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DERMATOSCOPIC AND IMMUNOHISTOCHEMICAL FEATURES OF DIAGNOSTICS OF THE DYSPLASTIC NEVI

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Ключові слова: *патоморфологія шкіри, імуногістохімія, дерматоскопія, дисплазія, меланома*

Abstract. Dermatoscopic and immunohistochemical features of diagnostics of the dysplastic nevi. Prokhach A.V., Svyatenko T.V., Antoniuk S.V. *Dysplastic nevi are the subject of debates between clinicians and pathologists. There is no standard diagnostic and treatment approach and this causes many disagreements. There is a need to study an immunohistochemical marker PTEN as a long-range diagnostic mechanism between early-stage melanoma and dysplastic nevi. A search for correlations between other markers (Ki-67, SOX-10, p16, PTEN) and dermatoscopic criteria was conducted. We observed 95 cases of clinically atypical melanocytic tumors in adult patients aged 18-65 years. We determined 13 dermatoscopic criteria that accompany atypical melanocytic formations such as structureless areas, irregular globules, atypical pigment network, gray dots, blotches, blue-white veil, negative pigment network, polymorphous vessels, "starburst" pattern, angulated lines, multiple colors, regression structures, pseudopods. During the study all obtained lesions were removed with the following pathology and immunohistochemistry. The use of immunohistochemical*

markers made it possible to separate early melanomas (n=19) and other (benign) tumors (n=22) from the primary cohort of patients who, according to the results of pathology, had moderate or severe grade of dysplasia. The most common dermatoscopic feature were structureless areas combined with other mentioned signs. The presence of PTEN expression in benign melanocytic tumors and the absence of PTEN in a primary cutaneous melanoma confirms its role in melanoma pathogenesis. In melanoma, along with other markers, SOX-10 expression indicates aggressiveness, atypia, and architectural disorders. Dysplastic nevi usually retain p16, which helps distinguish them from melanoma. The relatively low level of Ki-67 expression in dysplastic nevi is a criterion that helps to distinguish them from melanoma. We consider that application of this combination of immunohistochemical markers in routine practice can significantly improve the diagnosis of dysplastic nevi and melanoma, especially for diagnostic collisions among superficial atypical melanocytic proliferations. Usage of the phosphatase and tensin homolog protein can be useful for diagnostic not only group of "thin melanomas" but for non-pigmented nodular melanomas and for secondary metastatic melanoma lesions with unknown primary tumors.

Реферат. Дерматоскопічні та імуногістохімічні особливості діагностики диспластичних невусів. Прохач А.В., Святенко Т.В., Антонюк С.В. *Диспластичні невуси є предметом дискусій між клініцистами та патологоанатомами. Відсутній стандартний діагностичний та лікувальний підхід, і це викликає багато розбіжностей. Існує потреба у вивченні імуногістохімічного маркера PTEN як перспективного діагностичного механізму між меланомою на ранніх стадіях та диспластичними невусами. Проведено пошук кореляцій між іншими маркерами (Ki-67, SOX-10, p16, PTEN) та дерматоскопічними критеріями. Ми спостерігали 95 випадків клінічно атипових меланоцитарних пухлин у дорослих пацієнтів віком 18-65 років. Ми визначили 13 дерматоскопічних критеріїв, що супроводжують атипові меланоцитарні утворення: безструктурні ділянки, неправильні глобули, атипова пігментна сітка, сірі цятки, плями, синьо-біла вуаль, негативна пігментна сітка, поліморфні судини, візерунок «зірки», кутові лінії, множинні кольори, регресійні структури, псевдоподії. Під час дослідження всі отримані ураження були видалені з подальшим патогістологічним та імуногістохімічним дослідженнями. Використання імуногістохімічних маркерів дозволило відокремити ранні меланоми (n=19) та інші (доброякісні) пухлини (n=22) від первинної когорти пацієнтів, які за результатами патогістології мали дисплазію середнього або тяжкого ступеня. Найпоширенішою дерматоскопічною ознакою були безструктурні ділянки в поєднанні з іншими згаданими ознаками. Наявність експресії PTEN у доброякісних меланоцитарних пухлинах та відсутність у первинній меланомі шкіри підтверджує його роль у патогенезі. При меланомі експресія SOX-10 вказує, поряд з іншими маркерами, на агресивність, атипію та архітектурні порушення. Диспластичні невуси зазвичай зберігають p16, що допомагає відрізнити їх від меланоми. Відносно низький рівень експресії Ki-67 у диспластичних невусах є критерієм, який допомагає відрізнити їх від меланоми. Ми вважаємо, що застосування цієї комбінації імуногістохімічних маркерів у рутинній практиці може значно покращити діагностику диспластичних невусів та меланоми, особливо для діагностичних колізій між поверхневими атиповими меланоцитарними проліфераціями. Використання фосфатази та гомолога білка тензину може бути корисним для діагностики не лише групи «тонких меланом», але й непігментованих вузлових меланом та вторинних метастатичних уражень меланоми з невідомими первинними пухлинами.*

Diagnosis of dysplastic nevi (DN) remains a cornerstone of modern dermatology and dermatopathology [1]. Since the late 1970s, the diagnosis and treatment of dysplastic nevi has been a matter of controversy, and diagnostic uncertainty and the lack of a standardized nomenclature continue to cause confusion among clinicians, dermatopathologists, and patients [2, 3]. Most of the world's leading dermatologists consider DN as a precancerous melanocytic dermatosis, but in recent years there have been attempts to revise these scientific concepts.

According to the definition of the WHO classification of skin tumors, a dysplastic nevus is a benign melanocytic nevus that is clinically atypical and histologically characterized by architectural disorder and cytological atypia [4]. In terms of their clinic, pathomorphology, and genetics, dysplastic nevi lie between typical acquired nevi and superficial melanoma [2]. Like other melanocytic dermatoses, dysplastic nevi result from genetic, environmental, and phenotypic factors, including skin sensitivity to ultraviolet radiation. There are data on the genetic component of nevogenesis: genome-wide association studies of the number of nevi revealed several loci, but no unique loci for germline susceptibility to dysplastic nevi were found. It is likely that stimulation of the genome from chronic ultraviolet radiation and resulting cumulative sun damage (CSD) may contribute to clinical and morphological atypia [5].

Clinical diagnosis of dysplastic nevi does not have clear and specific criteria. The widely used ABCD clinical mnemonic rule published by Clarke in 1985 and modified by the International Agency for Research on Cancer (IARC) in 1990 (ABCD(E)) recommends the following criteria for identifying atypical (dysplastic) nevi: a macular component must be present in at least one site; in addition, at least three of the following signs must be present: ill-defined border, size of 5 mm or more, variegated color, uneven peripheral contour and erythema, rapid development of the lesion [1]. A meta-analysis of data shows that in 2 out of 3 cases the ABCD(E) rule gives

a false estimate and cannot be used for early diagnosis [2]. In the last 20 years, the use of dermatoscopy for the primary diagnosis of DN has been spreading. Although the method has high sensitivity for melanocytic neoplasia, which is clearly correlated with pathomorphology, its specificity for DN is insufficient.

There is a need to study the immunohistochemical marker PTEN as a long-time diagnostic mechanism among early-stage melanoma and dysplastic nevi. Searching for correlations between other markers (Ki-67, SOX-10, p16, PTEN) and dermatoscopic criteria is topical

MATERIALS AND METHODS OF RESEARCH

The study was conducted in accordance with the fundamental principles set forth in the "Rules of Ethical Principles for Conducting Medical Research Involving Human Subjects" as stated in the Declaration of Helsinki (1964-2013). All patients gave their consent to participate in the study and to the processing of their personal data. The study was approved by the local ethics committee of DSMU on November 16, 2022, protocol No. 3.

We observed 95 cases of clinically atypical melanocytic tumors in adult patients aged 18-65 years that had been dermatoscopically recorded and exited. We provided an exisional biopsy as the main diagnostic manipulation. At the preliminary stage of the study, 13 dermatoscopic criteria accompanying DN were identified and collected: structureless areas, atypical globules, atypical pigment mesh, gray spots, spots (hyperpigmentation), blue-white veil, negative pigment mesh, polymorphic vessels, star-shaped pattern, angular lines, multiple colors, regressive structures, pseudopodia [2, 6]. In all studied cases, a combination of the listed features was observed (Fig. 1).

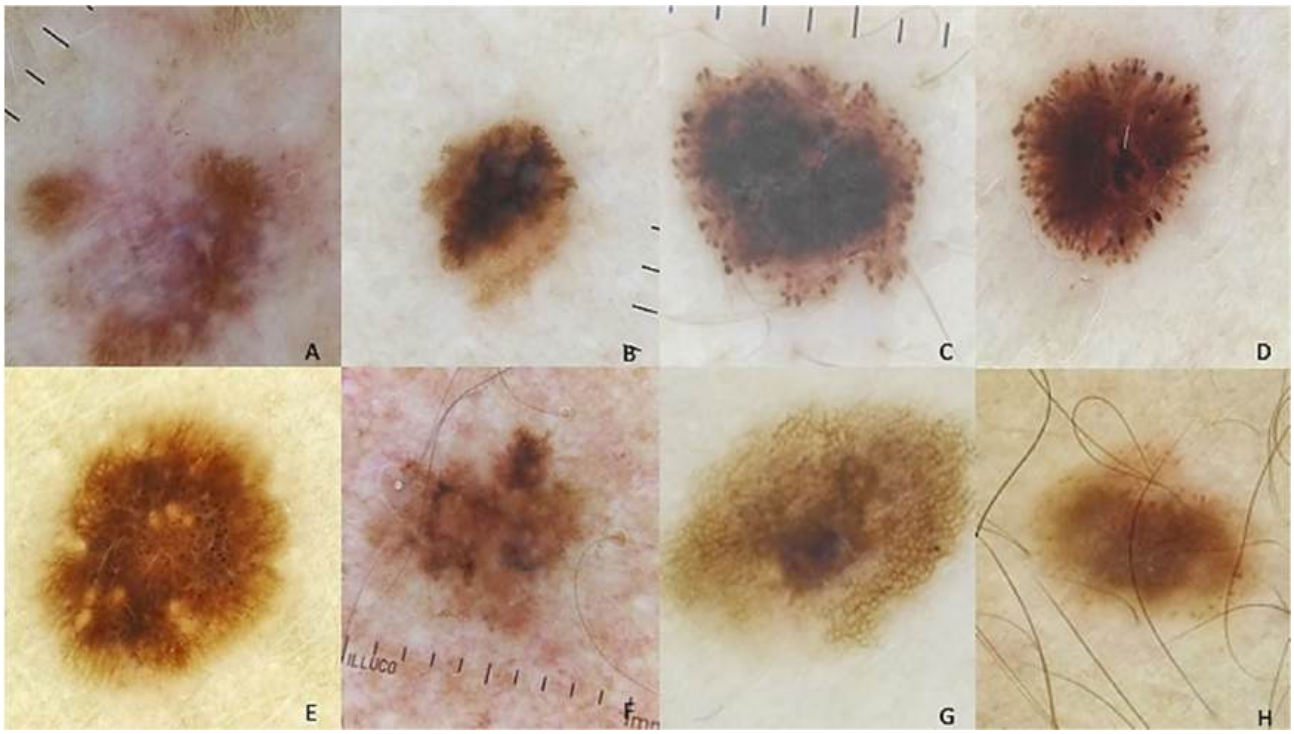

Fig. 1. A – structureless areas, atypical pigment network, regression structures, multiple colors, polymorphous vessels; B – blotches, irregular globules, pseudopods, blue-white veil; C – blotches, irregular globules; D – "starburst" pattern, blotches; E – negative pigment network, gray dots; F – atypical pigment network, multiple colors, blue-white veil, structureless areas; G – atypical pigment network, blue-white veil, angulated lines, blotches; H – irregular globules, structureless areas

All of them indicate clinical atypia, but can be observed in spitzoid tumors, typical acquired nevi, melanomas. Note that the severity of dermatoscopic signs may be related to the level of dysplasia [2]. Below are definitions of the criteria presented. Structureless areas are areas within the lesion that are devoid of any structures. The size should be at least 10% of the total surface area of the lesion. Atypical globules vary in size, shape, and color and can often appear focally and irregularly at the periphery of the lesion [2, 7]. An atypical pigment grid is unevenly canceled by lines that differ in width and degree of pigmentation, as well as "holes", heterogeneous in area and shape. An atypical grid is foci with wider and

darker pigment lines; the network often ends abruptly at the periphery of the lesion [6]. The atypical meshwork within the lesion may also appear disheveled and broken, called "branching bands." Gray dots (they are also called granules or peppercorns) arise due to small particles of melanin in melanophages or in the form of extracellular "dust" in the superficial dermis; this feature is associated with regression [2, 7]. A spot (zone of hyperpigmentation) is defined as an area that is at least 10% of the surface area of the lesion and is highly pigmented. In a spot, the pigment melanin is often present in all layers, including the stratum corneum, epidermis, and dermis [2, 7]. Blue-white veil is a fused blue pigmentation with a superficial white "matte" cloudiness [2, 7]. The negative pigment grid consists of relatively lighter areas that form the visible grid of the network, and relatively darker areas that fill the visible "holes". Polymorphic vessels are used to describe the vasculature of lesions that exhibit two or more types of vessel morphology [6]. The "starburst" pattern is characterized by several bands of pigmentation or large globules located symmetrically on the periphery of the lesion in the form of rays, like a star [2, 7]. Dermatoscopically, angular lines are straight lines that meet at an angle greater than 90 degrees but do not cross. They can form a full or partial polygonal shape. They are also known as polygons, zigzags or diamond patterns. The histological nature of these lines is not yet known, but they are thought to correspond to proliferation of atypical melanocytes at the dermoepidermal junction (DEJ) together with local accumulation of melanophages [2, 7]. Multicolor is associated with different shades in the lesion and appears as an additional feature in pigmented lesions. Regressive structures appear dermatoscopically as white scar-like depigmentation (multiple blue-gray granules with spots). Pseudopodia are bulbous and often curved projections seen at the edge of a lesion directly associated with the network or border of a solid tumor [2, 7].

Dysplastic nevi are classified according to different criteria, depending on their morphological, histological and clinical characteristics [8]. The main criteria include the degree of melanocyte atypia, clinical signs (appearance) and the risk of malignancy. Morphological diagnosis of dysplastic nevi is based on the analysis of certain histological features, which are classified into main (key) and secondary (additional) criteria. These criteria help distinguish dysplastic nevi from normal nevi and melanoma [4].

The main criteria include lentiginous melanocytic hyperplasia with uneven distribution of melanocytes in the epidermis and possible thinning or thickening of the epidermis. Another main diagnostic criterion is focal melanocytic atypia - nuclei enlarged by 1.5 times compared to basal keratinocytes, uneven coloring and unusual shape. Melanocytic atypia can vary from mild to severe, depending on the risk of malignant transformation [2, 4].

Secondary criteria include the “shoulder phenomenon”, in which epidermal melanocytes extend beyond the epidermal component of the nevus and is an important feature of dysplastic nevi and helps distinguish it from other skin lesions. An important criterion in the diagnosis of atypical nevi is superficial perivascular lymphoid cell infiltration in the dermis, which indicates an immune reaction of the body. Subepidermal concentric lamellar fibrosis in the papillary dermis around nevus cells and fusion of the epithelial ridges of papillary structures are also of diagnostic importance when conducting a histological examination. To establish the diagnosis of "dysplastic nevus", the presence of two main criteria and at least two secondary criteria is necessary [4, 8].

According to the International Melanoma Pathology Study Group (IMPSG), the diagnosis of melanoma is based on a comprehensive analysis of histological criteria, that is, on the selection of architectural and cytological criteria, namely [4, 8]:

a) width of formation >4 mm in fixed sections (>5 mm clinically);

b) the presence of an architectural disorder:

- irregular (i.e. horizontally oriented, overlapping the neighboring mesh and/or changing in shape and size) and/or discohesive meshes of intraepidermal melanocytes;

- increased density of melanocytes without a nest (for example, more melanocytes than keratinocytes on an area of 1 mm^2);

c) the presence of cytological atypia of melanocytes, which is classified into low-grade and high-grade. Mitoses in intraepidermal melanocytes are rare, but if they are present, this is a serious cytological sign and requires differential diagnosis with melanoma in situ.

These criteria make it possible to distinguish DN from typical acquired nevi and melanoma [9].

Immunohistochemical studies are also used for the differential diagnosis of DN (Fig. 2) from typical nevi and melanoma [9].

The main melanocyte markers are HMB-45, Melan-A (MART-1), SOX-10 and p16 [9, 10, 11]. Ki-67 is also an important marker in diagnosis, which indicates the mitotic activity of DN [10]. The proliferative index of Ki-67 in hot areas of the dermis of the DN is <10%, while in situ melanomas it increases sharply and can exceed 30% [10, 12].

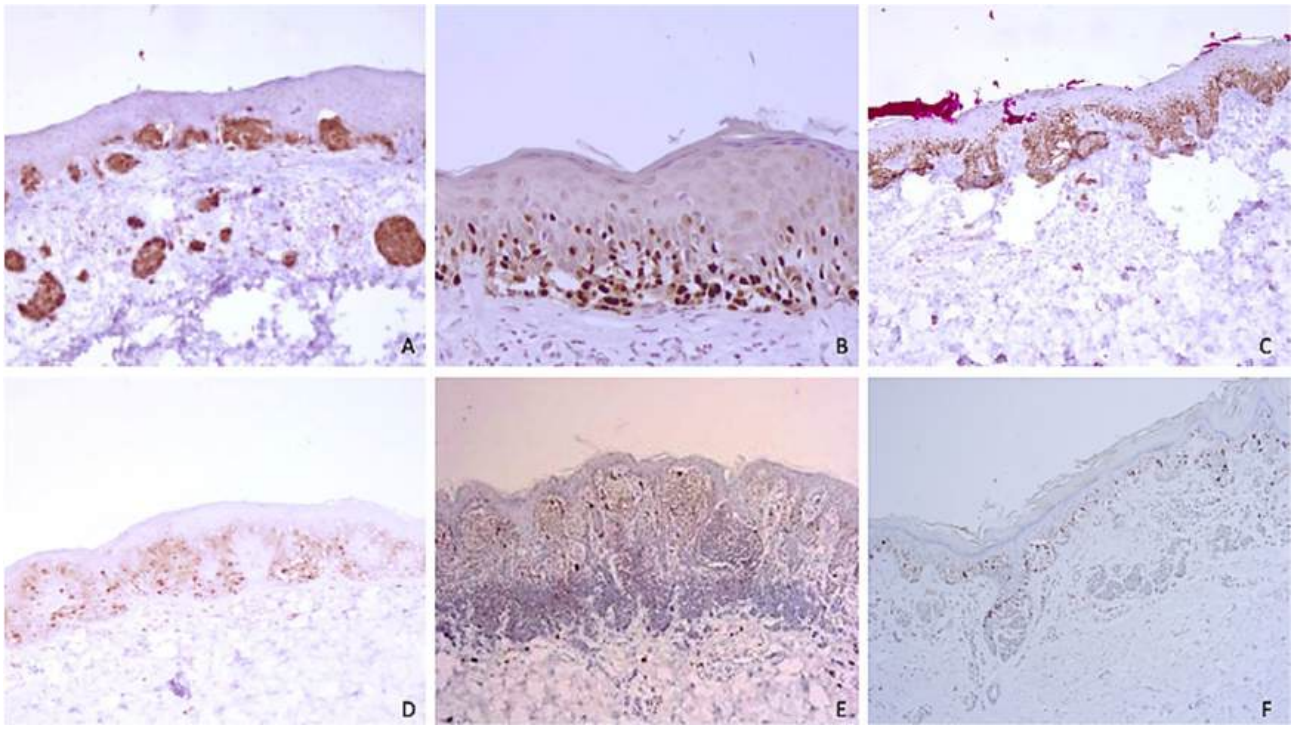

Fig. 2. A – p16 x100, significant diffuse nuclear-cytoplasmic expression of p16-INK4 in dermal melanocytes and mosaic intense expression in dermal-epidermal junction (DEJ) melanocytes with more intense nuclear expression; B – SOX10 x200, intense nuclear expression of melanocytes of the junctional and dermal components; C – HMB45 x100, focal expression in melanocytes at the DEJ and absence of expression in deep dermis; D – Melan-A x100, diffuse membrane expression in junctional melanocytes; E – PTEN x100, membrane expression of melanocytes of weak to moderate intensity in the vast majority of cells; F – Ki-67 x100, increased mitotic activity of junctional melanocytes compared to the dermal component, where only separate melanocytes express Ki-67

SOX-10 is a transcription factor widely expressed in melanocytes and used as a marker to identify melanocytic tumors, including DN and melanoma. It helps determine the melanocytic origin of tumors and distinguish melanocytic lesions from other types of tumors [10, 13]. Normally, SOX-10 is expressed in melanocytes throughout the nevus and its expression is stable and uniform. In dysplastic nevi, low-grade atypia is expressed without changes in intensity, which indicates the stable nature of the melanocytic lesion and the absence of pronounced atypia. In DN with a high degree of dysplasia (high grade), the expression of SOX-10 is more diffuse and intense, which indicates a more active proliferation of melanocytes [10, 14]. This may be due to a higher degree of atypia, potentially indicating a higher risk of malignancy. However, SOX-10 is not a specific marker for determining the degree of dysplasia; it remains positive in both typical and atypical melanocytic lesions [9, 10].

Therefore, SOX-10 is a useful marker for confirming the melanocytic origin of cells in DN, but its expression does not differ significantly in low and high grade dysplasias. Its main application is to confirm the melanocytic origin. In melanoma, SOX-10 expression can be more intense and diffuse, especially in conditions of active proliferation, which can indicate, along with other markers, aggressiveness, atypia, and architectural disturbances [4, 10].

Ki-67 is an important immunohistochemical marker and is used to evaluate the proliferative activity of cells in various types of tumors in neoplasias [2, 3]. Ki-67 expression in DN is usually limited to a small number of cells, indicating moderate proliferative activity [2, 4, 10]. The proliferative index (proportion of cells expressing Ki-67) in DN is up to 10%. In melanoma, the level of Ki-67 is much higher (10-30% or more), which reflects active cell division. Relatively low level of expression of Ki-67 in DN is an important diagnostic criterion that helps to distinguish them from melanoma. In DN, positive cells are usually located in the basal layer of the epidermis or near the DEJ. In melanoma, Ki-67 can be detected at different levels, including the dermis. Therefore, Ki-67 is an important marker for assessing proliferative activity in DN. Its low expression indicates a benign character of the formation, and an increase in the level may be an alarming signal that requires further study [4, 10].

p16 is a tumor suppressor protein encoded by the CDKN2A gene [3, 11, 14]. It acts as a cell cycle regulator, inhibiting CDK4/6 kinase activity and thereby preventing the transition of cells from the G1 phase to the S phase. In the context of DN, the study of p16 expression is important for assessing the risk of malignant transformation. We note that in dysplastic nevi, p16 is usually expressed in moderate amounts in the nuclei and/or cytoplasm of melanocytes [3, 11]. Pronounced expression of p16 is characteristic of benign or precancerous lesions, indicating preservation of its function as a tumor suppressor. Reduction or loss of p16 expression is often observed in melanomas and indicates tumor progression [4, 11, 13]. In DN, p16 is usually preserved, which helps to distinguish them from melanoma. p16 is detected in dysplastic nevi in the DEJ region, where proliferating melanocytes are located [4, 11]. In addition, reduced or absent expression of p16 has prognostic value and may indicate an increased risk of malignant transformation of a nevus into melanoma.

HMB-45 detects a glycoprotein associated with melanosomes of melanocytes. In DN, HMB-45 usually shows focal expression in melanocytes at the DEJ (in the superficial parts of the lesion). In the deeper parts (dermis), the expression disappears, which is a sign of benignity. In melanoma, the expression of HMB-45 is noted in the deep layers of the dermis, which reflects the progression of the process [11].

Melan-A detects a protein that is specific for melanocytes and melanoblasts. It is used for the diagnosis of DN as an additional marker to confirm the melanocytic nature of the cells, as its expression is diffuse and intense in both DN and melanomas [11, 13]. That is why we didn’t choose it for study.

Special attention should be paid to the PTEN (phosphatase and tensin homolog) marker: protein encoded by the PTEN gene, it plays a role in the growth and proliferation of embryonic melanoblasts, participates in the PI3KT/AKT and MAPK pathways [15]. PI3K generates phosphatidylinositol-3,4,5-triphosphate, a phospholipid that activates both AKT proteins (which play regulatory roles in the cell cycle, proliferation, survival, and neoplastic transformation) and mTOR proteins (which intervene in tumorigenesis). Within of the PI3K/AKT/mTOR pathway, phosphatases and tensin homolog of the tumor suppressor gene should be especially noted, PTEN, whose primary function is to inhibit AKT activation by degrading phosphatidylinositol-3,4,5-triphosphate through its phosphatase activity [16].

KIT and PTEN mutations in the PI3K/AKT/mTOR pathway are heterogeneous, affect different genes, and may coexist with BRAF (17%) or NRAS (9%) mutations. 43 somatic KIT mutations are found in 2% of melanomas. They appear to be particularly common in acral melanomas (40% of acral lentiginous melanomas have KIT mutations) and mucosal melanomas (23%). Finally, somatic PTEN mutations have been found in 22% of melanomas [15, 16, 17].

Although various studies have shown mutations in the tumor suppressor gene, PTEN/MMAC1, in primary, metastatic, and cultured cutaneous melanoma samples, little is known about the pattern of PTEN protein expression during early melanocytic tumor progression [15]. We note that PTEN shows absence of expression in thin melanomas thereby it can be useful in diagnostic between dysplastic nevus, melanoma in situ and other melanocytic malignant/benign proliferations (spitzoid tumors, SAMPUS, MELTUMP, STUMP etc.) [18].

Statistical processing of the study results was carried out using descriptive and analytical biostatistics methods implemented in the STATISTICA packages (StatSoft Inc., ver.6.1, serial number AGAR909E415822FA) and MedCalc (www.medcalc.org, trial version 23.3.7). Quantitative variables are presented as median (Me) with quartiles (Q1-Q3). Comparisons between the three groups were performed using the Kruskal-Wallis test (H) with pairwise posterior comparisons using Dann's test. The relationship between the characteristics was assessed using the Spearman rank correlation coefficient (r). To assess the discriminatory power of the indicators, ROC analysis (Receiver Operating Characteristic curve analysis) was used to calculate the area under the ROC curve (AUC) with a 95% confidence interval (95% CI), determine the optimal cut-off point and the corresponding sensitivity (Se) and specificity (Sp) indicators of the criteria. All statistical tests were two-sided, and the results were considered significant at $p<0.05$.

RESULTS AND DISCUSSION

The study shows that most common criterion is structureless area that is presented in majority of lesions. Generally, they are combined with other mentioned signs. The use of immunohistochemical markers made it possible to separate early melanomas (n=19) and other (benign) tumors (n=22) from the primary cohort of patients who, according to the results of pathology, had moderate or severe grade of dysplasia. After the all tests, the cohort with DN was designated in quantity of 55 cases. Due to the international recommendations in group with early melanomas a wide excision was performed. The expression levels of immunohistochemical markers Ki-67, SOX-10, p16 and PTEN were determined in each group. The study shows high expression of a SOX-10 antigen in all of lesions (50-90%) indicating on melanocytic origin of them. A negative correlation

was found between the level of SOX-10 expression and the degree of malignancy (r= -0.275, p=0.007). The decrease in SOX-10 expression in malignant tumors may reflect the process of "degradation" of melanocytes and the loss of their normal characteristics. We observed low level of Ki-67 (10-30%) and proliferative index (up to 10%) in the DN that indicates a benign character of the formations. A strong positive correlation was found between the level of Ki-67 expression and the degree of malignancy (r=0.743, p<0.001). This confirms the role of Ki-67 as an important marker of the proliferative activity of tumor cells. The higher the level of Ki-67, the greater the likelihood that the formation is malignant. Lost or reducing of p16 expression notes in early melanomas (0-20%) and interpetates in medium to high-moderate significances in DN and other benign melanocytic tumors (30-90%). PTEN protein as inhibitor of melanogenesisshows high expression in all benign lesions (50-90%) and loss of sensitivity in malignant melanocytic tumors (0-20%) (Table).

Expression levels of immunohistochemical markers in different groups of melanocytic lesions, Me (Q_1-Q_3)

Immunohistochemical markers	Benign nevi -1	Dysplastic nevi -2	Malignant tumours -3	Statistical criterion
Ki-67, %	9 (7-12) $p_{2,3}$	16 (12-19) $p_{1,3}$	27 (25-30) $p_{1,2}$	H=52,71, p<0,001
SOX-10, %	70 (60-90) p_{3}	65 (59-70)	63 (59-67) p_{1}	H=7,27, p=0,026
p16, %	71 (60-80) p_{3}	75 (66-83) p_{3}	13 (8-20) $p_{1,2}$	H=45,34, p<0,001
PTEN, %	79 (60-85) p_{3}	76 (70-81) p_{3}	10 (0-15) $p_{1,2}$	H=45,40, p< 0,001

Note. $p_{1,2,3}$ – statistically significant differences (p<0.05) compared to the corresponding group 1, 2, 3 by Dann's test.

p16 and PTEN: Negative correlations were found between the expression levels of p16 (r= -0.500, p<0.001) and PTEN (r= -0.514, p<0.001) and the grade of malignancy. This suggests that loss of function of these tumor suppressors plays an important role in the development and progression of melanoma.Applying of HMB-45 and Melan-A did not give a significant priority (the same level of expression in groups with benign melanocytic tumors, dysplastic nevi and melanomas) especially in diagnostic between superficial melanocytic tumors.

The results of ROC analysis confirmed the high prognostic significance of immunohistochemical markers Ki-67, PTEN, p16 in the diagnosis of severe dysplastic nevus and melanoma in situ. At the same time, excellent prognostic characteristics were provided by the level of Ki-67 expression greater than 24%: area under the ROC curve AUC=0.944, 95% CI (0.865-0.984), sensitivity – Se=84.2%, specificity – Sp=94.4%; p16 expression level ≤35%: AUC=0.999, 95% CI (0.948-1.00), Se=100%, Sp=98.1%; PTEN expression level ≤25%: AUC=1.00, 95% CI (0.951-1.00), Se=100%, Sp=100% at p<0.001.

Often DN and melanoma show common dermatoscopic features, neverthelessdermatoscopy abided simple, sensitive, not invasive method for diagnostic of the melanocytic lesions. Our study demonstrated that intensity level of this features correlated with histopathology and will help to build a diagnostic protocol. Different reviews show lack of clinical diagnostic of dysplastic nevi [2, 19]. Mnemonic ABCD'e as used as clinician rule for melanoma diagnostic is incorrect and leads to diagnostic bias in 2 from 3 cases also lack of standardized nomenclaturecontinuetocauseuncertaintyamongcliniciansand pathologists. At the same time dermatoscopy should be used for clinical diagnostic all pigmented lesions [2]. Do we need to rethink the diagnoses of severe dysplastic nevus and melanoma in situ? The study of the problem is still ongoing but there are some pieces of evidence to reject or support diagnostic thresholds. First, these are pieces of evidence of the natural origin of these lesions, which to our opinion was occasional as both severe dysplastic nevus and melanoma in situ are commonly managed with excision [2]. According to the data of the one statistic model study, only 3% of malignant lentigo (a subtype of melanoma in situ) could evolve into lentigo maligna melanoma (a subtype of invasive melanoma) [19]. Second, was evidence on the reliability of diagnostic criteria for the two types of lesions. One of the study – by Elmore et al. [20] detected bad reproducibility for diagnoses of severelydysplasticnevusandmelanomainsitu.Third, was diagnostic shift in the diagnostic threshold over

time, so that a more 'malignant' diagnostic label would now be applied even though the same melanocytic tumor was recognized benign previously. We found two studies giving evidence on diagnostic shift, both at high risk of bias. These studies both propose an implicit lowering of the diagnostic thresholds for melanoma and severe dysplastic naevus over time, leading to extension of the disease determination [2, 19]. Thereby, accidental evidence of natural origin gives indefinite but likely low risk of melanoma development in situ into invasive one, and insignificant risk of evolving from severe dysplastic nevus into invasive melanoma. These types of lesions may be better conceptualized as risk factors for, rather than obligate precursors to, invasive melanoma. There is strong evidence of low reproducibility for diagnosis of both types of lesions, and some evidence that disease definitions have expanded over time. There is need for active discussion, in both clinical and pathology communities, on the benefits and weakness of changing diagnostic thresholds and/or terminology to address potential overdiagnosis.

CONCLUSIONS

1. We consider that application of this combination of immunohistochemical markers in routine practice can significantly improve the diagnosis of dysplastic nevi and melanoma, especially for diagnostic collisions among superficial atypical melanocytic proliferations.
2. Usage of the phosphatase and tensin homolog protein can be useful for diagnostic not only of "thin melanomas" group but for non-pigmented nodular melanomas and for secondary metastatic melanoma lesions with unknown primary tumors.

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Prokhach A.V. – conceptualization, methodology, investigation, formal analysis, resources, data curation, writing – original draft;

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