causative agent responsible for exacerbation of clinically asymptomatic PTC, especially after clinical improvement that started after they were discontinued. The mechanism by which estrogens induce PTC is still unknown and the onset of PTC ranges from two months to seven years after initiation of estrogen therapy (15). This latency period was consistent with a delay in onset of symptoms which lasted about 8 months in our patient. Hypertrichosis was the leading symptom during the last eight years in our patient and the reason for laser hair removal treatment. Also, hypertrichosis was an indication for introduction of oral contraceptives, consequently leading to exacerbation and clinical manifestations of PCT. Hypertrichosis may be the first diagnostic sign of PTC (16, 17). Kapoor et al. described a female patient with hepatitis C infection and hypertrichosis that persisted for 29 years before other clinical manifestations of PCT developed (17). Facial hypertrichosis usually develops gradually and it is more apparent in females. The thickness, color and density of these hairs vary from person to person. These are particularly prominent along the temples and the cheeks, but may occasionally involve the trunk and extremities, and may continue to grow. Hypertrichosis may also be a symptom of PTC in women and young children. Some Turkish reports of hexachlorbenzene poisoning described children as “monkey-children”. The mechanism of this phenomenon is unknown; it is believed that the surface receptors of growth factors for hair bulb keratinocytes are activated by the dual action of light and porphyrins (18).

Effective treatments for PTC include: sun

avoidance, use of sunscreens and elimination of the underlying cause like alcohol abuse, discontinuation of estrogen therapy (19), or treatment of hepatitis C with interferon-alpha (20). However, venesection 300 - 500 ml every two weeks, and low dose antimalarial agents are usually required. Venesection leads to resolution of blisters within 2-3 months, and normalization of porphyrin concentrations within 13 months. At that point, treatment is usually discontinued. Antimalarial agents (chloroquine or hydroxychloroquine twice weekly) are safe, cheap, convenient and effective in the treatment of PTC, resolving blistering and skin fragility within 6 months and normalizing urinary porphyrin excretion after 6-15 months (21-27). Our patient responded well to the treatment. However, it has recently been shown that the genetic background of PCT patients, particularly the presence of common hemochromatosis gene mutations, C282Y and H63D, may predict the outcome of chloroquine treatment: PCT patients homozygous for C282Y seemed to retain high serum iron, ferritin, and transferring level and failed to respond to chloroquine therapy (28). Hypertrichosis usually resolves slowly compared to other clinical manifestations (24). Long-term follow-up is necessary for all patients with PTC.

Conclusion

This case highlights the importance of a detailed clinical history for all patients with signs of hypertrichosis (not hirsutism) undergoing laser hair removal. They should be routinely tested for porphyria, since hypertrichosis, often the reason for female patients to visit dermatologist may be the initial symptom of porphyria cutanea tarda.

Abbreviations

PCT - porphyria cutanea tarda
UROD - uroporphyrinogen decarboxylase
AST - aspartate aminotransferase
ALT - alanine aminotransferase
ELISA - enzyme-linked immunosorbent assay
HbsAg - hepatitis B surface antigen
HCV - hepatitis C virus
HIV - human immunodeficiency virus
TIBC - total iron bind capacity
UIBC - unsaturated iron bind capacity
E - eosinophils
Hgb - haemoglobin
URPOR - uroporhyrin
COPOR - coproporphyrin
HEP - hepatoerythropoietic porphyria
EPP - erythropoietic protoporphyria
CEP - congenital erythropoietic porphyria
CYP - cytochrome P
TFRC - transferring receptor 1 gene

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Porfirija kutanea tarda - prikaz slučaja

Sažetak

Uvod: Porfirija kutanea tarda (PCT) metabolički je poremećaj koji nastaje kao rezultat smanjene aktivnosti uroporfirinogen dekarboksilaze. Opisuju se dva tipa PCT: stečeni, tzv. izolovani ili tip I, koji se javlja češće, kod oko 80% svih obolelih i nasledni, familijarni ili tip II koji se nasleđuje dominantno ali sa malom penetracijom inkriminisanog gena. Oba tipa se javljaju povezano sa određenim, tzv. faktorima rizika ili deklanširajućim faktorima, kao što su: alkohol, estrogeni, prezasićenost gvožđem, infekcija virusom hepatitisa C, izloženost halogenim aromatičnim ugljovodonicima koji svi uzrokuju smanjenje enzima uroporfirinogen dekarboksilaze (UROD) u jetri. U PCT je utvrđen visok nivo molekularne heterogenosti s obzirom da je kod pacijenata sa PCT tip II do danas utvrđeno više od 105 različitih mutacija gena odgovornog za sintezu UROD enzima (gen mapiran na hromozomskoj regiji 1p34). Ipak, rastuća incidencija PCT kod žena se pripisuje upotrebi estrogena kako u obliku tableta za kontracepciju tako i u okviru suplementarne hormonske terapije.

Prikaz slučaja: U radu je prikazan slučaj osobe ženskog pola, stare 23 godine, kod koje su zbog hirzutizma na licu i vratu koji je bio prisutan u poslednjih osam godina, sprovedena četiri tretmana aleksandritnim laserom. Posle četiri tretmana, manifestovala se ranica na vrhu nosa. Nakon detaljno uzete anamneze, pacijentkinja je navela da su joj se na koži lica u periodu 7–19. godine povremeno javljali vodeni plikčići, i to na koži lica i šaka. Promene su se javljale naočito u vezi s povećanom i produženom ekspozicijom suncu, a spontano su nestajale ostavljajući blage ožiljke. U 15. godini života primetila je povećanu kosmatost na licu i na vratu, kao i tamnu boju mokraće. Poslednje dve godine pre nego što je došla na pregled kod nas, pacijentkinja se javila gastroenterologu zbog povremenih tupih bolova u predelu gornjeg abdomena koji su bili praćeni trostrukim povećenjem serumskih transaminaza, povećanim nivoom bakra u urinu i serumu i povećanim nivoom feritina u serumu. Ultrasonografski pregled gornjeg abdomena je otkrio samo dva konkrementa u žučnoj kesici. Anamneza u smislu uzimanja drugih lekova, potrošnje alkohola ili preležanog virusnog hepatitisa bila je negativna. Porodična anamneza, u smislu prisustva porfirije i povećane kosmatosti (hipertrihoze) kod srodnika, bila je negativna. Laboratorijski nalazi koji su odstupali od uobičajenih fizioloških vrednosti bili su: povišena vrednost asparataminotransferaze i alanin-aminotransferaze, feritina u serumu; povišene vrednosti bakra u 24-časovnom urinu; 60 puta povećan nivo porfirina i nivo koproporfirina u 24-časovnom urinu. Histopatološki pregled bioptiranog uzorka obolele kože sa nadlanice odgovarao je ranim lezijama kod PCT, a histopatološki pregled bioptiranog uzorka jetre je pored

blagog periportalnog zapaljenskog mononuklearnog infiltrata otkrio depozite gvožđa u periportalnom makrofagnom prostoru kao i u malim grupama periportalno lokalizovanih hepatocita. Pacijentkinja je bila na terapiji oralnim kontraceptivima tokom poslednjih 8 meseci. Nije bilo upotrebe drugih lekova. Nakon isključivanja drospirenona i etinilestradiola (Yaz tbl.), primećeno je postepeno kliničko i laboratorijsko poboljšanje koje je ukazivalo na kauzalnu ulogu leka.
Dijagnoza PCT postavljena je na osnovu kliničkog, laboratorijskog i histopatološkog pregleda.
Lečenje je započeto ukidanjem oralnog kontraceptiva i niskim dozama antimalarika hidroksihlorokvina (200 mg 2 x nedeljno) i periodičnim flebotomijama (300–500 ml u početku uz konsultaciju hematologa). Kliničko poboljšanje bilo je evidentno 4 nedelje nakon započinjanja lečenja i manifestovalo se sledećim: prestanak pojave novih lezija; svetlija boja mokraće; smanjenje uroporfirina i koproporfirina u 24-časovnom urinu. Sve vreme tokom naredne tri godine, kada je pacijentkinja redovno klinički i laboratorijski kontrolisana, nije bilo recidiva tj. pojava novih promena na koži i laboratorijskih odstupanja.
Diskusija: Treba naglasiti da negativna porodična anamneza ne isključuje postojanje tipa II PCT, s obzirom na nisku penetrantnost mutacije PCT gena u ovom autozomno-dominantno nasledom obliku bolesti. Tako su pojedini autori definisali tip III PCT u kome oboleli imaju normalan nivo UROD enzimske aktivnosti u eritrocitima a imaju istovremeno obolele srodnike u porodici. Biohemijski PCT karakterišu povišene vrednosti porfirina (u serumu i urinu) i to prvenstveno zbog povećane akumulacije uroporfirina u jetri. Uroporfirini predstavljaju supstrat na čiju oksidaciju utiče UROD enzim, a koji u PCT cirkuliše u povećanim količinama u plazmi i urinu. Kod klinički manifestne PCT, aktivnost UROD enzima mora biti manja od 25% (po nekima manja i od 20%) od normalne aktivnosti, stoga 50% enzimska aktivnost koja je prisutna kod oboleleih od tipa II PCT može predstavljati samo predisponirajući faktor, ali je nedovoljno niska da bi izazvala simptome PCT. Stoga je neophodno prisustvo drugih genetskih i spoljašnjih faktora koji bi doprineli povećanoj prijemčivosti jedne osobe za obolevanje kako od tipa I tako i od tipa II PCT. Treba znati da je nizak nivo enzimske aktivnosti UROD enzima (manje od 25% od normalnih vrednosti) u klinički manifestnoj PCT, posledica oksidacije uroporfirinogena u uroporfomeren koji deluje kao kompetitivni inhibitor UROD enzimu u jetri. Ovaj enzimski proces je zavisan od gvožđa. Serumski nivo gvožđa i feritina je povećan, ali može biti i na gornjoj granici normalih vrednosti. Bitno je da PCT postaje klinički manifestna samo ukoliko postoji povećana aklumulacija gvožđa u jetri. Za razliku od jetre, nivo gvoža u serumu može biti povećan kod samo 50% obolelih. Iako se određivanje nivoa UROD aktivnosti u eritrocitima smatra tehnikom skrininga za diferencijaciju tipa I od tipa II PCT, ova metoda nije dovoljno pouzdana zato što pojedini pacijenti sa tipom II mogu imati smanjenu UROD aktivnost koja se preklapa sa najmanjom vrednosti (intermedijerni nivo) UROD aktivnosti kod osoba sa tipom I PCT. Zbog toga je potrebno dodatno molekularno genetsko ispitivanje. Ovo ispitivanje nije indikovano samo kod onih osoba koje imaju intermedijerni nivo UROD aktivnosti u eritrocitima. Ovo ispitivanje treba sprovoditi i u cilju postavljanja egzaktne dijagnoze kod pacijenata koji nemaju obolele srodnike, a imaju mutacije na UROD genu. Nažalost, mi nismo bili u mogućnosti da sprovedemo genetsko ispitivanje.Postoji mnogo radova u kojima se navodi da estrogeni mogu biti okidači kod PCT. Ipak, mehanizam kojim estrogeni utiču na ispoljavanje bolesti nisu u potpunosti razjašnjeni. Iako dietilstilbestrol i estrogen izazivaju povećanu sintezu aminolevulonske kiseline u jetri, kojom se ne može objasniti ekskrecija porfirina karakteristična za PCT. Štaviše, većina pacijenata koja uzima estrogene ne pokazuje klinička niti biohemijska odstupanja karakteristična za PCT.
Zaključak: Ovim radom želimo da naglasimo značaj hipertrihoze, kao prve manifestacije PCT jer to može biti prvi i jedini klinički znak, koji tokom dugog vremenskog perioda prethodi pojavi drugih kliničkih znakova i simptoma.

Ključne reči

Porfirije; Estrogeni + neželjena dejstva; Hipertrihoza; Uklanjanje malja; Antimalarici

A Report on the 2nd/19th Congress of the Serbian Association of Dermatovenereologists

The 2nd/19th Congress of the Serbian Association of Dermatovenereologists was held from 12-15 June 2013 in Sava Center, Belgrade. The Congress was attended by 400 participants from Serbia and regional countries - Macedonia, Bulgaria, Bosnia and Herzegovina, Montenegro, Croatia, Slovenia and Hungary. The Congress participants had an opportunity to attend lectures given by 28 prominent experts invited from regional countries, Europe, United States, and from Serbia. This was an opportunity to exchange the latest knowledge and experiences in the field of dermatology. The main topics of the Congress, proposed by the Scientific Committee, were: prevention, diagnosis and treatment of melanoma and nonmelanoma skin cancer; new treatment options for psoriasis; diagnosis and treatment of autoimmune and inflammatory skin diseases; sexually transmitted diseases and esthetic dermatology. The free topic session included some outstanding and up-to-date lectures on contact dermatitis, dermatological surgery, pediatric dermatology and cutaneous vasculitis. On the day before the Congress, "Update on Dermoscopy" course was organized for all dermatologists, with Professor Giuseppe Argenziano and Professor Iris Zalaudek – world leading experts in the field of early detection of skin cancer. The course was of great interest, since it was attended by more than 300 dermatologists.

The Congress opening ceremony was held at the Belgrade National Theatre, and it included speeches by Prof. Erwin Tschachler, (President Elect of the European Academy of Dermatology and Venereology), Prof. Giuseppe Argenziano (President of the International Society of Dermoscopy), Prof. Jean-Jacques Grob (President of the European Association of Dermatological Oncology) and Congress President, Prof. Radoš Zečević from the Military Medical Academy in Belgrade, who welcomed the guests and expressed his gratitude to all the participants for attending this meeting dedicated to dermatology. After the opening ceremony, the ballet "Who is Singing Out There" was performed by the National Theatre Ballet Company, warmly welcomed by the audience. The welcome reception took place at the Central House of the Army of Serbia.

Figure 1a. Promotion of the book "Current Treatment of Psoriasis": reviewer Prof. Dr. Marina Jovanović and the authors (seated from left to right) Lidija Kandolf Sekulović, Željko P. Mijušković, Radoš D. Zečević and Danilo Vojvodić

Figure 1b. Promotion of the book "Current Treatment of Psoriasis": reviewer Prof. Dr. Marina Jovanović and the authors (seated from left to right) Lidija Kandolf Sekulović, Željko P. Mijušković, Radoš D. Zečević and Danilo Vojvodić

The first day of the Congress was dedicated to dermatologic oncology. Lectures on dermoscopy and treatment of melanoma and non melanoma skin cancers took place in the morning, followed by "Melanoma in Europe" session where experts in melanoma from the region and Europe shared their experience on early diagnosis and epidemiology of this disease. In the afternoon, a session on updates on diagnosis and treatment of melanoma was organized including lectures of the leading world experts: Prof. Axel Hauschild, Prof.

Figure 2. The President Elect of the European Academy of Dermatology and Venereology Prof. Erwin Tscachler with a honorary membership award of the Serbian Association of Dermatovenereologists and Prof. Radoš Zečević, the President of the Congress (on the left) and Prof. Miloš Nikolić, the President of the Serbian Association of Dermatovenereologists (on the right)

Figure 3. Prof. Lidija Kandolf Sekulović and Assist. Prof. Željko Mijušković from the Military Medical Academy in Belgrade (standing in the middle) with invited lecturers from abroad

Claus Garbe and Prof. Jean Jacques Grob. A round table on "Five burning questions in melanoma treatment in Serbia" was co-chaired by Prof. Kandolf Sekulović and Assoc. Prof. Mijušković. This session raised the attention not only of dermatologists, but also surgeons and oncologists from Serbia. The second day of the Congress was about psoriasis, where Prof. Griffiths, Prof. Bata-Szorg, Prof. Zečević and other regional experts shared their thoughts on this topic. The midday was a time for discussion about treatment options for autoimmune bullous and inflammatory diseases with Prof. Thomas Ruzicka, Prof. Marinović, Prof. Medenica and Prof. Plewig. In the afternoon, Prof. Tscachler and Prof. Skerlev discussed the updates on sexually transmitted diseases with the colleagues from Serbia – Assistant Prof. Bjekić and Assistant Prof. Golušin. Friday evening was a time for a less formal gathering of colleagues at the restaurant "Writers' Club" hosted by the President of the Congress.

Esthetic dermatology was the main topic on the last day of Congress, with Prof. Binić, Prof. Kazandjijeva and Prof. Katsambas as the main speakers, while in the afternoon Prof. Hohl gave his lecture on hereditary tumor syndromes and emerging therapies, Prof. Nikolić on vasculitides, Prof. Marina Jovanović about her lifelong experience in diagnosis and treatment of allergic dermatoses and Prof. Krunić on dermatologic surgery today.

Considering the number of participants, the up-to-date topics, and invited speakers, this Congress can be recognized as one of the largest gatherings of dermatologists in our region in 2013.

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A Report on the 8th World Congress of Melanoma, Hamburg 2013

The 8th World Congress of Melanoma was held in Hamburg, Germany, July 17-20, 2013. There were about 1.000 participants from all over the world, engaged in research, diagnosis and treatment of melanoma and other skin malignancies. The Congress attracted various healthcare professionals: dermatologists, surgeons, oncologists, molecular biologists, immunologists, etc. Yet, it was organized by two dermatologists, Prof. Axel Hauschild (Department of Dermatology, Kiel, Germany) and Prof. Claus Garbe (Department of Dermatology, Tuebingen), pointing to the importance of involving dermatologists into dermatologic oncology today and in the future. The Congress was held jointly with the 9th Congress of the European Association of Dermatological Oncology and the 7th Meeting of Interdisciplinary Melanoma Centers.

During the four days of the Congress, latest results in the field of melanoma diagnosis and treatment were presented, as well as evidence of considerable progress in the development of biological (target and immunological) therapy with unprecedented efficacy in the treatment of metastatic melanoma. In particular, studies of combining BRAF- and MEK-inhibitors, and treatment with anti-PD1 antibodies showed promising in effective treatment of metastatic melanoma, for decades considered to be a treatment-resistant disease. Apart from the updates of the latest studies on melanoma diagnosis and treatment, this Congress was also well covered by several sessions with interactive case reports in the field of dermoscopy and clinical management of melanoma patients.

Dermatologists from Serbia had two oral presentations: "Vitamin D Levels and VDR Receptor Gene Polymorphisms in Melanoma Patients" (J Deutsch Dermatol Ges 2013; 11 in press), and "The Number of Myeloid Derived Suppressor Cells in Melanoma Patients Reflects Disease Progression" (J Deutsch Dermatol Ges 2013; 11 in press), by Prof. Lidija Kandolf Sekulović and Assistant Prof. Željko Mijušković, respectively. They were also authors and co-authors in 2 poster presentations. In addition, Prof. Lidija Kandolf Sekulović chaired one of the sessions at the congress, and was elected as the board member of the European Association of Dermatological Oncology, as a representative from Serbia.

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A Report on the 22nd Congres of the European Academy of Dermatology and Venereology, Istanbul 2013

After the successful 5th EADV Spring Sypmposium in 2008, the 22nd Congres of the European Academy of Dermatology and Venereology was held at the Istanbul Congress Center.

The motto of the 22nd EADV Congress was „Dermatovenereology in a Changing World".

In the industrially as well as socially changing world, dermatovenereology is becoming more and more popular. The latest developments in the pharmaceutical industry have provided us with new drugs and modalities that facilitate both the diagnosis and treatment of many diseases.

There were more than 150 sessions including workshops, symposia, focus sessions, test yourself, forums and 10 courses. Free communications were divided into 9 categories. There were several plenary lectures: „New ways of looking at skin diseases", „Eosinophils: friend or foe", „Why pemphigus recurs after therapy ", „Antimicrobial peptides", „Behcet's Disease" and „Genetics". Also, spotlight sessions summarized practical advances in all areas; Controversy sessions with interactive platforms for discussions on the most delicate and dificult issues, and Masters of dermatology sessions held by retired colleagues who share their experience.

Prof. Ljiljana Medenica was the co-chair in the workshop „Aging of the skin: New therapeutic approaches". At this workshop Lj. Medenica delivered a lecture „Platelet rich plasma treatment (PRP) in antiageing". Miloš Nikolić was the co-chair in the workshop „Red flags and emergencies in dermatology", and delivered a lecture „Toxic

Figure 1. Miloš Nikolić from Serbia, Ronni Wolf from Israel and Adam Reich from Poland (Presidency of the Session – seated from left to right)

Figure 2. All Session participants: Adam Reich (Poland), Ronni Wolf (Israel), Marcia Ramos-e-Silva (Brazil), Miloš Nikolić (Serbia) and Uwe Wollina (Germany) - from left to right

epidermal necrolysis in systemic sclerosis". „ Not every acne is an acne" Assistant Prof. Mirjana Milinković was the co-chair, in the workshop, and delivered a lecture „Acneiform eruptions caused by hormones".

There were 20 E-posters from Serbia, whose authors were dermatovenereologists from Belgrade, Novi Sad, Niš, Leskovac, Užice and Kosovska Mitrovica.

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2013/2014

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
2-6 October, 2013	22nd EADV Congress, Istanbul, Turkey	10 April 2013	www.eadv.org
18 October, 2013	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Vojvodina, Novi Sad, Serbia	No abstract submission	www.sld.org.rs
8 November, 2013	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Kragujevac, Serbia	No abstract submission	www.sld.org.rs
5-7 December, 2013	22nd COSMODERM - Congress of the European Society of Cosmetic and Aesthetic Dermatology, Zilina, Slovakia	No deadline information	www.escad.org
4-7 December, 2013	11th International Congress of Dermatology, New Delhi, India	31 May 2013	www.icddelhi2013.com
28 February, 2014	Symposium on Psoriasis, Military Medical Academy, Belgrade, Serbia	No abstract submission	www.sld.org.rs
7 March, 2014	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Serbia, Belgrade, Serbia	No abstract submission	www.sld.org.rs
11 April, 2014	Symposium on Autoimmune Bullous Diseases, Military Medical Academy, Belgrade, Serbia	No abstract submission	www.sld.org.rs
11 April, 2014	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Military Medical Academy, Belgrade, Serbia	No abstract submission	www.sld.org.rs
23-26 April, 2014	9th European Lupus Meeting Athens, Greece	15 January 2014	www.lupus2014.org
7-10 May, 2014	10th EADO Congress Vilnius, Lithuania	1 February 2014	www.eado2014.com
10 May, 2014	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Niš, Prolom Banja, Serbia	No abstract submission	www.sld.org.rs
22-25 May, 2014	11th EADV Spring Symposium Belgrade, Serbia	17 January 2014	www.eadvbelgrade2014.org
5-7 June, 2014	23rd COSMODERM – Congress of the European Society of Cosmetic and Aesthetic Dermatology, Venice, Italy	No deadline information	www.escad.org
12-14 June, 2014	12th European Congress of the Society for Pediatric Dermatology, Kiel, Germany	20 January 2014	www.espd2014.com

Prepared by: Dr. Tatjana Roš, Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia, E-mail: t.rosh@nscable.net

AUTHOR GUIDELINES

Serbian Journal of Dermatology and Venereology is a journal of the *Serbian Association of Dermatologists and Venereologists*. The journal is published in English, but abstracts will also be published in Serbian language. The journal is published quarterly, and intended to provide rapid publication of papers in the field of dermatology and venereology. Manuscripts are welcome from all countries in the following categories: editorials, original studies, review articles, professional articles, case reports, and history of medicine.

Categories of Manuscripts

1. Editorials *(limited to 5 pages) generally provide commentary and analyses concerning topics of current interest in the field of dermatology and venereology. Editorials are commonly written by one author, by invitation.*

2. Original studies *(limited to 12 pages) should contain innovative research, supported by randomized trials, diagnostic tests, outcome studies, cost-effectiveness analysis and surveys with high response rate.*

3. Review articles *(limited to 10 pages) should provide systemic critical assessment of literature and other data sources.*

4. Professional articles *(limited to 8 pages) should provide a link between the theory and practice, as well as detailed discussion or medical research and practice.*

5. Case reports *(limited to 6 pages) should be new, interesting and rare cases with clinical significance.*

6. History of medicine *(limited to 10 pages) articles should be concerned with all aspects of health, illness and medical treatment in the past.*

7. Short Communications *(limited to 3 pages) should disseminate most current results and developments in the shortest possible time. They will be reviewed by expert reviewers and evaluated by the Editor.*

The journal also publishes book reviews, congress reports, as well as reports on local and international activities, editorial board announcements, letters to the editor, novelties in medicine, questions and answers, and "In Memoriam". All submitted manuscripts will undergo review by the editor-in-chief, blind review by members of the manuscript review panel or members of the Editorial Board. Manuscripts submitted to this journal must not be under simultaneous consideration by any other publisher. Any materials submitted will NOT BE RETURNED to the author/s.

All manuscripts should be submitted to the **Editor in Chief: Prof. Dr. Marina Jovanović***, Clinic of Dermatovenereologic Diseases, Clinical Center of Vojvodina, Hajduk Veljkova 1-3, Novi Sad, Serbia, by mail to: serbjdermatol@open.telekom.rs.*

Manuscripts for submission must be prepared according to the guidelines adopted by the International Committee of Medical Journal Editors (www.icmje.org). Please consult the latest version of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

1. Manuscript Preparation Guidelines

The manuscript should be written in English, typed in double spacing throughout on A4 paper, on one side only; Use Times New Roman, font size 12, with 30 lines and 60 characters per line. Articles must be written clearly, concisely and in correct English. Accepted manuscripts in need of editing will be returned after editing to the corresponding author for approval. When preparing their manuscripts, authors should follow the instructions given in the *Categories of Manuscript:* the number of pages is limited (including tables, figures, graphs, pictures and so on to 4 (four)), and all the pages must be numbered at the bottom center of the page.

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

- The title of the article, which should be informative, without abbreviations and as short as possible;

- A running title (limited to 30 characters);

- Authors' names and institutional affiliations;

- The name, mailing address, telephone and fax numbers, and email of the corresponding author responsible for correspondence about the manuscript. Furthermore, authors may use a footnote for acknowledgements, information and so on.

1.2. Abstracts

A structured abstract in English *(limited to 150 words) should follow the title page. The abstract should*

provide the context or background for the study, as well as the purpose, basic procedures, main findings and principal conclusions. Authors should avoid using abbreviations.

- An **abstract in Serbian language***, (limited to 150 words) should follow the second page. It should contain a briefing on the purpose of the study, methods, results and conclusions, and should not contain abbreviations.*

1.3. A list of abbreviations

Use only standard abbreviations, because use of non-standard abbreviations can be confusing to readers. Avoid abbreviations in the title, abstract and in the conclusion. A list of abbreviations and full terms for which they stand for should be provided on a separate page. All measurements of length, height, weight, and volume should be reported in the metric units of the International System of Units – SI, available at http://www.bipm.fr/en/si/.

1.4. Cover Letter

Manuscripts must be accompanied by a cover letter, which should include a date of submission, statement that the manuscript has been read and approved by all the authors and that the authorship requirements have been met. It should also include the name, address, and telephone number of the corresponding author, who is responsible for communicating with other authors about revisions and final approval of the proofs. The original copy of the cover letter, signed by all authors, should be enclosed with the manuscript.

2. Tables and illustrations

Tables *should capture information concisely and precisely. Including data in tables, rather than in the text, reduces the length of the article itself.*

- Submit tables in separate files, not included in the manuscript. Tables are to be double spaced and numbered sequentially, with Arabic numbers (Table 1, Table 2, etc.), in order of text citation. Each column, including the first, must have a heading. Provide a brief title for each table. Put all explanatory matter in footnotes, including any nonstandard abbreviations used in the table.

- **Figures** should be submitted in a separate file, not included in the manuscript document. Cite figures consecutively, as they appear in the text, with Arabic numbers (Fig. 1, Fig. 2, Fig. 3, etc.). Each figure must be assigned a title, as well as a legend. Legends should appear on a separate page, not with each figure. The **Legend Page** is to be numbered in sequence after the last page of the references list. Figures should be professionally drawn, as sharp black-and-white or color photographs. If photographs of persons are used, either the subjects must not be identifiable, or their pictures must be accompanied by written permission to use them.

3. References

References in the text, tables and legends should be identified by Arabic numerals in parentheses. Number references consecutively in the order in which they are first mentioned in the text. The *Vancouver System* of referencing should be used. List each author's last name and initials; full first names are not included. List all authors, but if the number exceeds six, give the first six followed by „et al." National journals, which are not indexed in *Index Medicus*, should be abbreviated according to the style in the *List of Abbreviated Titles of Yugoslav Serial Publications* available on http://vbsw.vbs.rs. For further information please visit www.ICMJE.org.

4. Additional information

Accepted manuscripts are edited and returned to the corresponding author for approval. Then a final version of the manuscript will be requested in a defined period of time. Authors will be notified of acceptance or rejection by email, within approximately 4 weeks after submission.

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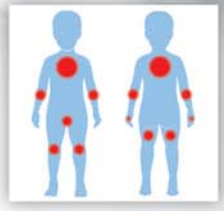

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