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EXPRESSION OF VASCULAR ENDOTHELIAL GROWTH FACTOR IN MELANOCYTIC NEVI

EKSPRESIJA VASKULARNOG ENDOTELNOG FAKTORA RASTA U MELANOCITNIM NEVUSIMA

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Summary – Melanocytic nevi represent a benign neoplastic proliferation of melanocytes. The level of vascular endothelial growth factor expression in these proliferations is low in most cases; whereas an increased expression of this factor may be an indicator of pre-neoplastic changes in melanocyte lesions. We performed a semi-quantitative assessment of the level of vascular endothelial growth factor expression (score 0 to 3) on samples taken from 34 patients with benign melanocyte alterations of the skin. Melanocytic nevi showed an expression of vascular endothelial growth factor in 79.41% of the cases. The low level of expression (score 1) was seen in 70.59% cases. The results showed no statistically significant difference in the presence and level of vascular endothelial growth factor expression in relation to the following morphological parameters: histological type, a defect in the surface, density of inflammation infiltrate, mitotic index, growth phase and cell type.
Key words: Vascular Endothelial Growth Factor A; Nevus, Pigmented; Skin; Melanocytes; Precancerous Conditions

Introduction

Melanocytic nevi are a benign neoplastic proliferation of melanocytes, or a variety of hamartomatous and/or neoplastic lesions in the skin. Clinically, there are several variants of melanocytic nevi: lesions at the level of skin, slightly elevated lesions, papillomatous alterations and pendulous forms of melanocytic nevi [1]. The formation of ordinary melanocytic nevi is directly associated with the exposure to the sunlight [2]. Certain phenotypic features (light skin, red or blond hair, blue eyes, etc.) are important in the development of common acquired nevomelanocytic nevi [3]. Besides the skin, common acquired nevi can also be developed under fingernails or on the mucus (for example on the conjunctiva), while in the oral cavity nevi are rarely described [4]. However, unlike melanoma lesions, nevi after a period of growth become stagnant, and then evolve [5,6].

Nevomelanocytic nevi are formed by nevomelanocytic clusters in the epidermis (junctional nevus), in the dermis (intradermal nevus) or on both places (compound nevus) [3]. Nevomelanocytic nevi are distinguished from other nevi by their ability of malignant altering towards melanoma of the skin [7]. In junctional nevi, the cells form a ”nest” in the lower parts of the epidermis or the upper dermis, but with still intact connections with the epidermis [1].

Congenital nevomelanocytic nevi appear at birth [3,8]. According to the affected surface, congenital nevi are classified into small (diameter less than 1 cm), medium (1.5 to 19.9 cm in diameter) and large or giant (diameter larger than 20 cm) [9]. Small and medium nevi may be junctional, mixed and intradermal (with superficial or deeper localization in the dermis) [10]. Several research teams have established a connection between melanoma and the existence of giant congenital nevi [11,12]. Melanoma develops from congenital nevi in 6-12% of cases [13].

Dysplastic nevi tend to alternate malignantly into melanoma. The criteria for clinical diagnosis are: diameter larger than 5 mm, irregular edges, asymmetry, uneven pigmentation [14]. The existence of dysplastic nevi should be taken into consideration if a person has more than 100 nevi on the body, if there are more than two atypical nevi, if more than one nevi are found on the scalp, if there are more than two nevi on the dorsum of the foot and if more than one iris nevi exist [4].

Angiogenesis means the formation of new capillary blood vessels from the existing vascular network; it is a very complex process involving extravasation of protein and plasma, decomposition of extracellular matrix, migration and proliferation of endothelial cells and forming of capillary tubes. The skin retains the ability of quick neovascularization, secondary angiogenesis in response to numerous pathological stimuli, such as injuries, inflammatory dermatoses and neoplasia [15]. The research fields are mainly related to the study of factors that stimulate or inhibit angiogenesis [16]. It is significant to note that in both the healthy and affected skin, angiogenic factors originate from the epidermis (VEGF, b-FGF). On the other hand, anti-angiogenic factors are present in the dermis [17].

Vascular endothelial growth factor (VEGF) is a soluble homodimeric glycoprotein that binds to the receptors with tyrosine kinase activity on endothelial cells [18,19]. Five subtypes of VEGF with different molecular weight have been described. Among them, VEGF-B (23 kd) and VEGF-C (34 kd) have a significant place. An increased expression of VEGF-B was observed in healthy tissue of the cardiac muscle, skeletal muscles, pancreas and prostate; whereas an increased expression of VEGF-C was recognized in the tissue of

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Abbreviations
VEGF – vascular endothelial growth factor
VEGFR – vascular endothelial growth factor receptor

the small intestine, placenta and ovary [20.21]. Some studies have shown that there is an expression of VEGF-A factor in normal structures of the eye (especially the retina), but it is particularly pronounced in pathological processes such as diabetic retinopathy and uveal melanoma [22]. Angiogenesis in the skin is regularly associated with an increased expression of VEGF in epidermal keratinocytes [23]. According to the literature, the degree of VEGF expression in benign melanocytic alterations (nevi) is low in most cases, and an increased expression of VEGF in dysplastic nevi may be an indicator of paraneoplastic changes in melanocytic lesions [24,25].

The aim of this study was to determine the level of VEGF expression in melanocytic nevi of the skin of different regions, and to investigate the relation between the level of VEGF expression and morphologic parameters (histological type, a defect on the surface, the density of inflammatory infiltrate, mitotic index, stage of growth and cell type).

Material and methods

The research was done on bioptic skin samples of 34 patients (25 women and 9 mesn) with melanocytic skin alterations, taken at the Clinical Centre of Banjaluka in the period from 2004 to 2007. Histological analysis confirmed the diagnosis of benign melanocytic alteration.

The following was determined in all the subjects:

– The histological type was determined by the analysis of histological samples according to the WHO histological classification [26];
– The thickness of alteration: measured vertically in millimetres from the granular layer of the epidermis to the place of deepest invasion, or from the base of the defect to the place of deepest invasion;
– The width of the lesion: measured microscopically in millimetres, from one side edge of the alteration to the other side edge;
– Tumour infiltration by lymphocytes: absent - no lymphocytes in the tumour stroma; a thin infiltrate present - from 1 to 10 lymphocytes on one visual field at high magnification; a medium dense infiltrate present - from 11 to 20 lymphocytes on one visual field at high magnification; a dense infiltrate present - more than 20 lymphocytes on one visual field at high magnification. The assessment was done in the stroma of the tumour and on the border of the tumour and surrounding tissue.
– Mitotic index: the number of mitosis was determined in 10 visual fields at high magnification. The width of visual field was 1.4 mm. Visual fields, which were quantified, represent the peripheral parts of the tumour (to the surrounding tissue);
– The estimation of growth phase:
radial growth phase - present or absent
vertical growth phase - present or absent (expansive tumour clusters located in the papillary and/or reticular dermis) [26];
– The presence of surface defect: assessed histologically, on the basis of continuity of the epidermis above the lesion (present or absent ulceration);
– Cell type of the nevus: epitheloid cells, spindle cells, mixed type (epitheloid + spindle cells);
– Localization: alterations have been classified according to the localization into the following subgroups: head and neck, trunk, extremities.
– Expression of VEGF: assessment of expression from 0 to 3.

The epitope unmasking was performed by the pretreatment in a microwave oven and by soaking the slides in Target Retrival Solution pH 9.0 (Daco S2367). As the primary antigen, we used the commercial mouse monoclonal anti-human VEGF antibody (Daco M7273), the concentration of VG1 with dilution 1:25. For visualization, we used the LSAB + (Daco K0690) system and chromogen DAB Liquid (K3466).

The presence or absence of factors and the intensity of their presence was assessed by semi-quantitative scale from 0 to 3, taking the level of immuno-staining of keratinocytes as an internal control. The quantification was as follows:

– score 0, no difference in immunostaining for VEGF between melanocytes and keratinocytes;
– score from 1 to 3, a higher level of VEGF expression in tumour cells compared to keratinocytes:
– score of 1 - less than 25% tumour cells show an expression of higher intensity compared to the level of staining of keratinocytes;
– almost 2 - 25 - 75% of tumour cells show an expression of higher intensity compared to the level of staining of keratinocytes;
– score of 3 - more than 75% tumour cells show an expression of higher intensity compared to the level of staining of keratinocytes **(Figure 1).**

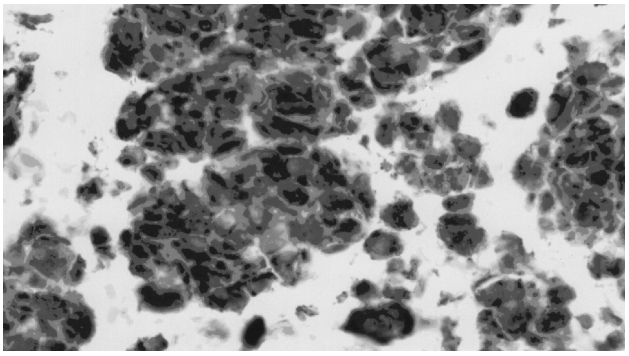

Fig. 1. *VEGF expression in nevus, score 2 (anti-VEGF x 200)*
Slika 1. Ekspresija VEGF u nevusu, skor 2 (anti-VEGF x 200)

The results were analyzed by methods of descriptive and correlative statistics and are shown in tables. The statistical analysis was performed using the SPSS software version 15.0, and the following tests were applied: Chi square and related methods

of analysis of categorical variables (Fisher's exact test) and Mann Whitney test.

Table 1. Characteristics of examinees
Tabela 1. *Karakteristike ispitanika*

		Broj ispitanika *Number of examinees*
Starost/*Age*	prosečna starost godina 29,08/*average age in years* 29.08	
Pol/Sex	M/M	9
	Ž /F	25
Lokalizacija *Localization*	glava i vrat/*head and neck*	3
	trup/*trunk*	26
	ekstremiteti/*extremities*	5
Histološki tip nevusa *Histologic type of nevus*	*dermal*	19
	compound	8
	congenital	5
	dysplastic	2
Defekt na površini *Ulceration*	prisutan/*present*	7
	odsutan/*absent*	27
Faza rasta *Growth phase*	radijalna/*radial*	1
	vertikalna/*vertical*	20
	vertikalna i radijalna *vertical and radial*	13
Stepen ekspresije VEGF *Level of VEGF expression*	0	7
	1	24
	2	3
	3	0

Results

Table 1 presents characteristics of the patients.

Our study included bioptic samples from 34 patients with melanocytic nevi taken at the Clinical Centre Banjaluka in the period from 2004 to 2007. The diagnosis of benign melanocytic alteration was made by the histological analysis. The average age of all patients was 29.08 years. In our material, the following histological variants of benign melanocytic alterations were verified: dermal melanocytic nevus in 19 (55.88%) cases, compound nevus in 8 (23.53%) cases, congenital nevus in 5 (14.71%) cases, dysplastic nevus in 2 (5.88%) cases **(Figure 2)**.

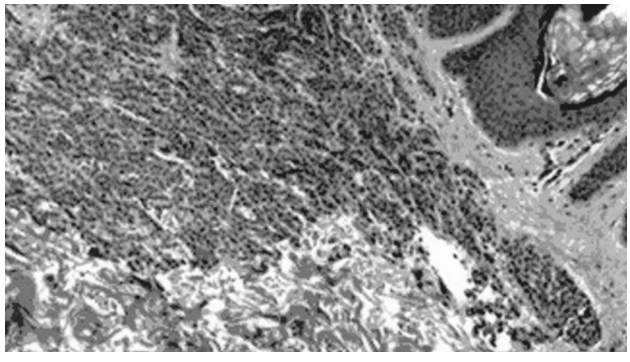

Fig. 2. Pigmented nevus - dermal type, (HEx100)
Slika 2. *Pigmentni nevus - dermalni tip (HEx100)*

VEGF expression in benign melanocytic skin alterations (nevi)

Table 2 presents the expression of VEGF in nevi. The majority of benign melanocytic alterations in the skin showed a low level of expression of VEGF (score 0 and 1) in 91.18% of cases (Chi-square of 21.658 with a degree of freedom (df) 1, $p<0.001$). A high level of expression (score 2 and 3) has rarely been verified in benign melanocytic alterations, i.e. in 8.82% cases.

The relationship between VEGF expression and the histological type of nevus

Table 2 shows the level of VEGF expression in relation to the histological type of nevus. There was no statistically significant difference in the level of VEGF expression regarding the histological type of nevus (Chi-square of 20.62 with a degree of freedom (df) 4 $p = 0.724$).

The relationship of VEGF expression and the presence of defects on the surface of nevi

A defect in the epidermis was found in 7 (20.59%) cases **(Table 2).** There was no statistically significant difference, bearing in mind the level of VEGF expression and the presence of a defect in nevi (Fischer's test, $p = 0.101$).

The relationship between VEGF expression and the thickness of alteration

In the nevi with the levels 0, 1 and 2 of immunostaining for VEGF, the average thickness values of the lesion were 1.81 mm, 2.55mm and 2.26 mm, respectively **(Table 3)**. Benign melanocytic alterations with low expression of VEGF have the average thickness of 2.38 mm, and for those with high expression, the average thickness is 2.26 mm. On the basis of statistical analysis results, it can be concluded that there is no statistically significant difference in the expression of VEGF and nevi thickness (Chi square = 1.009, sig = 0.604).

The relationship between VEGF expression and the average width of the lesion

In the nevi with the levels 0, 1 and 2 of immunostaining for VEGF, the average lesion widths were 4.75 mm, 6.04 mm and 4.5 mm, respectively (Table 3). Benign melanocytic lesions with a low expression of VEGF have the average width of 5.75 mm, and those with a high expression (score 2 and 3) have the average width of lesion is 4.5 mm. According to the analysis by Mann-Whitney test, it can be concluded that there is no statistically significant difference in the level of VEGF expression and the width of the lesion ($U = 38.000$ for the significance of 0.605).

The relationship between VEGF expression and the density of lymphocytic infiltrate in the nevus

An inflammatory infiltrate was present in 20 (58.82%) cases. In cases where an inflammatory infiltrate was present, an average density of infiltration was usually seen (in 50% of cases) **(Table 2).** The analysis

Table 2. Relationship of level of VEGF expression and morphological parameters in nevus
Tabela 2. *Odnos stepena ekspresije VEGF i morfoloških parametara u nevusima*

		Stepen imunobojenja za VEGF *Level of immunostaining for VEGF*			
		0	1	2	3
Morfološki parametar *Morphological parameter*	Nevus *Nevus*	7 (20,59%)	24 (70,59%)	3 (8,82%)	
	dermal	3 (15,79%)	15 (78,95%)	1 (5,26%)	
Histološki tip *Histological type*	*compound*	2 (25%)	5 (62,5%)	1 (12,5%)	
	congenital	1 (20%)	3 (60%)	1 (20%)	
	dysplastic	1 (50%)	1 (50%)		
Prisustvo defekta na površini *Presence of ulceration*	prisutan *present*	1 (14,29%)	4 (57,14%)	2 (28,57%)	
	odsutan/*absent*	6 (22,22%)	20 (74,07%)	1 (3,71%)	
Gustina limfocitnog infiltrata *Density of lymphocyticinfiltrate*	gust infiltrat *dense infiltrate*	1 (20%)	3 (60%)	1 (20%)	
	srednje gust infiltrat *medium dense infiltrate*	3 (30%)	6 (60%)	1 (10%)	
	redak infiltrat *thin infiltrate*	3 (60%)	2 (40%)		
Faza rasta *Growth phase*	vertikalna/*vertical*	4 (20%)	16 (80%)		
	radijalna/*radial*		1 (100%)		
	vertikalna i radijalna *vertical and radial*	3 (23,07%)	3 (23,07%)	3 (23,07%)	
Lokalizacija *Localization*	glava i vrat *head & neck*		2 (66,67%)	1 (33,33%)	
	trup/*trunk*	7 (26,93%)	17 (65,38%)	2 (7,69%)	
	ekstremiteti/*extremities*		5 (100%)		

showed no statistically significant difference between the nevi with different density of lymphocytic infiltrate and manifestation of VEGF (Chi square 1.019 with a degree of freedom (df) 2 where p = 0.601).

Table 3. Relationship of level of VEGF expression and average thickness and width of nevus
Tabela 3. *Odnos stepena ekspresije VEGF i prosečne debljine i širine nevusa*

	Stepen imunobojenja za VEGF *Level of immunostaining for VEGF*			
	0	1	2	3
Prosečna debljina nevusa *Average nevus thickness*	1,81 mm	2,55 mm	2,26 mm	
Prosečna širina nevusa *Average nevus width*	4,75 mm	6,04 mm	4,5 mm	

The relationship between VEGF expression and mitotic index/10 hpf

In our study, the mitotic activity was verified in only one case (2.94%) and VEGF expression in this case was 1.

The relationship between VEGF expression and the radial/vertical growth phase of nevus

Benign melanocytic lesions in 20 (58.82%) cases were in the vertical growth phase, in both vertical and radial phase in 13 (38.24%) cases, and in the radial phase in only one case (2.94%). The relationship between the growth stage of benign melanocytic alterations and the level of VEGF expression is shown in **Table 2** The statistical analysis showed that there was no statistically significant difference in the level of VEGF expression and growth stage of nevi (Chi-square 5.315 with a degree of freedom (df) 2 where p = 0.07).

The relationship between VEGF expression and the nevus cell type

All examined nevi were of epitheloid cell type.

The relationship between VEGF expression and localization of the nevus

In our study, benign melanocytic lesions were usually localized on the trunk in 26 (76.47%) cases, and then on the limbs in 5 (14.71%) cases, and the head and neck in 3 (8.82%) cases. The relationship of VEGF expression and localization of benign melanocytic alterations is shown in **Table 2.** The Chi square test analysis showed that there was no statistically significant difference in the expression of VEGF, given the location of nevi (Chi-square 2.765 with a degree of freedom (df) 2 where p = 0.251).

Discussion

Hyperplasia, benign tumours, dysplasia, and malignant tumours originating from melanocytes have become more frequent pathological conditions in our population. There is still some doubt in the definition of the term ”nevus” [1]. Early diagnosis and differentiation of benign and malignant tumours of the skin is of utmost importance. So far, there has been insufficient number of studies which would indicate that routine screening of the skin (periodic self-examination and examinations of skin done by doctors) might be important in the prevention of malignant skin tumours, and thus contribute to better treatment and cure of patients with these diseases [27].

In our study, we found that melanocytic nevi showed an expression of VEGF in most cases (79.41%). The expression was generally of a low grade (level of immunostaining 1).

The level of VEGF expression in malignant melanocytic alterations (melanoma) in most cases is high, as confirmed by numerous studies. In one study, 39 melanomas were investigated. The intensity of immunostaining for VEGF had a degree of 0 in 2 cases (5.13%), stage 1 in 13 cases (33.33%), stage 2 in 13 cases (33.33%) and stage 3 in 11 cases (28.2%). Thus, low levels of VEGF expression were present in 38.46% of cases (score 0 and 1), while the high level of VEGF expression was present in 61.54% of the cases (score 2 and 3) [28]. In their research, Carazo and Peyri have reported that the majority of melanomas show a lower level of expression (score 0 and 1). A logical explanation for this difference is that these authors studied a selected group of melanoma (”thin melanomas”, i.e. Breslow thickness less than 1 mm), while in the previous re-

search an unselected group was studied (Breslow thickness greater than 1 mm) [29].

The results of Einspahr and associates suggest that the degree of VEGF expression might be an important parameter indicating the malignant transformation of melanocytic skin lesions. The study demonstrated that the level of VEGF expression in benign melanocytic lesions was low or absent; in dysplastic nevi, it was significantly higher, and the expression was much higher in malignant melanocytic alterations (melanoma). Thus, an increased expression of VEGF might be a good indicator of pre-neoplastic changes in melanocytic lesions [24]. Stefanou et al. studied the expression of VEGF in benign and malignant melanocytic skin alterations. They proved the presence of VEGF expression only in melanomas, and they claim that expression of VEGF might help in the differentiation of dysplastic nevus and melanoma [25].

Brychta et al. determined the presence of VEGF expression in benign and malignant melanocytic skin alterations. A high level of VEGF expressions is statistically significantly more often verified in melanomas than in nevi. They also demonstrated that the expression of VEGF was more frequent and intense in stromal cells (fibroblasts, endothelial cells, macrophages) in melanomas compared to nevi [30].

In this research, no difference was demonstrated in the level of VEGF expression and morphological parameters: histological type, a defect on the surface, the density of inflammatory infiltrate, mitotic index, stage of growth and cell type. Brychta et al. pointed to a significantly higher expression of VEGF in dysplastic nevi [30].

Pisacane and colleagues assessed the expression of VEGF and VEGF receptor (VEGFR-2) in benign and malignant melanocytic skin alterations. They noted that there was an expression of VEGFR-2 in different parts of cells in the majority of melanomas (88%). The nuclear expression was associated with in situ and micro-invasive melanomas, and the nuclear membrane and cytoplasmic expression with invasive melanomas. The nuclear membrane expression of VEGFR-2 was present in majority of complex nevi (83%). They also found the cytoplasmic expression of VEGF in 72% of in situ and micro-invasive melanomas, 84% of invasive melanomas and 91% of compound nevi [31].

A comparative study done within a doctoral dissertation has found that melanocytic alterations show the expression of VEGF, regardless of the clinical behaviour: benign melanocytic alterations show a low level of expression of VEGF more often, and malignant melanocytic alterations show a high level of expression of VEGF more often [28].

Conclusions

Melanocytic nevi show the expression of vascular endothelial growth factor in 79.41% of cases. The expression is generally of low level in 91.18% of cases. The localization of the nevus does not affect the presence and degree of expression of vascular endothelial growth factor-A. The presence and degree of vascular endothelial growth factor expression do not show a difference regarding morphological parameters: histological type, a defect on the surface, the density of inflammatory infiltrate, mitotic index, stage of growth and cell type.

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Sažetak

Uvod

Melanocitni nevusi su benigne neoplastične proliferacije melanocita, to jest varijetet hamartomskih i/ili neoplastičnih lezija u koži. Stepen ekspresije vaskularnog endotelnog faktora rasta u benignim melanocitnim promenama (nevusi) nizak je u najvećem broju slučajeva, a povećana ekspresija vaskularnog endotelnog faktora rasta može biti pokazatelj preneoplastičnih promena u melanocitnim lezijama.

Materijal i metode

U našem istraživanju procenjen je stepen ekspresije vaskularnog endotelnog faktora rasta na materijalima 34 pacijenta s benignim melanocitnim promenama kože. Izvedena je semikvantitativna procena ekspresije vaskularnog endotelnog faktora rasta (scor 0–3).

Rezultati i diskusija

Nevusi pokazuju ekspresiju vaskularnog endotelnog faktora rasta u 79,41% slučajeva. Nizak stepen ekspresije (skor 1) utvrđen je u 70,59% slučajeva. Rezultati ne pokazuju statistički značajnu razliku u prisustvu i stepenu ekspresije vaskularnog endotelnog faktora rasta u odnosu na morfološke parametre: histološki tip, defekt na površini, gustina inflamacijskog infiltrata, mitotski indeks, faza rasta i ćelijski tip. Naše istraživanje ekspresije vaskularnog endotelnog faktora rasta podudara se s istraživanjima većine autora koji ukazuju na to da ekspresija vaskularnog endotelnog faktora rasta postoji u nevusima, a da je stepen ekspresije veći u displastičnim nevusima i melanomima.

Zaključak

Melanocitni nevusi pokazuju ekspresiju vaskularnog endotelnog faktora rasta. Prisustvo i stepen ekspresije vaskularnog endotelnog faktora rasta ne pokazuje razliku s obzirom na različite morfološke parametre.

Key words: *Vaskularni endotelijalni faktor rasta; Pigmentirani nevus; Melanociti; Prekancerozna stanja*

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