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PARTICULARITIES OF MELANOCYTIC NEVUSES OF CHILDREN

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Цель. Определить клинико-морфологические особенности рецидивирующего течения меланоцитарных образований кожи у детей.

Материал и методы. Исследование основано на изучении данных архива «Винницкого областного патологоанатомического бюро Винницкого областного совета» (Украина) 468 гистологических протоколов удаления невусов за весь период исследования (с 2018 по 2020 гг.).

Результаты. В целом срок между первичным хирургическим вмешательством по удалению /"самоудалению" пигментного образования до рецидива меланоцитарных невусов составлял от 3 до 6 месяцев. Рецидивы меланоцитарных невусов у детей встречались на разных участках кожи, но чаще всего на туловище (44,44%), волосистой части головы и шее (27,78%). Рецидивы меланоцитарных невусов у детей встречались на разных участках кожи, но чаще всего на туловище (44,44%), волосистой части головы и шее (27,78%). Типичным дерматоскопическим признаком при рецидивах пигментных невусов было наличие рубцовой ткани по периферии образования. Контуры рецидивной пигментированной опухоли при дерматоскопии не имели четкой симметрии.

Заключение. Разница в морфологическом строении разных типов меланоцитарных невусов объясняет низкую частоту клинических и гистологических диагнозов при рецидивирующей патологии в детском возрасте, что, с учетом наличия атипичных клеток меланоцитарного происхождения в зоне рубца, обуславливает необходимость дифференциальной диагностики при рецидивах меланомы кожи, особенно в случаях отсутствия гистологического подтверждения образования первичных меланоцитов.

Ключевые слова: меланоцитарный невус, хирургия, дети, онкология

Objective. Determination of clinical and morphological features of the recurrent course of melanocytic skin lesions in children.

Methods. The study is based on the data analysis of 468 histological protocols of removing nevi taken from the archives of «Vinnytsia Regional Pathological Bureau of the Vinnytsia Regional Council» (Ukraine) during the whole period of the study (from 2018 to 2020).

Results. In general, the terms between the primary surgical removal / «self-removal» of the pigmented formation before the recurrence of melanocytic nevi made up 3-6 months. Melanocytic nevi recurrences in children occurred in different areas of the skin, but most often on the trunk (44.44%) and scalp and neck (27.78%). A typical dermatoscopic sign of pigmented nevi recurrences was the presence of scar tissue on the periphery of the lesion. The confines of a recurrent pigmented tumor on dermatoscopy were not clearly symmetrical.

Conclusion. The existing difference in the morphological structure of different types of melanocytic nevi explains the low frequency of clinical and histological diagnoses in recurrent pathology in childhood; the possibility of atypical cells presence of melanocytic origin in the scar area necessitates differential diagnosis in case of the skin melanoma recurrence, especially in cases of histological verification absence of the primary melanocytic lesion.

Keywords: melanocyte nevus, surgery, children, oncology

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Particularities of Melanocytic Nevuses of Children
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Научная новизна статьи
Меланоцитарная патология кожи является одной из наиболее сложных проблем хирургии детского возраста. Проблемы меланоцитарных невусов кожи детей делятся на две основные категории, а именно наличие известных и пограничных патологий следует рассматривать в сфере возможной злокачественной потенции, включая меланому кожи и возможность рецидивирующих меланоцитных образований.

What this paper adds
Melanocytic skin pathology is one of the most complex problems in pediatric surgery. The problems of the skin melanocytic nevi in children are divided into two main categories, namely the presence of well-known and borderline pathologies that should be considered in terms of possible malignant potency, including skin melanoma and the possibility of recurrent melanocytic lesion.

Introduction

Melanocytic skin pathology is one of the most complex problems of pediatric surgery. The problems of the skin melanocytic nevi (MCN) in children are divided into two main categories, namely the presence of well-known and borderline pathologies that should be considered in terms of possible malignant potency, including the skin melanoma (MS) and the possibility of recurrent melanocytic lesions (12). Actually these aspects of the problem cause diagnostic and treatment errors, which eventually lead to various complications and unsatisfactory oncological and aesthetic consequences of treatment [1].

Recurrentl melanocytic nevi (RMN) usually appear after incomplete removal of pigmented nevi (PN) due to their traumatic injuries (shaving, scarification as the result of injury, self-removal, superficial removal, etc.). Particular diagnostic problems arise in cases of lack of histological examination of primary drugs, such as after electrodissection [2].

People with dark skin and young patients are more exposed to an increased risk of the pathology recurrence. The occurrence of RMN is inversely related to the increase of patients' age [3].

The term «phenomenon of recurrent nevus» was first proposed by R. Kornberg and A.B. Ackerman in 1975 after studying the case of PN injuring, which was mistakenly diagnosed as pseudo melanoma [4,5].

RMN are more often localized on the trunk (especially on the back), face and limbs. Recurrence usually occurs within the first 6 months after the PN initial removal and is clinically characterized by the scar macular zone with variegated hypo- and hyperpigmentation, with linear strokes, or diffuse pigmentation. The RMN histological pattern consists of connective tissue melanocyte component of varying degrees of pigmentation that covers fibrous scar tissue and deep residual monoformical nevus cells without mitotic figures, which allows us to define it as three-zonal [6]. Regardless of the structure and nomenclature of the primary PN, histopathologically, the three-zonal pattern of RMN has three features, i.e. an atypical intermediate proliferation of melanocytes, which spreads above the basal level; visible fibrous scar tissue of the dermis, which contains large, irregularly shaped melanocytic nests; residual nevi cells, adjacent to the scar or below it [7, 8, 9].

Modern researchers have put forward numerous theories of recurrent PN occurrence: sowing during the primary removal of pigment lesion; functional stimulation after partial removal as a return to an earlier stage of the natural course of the nevus; "signal" activation of the growth stimulation that is mediated by residual nevus cells; prolonged growth of residual epithelial melanocytes; repopulation of melanocytes from the lower part of hair follicles due to their migration and repopulation of some depigmented areas and others [8, 10, 11].

The mechanism of PN recurrence presently has no definitive explanation, which in turn creates significant difficulties in the pathology diagnosis and treatment [12].

Objective. Determination of the clinical and morphological features of the recurrent course of melanocytic skin lesion in children and their development based on the radicalization method of surgical nevi excision.

Methods

This section of the study is dynamic in terms and is based on the data analysis from the archives of «Vinnytsia Regional Pathological Bureau of Vinnytsia Regional Council» (Ukraine) of 468 histological protocols of removing nevi during the whole period of the study (from 2018 to 2020). The study was conducted according to the plan designed on the basis of the Pediatric Surgery Clinic of Vinnytsia National Medical University (Ukraine), the structure of which is displayed in the Table 1.

Table 1

Design of Research

I stage Retrospective analysis of medical records of outpatients and inpatients in whom melanocyte nevi were removed in the pediatric surgery clinic.
II stage Retrospective analysis of medical records of outpatients and inpatients in whom melanocyte nevi were removed in other medical institutions, or after their unauthorized (spontaneous) removal.
III stage Analysis of the archive of histological protocols for the entire study period in order to compare the correspondence of clinical and morphological diagnoses. Study of microscopic features of recurrent melanocyte nevi in histological materials.
IV stage Clinical and instrumental-diagnostic examination of patients with complaints of pigment in the area of the postoperative scar after removal of melanocyte formation, using the dermatoscopic method.

Simultaneoiusly with the study of the archival data of histological protocols, the other object of analysis was the records of outpatients and inpatients of retrospective and prospective periods of the study. Such analytical method of various medical records revealed 18 (3.85%) cases of recurrent (prolonged) melanocytic nevi in patients of different ages, 10 (55.56%) girls and 8 (44.44%) boys.

In this part of survey clinical, instrumental (dermatoscopy), morphological research methods and statistical processing of the material were used.

The research was conducted in accordance with the Declaration of Helsinki and approved by the inspection authority (e.g. the ethics committee) in case of human or animal studies.

Statistics

The software MS Statistica 10.0 was used in the study.

Results

Clinical and dermatoscopic manifestations of recurrent melanocytic nevi.

The typical clinical picture of recurrent melanocyte nevi was visually presented as areas of hyperpigmentation in the postoperative scar area. The areas of hyperpigmentation were like foci with extremely variable geometric outlines, coloring from pale brown to dark brown of varying intensity, which did not extend beyond the scar tissue. In the majority of cases, the areas of hyperpigmentation were located eccentrically, which is also typical for recurrences of malignant MS, but sometimes they localized in the central part of the scar in the form of single or multiple fragments. The size of such foci of hyperpigmentation ranged from 2 to 8 mm.

Patients with MN recurrence during hospitalization complained of itchy skin in the area of the postoperative scar and neoplasms and exfoliation of the epithelium in this area. The presence of hair shafts in the center of the tumor, in three clinical cases with the recurrence period of more than 4 months, confirmed the recurrent course of the pathology.

In general, the timeline between the primary surgical removal / "self-removal" of the pigment lesion before the MN recurrence comprised from 3 to 6 months (Tab. 2).

In the vast majority of cases - 11 (61.11%), relapses occurred in the period from 4 to 5 months after the initial intervention (surgery / traumatic injury), which corresponds mainly to the benign nature of the proliferative process according to B. Hiscox et al., (2017) [12].

Recurrences of MN in patients appeared in different areas of the skin, but most often on the trunk (44.44%) and scalp and neck (27.78%) (Tab. 3).

The gender distribution of patients was as follows: the study involved 10 females (55.6 %) and 8 males (44.4 %).

During the dermatoscopic examination of recurrences of pigment lesions, which was carried out in all cases of their occurrence, pigment spots in the form of lumps of melanin were visualized. The identified hyperpigmented globules were detected simultaneously with the phenomenon of "radial radiance", that is absent in MS, that border with unstructured zones.

A typical dermatoscopic sign in PN recurrences was the presence of the scar tissue on the lesion periphery. The confines of the recurrent pigmented tumor on dermatoscopy were not clearly

Table 2

Time ranges of recurrence

Time	Number of cases	
	Absolute value	%
Up to 3 months	3	16.67
Up to 4 months	4	22.22
Up to 5 months	7	38.89
Up to 6 months	4	22.22
Total	18	100.0

Table 3

The frequency of recurrence melanocyte nevi depending on the location

Localization of foci	The number of cases	
	Absolute value	%
Head, neck	5	27,78
Torso	8	44,44
Upper extremities	3	16,67
Lower extremities	2	11,11
Total	18	100.0

symmetrical.

To illustrate the clinical features and dermatoscopical signs of recurrent nevi, a clinical example is presented.

Clinical example. Patient S., Age 12 was hospitalized on March 27, 2019 with a preliminary diagnosis: nevus on the back. It is known from the anamnesis that the skin pigment lesion on the back area has been present since birth, but about 4 months ago there was a traumatic injury of the lesion, which led to a partial (approximately 1/5 by size) loss of PN size. The damaged skin areas healed with primary tension, but over the past two months, the PN portion remained after the injury began to increase in size, protruding above the surface of the skin, with periodic bleeding directly from the lesion.

While examining the patient, there was a pigment lesion on the back with a total diameter of up to 10.0 mm, brown, which 4.0 mm protrudes above the skin surface. The lesion was surrounded by a radial zone in the form of a pale pink belt with a purple tinge. At 3 and 9 o'clock position small fragments of scar tissue of triangular shape were determined, which led directly into the bulk of the neural formation. Zones of hyperpigmentation were characterized by an eccentric accumulation of melanin.

On dermatoscopy the phenomenon of "radial radiance" had weak expressiveness, on the lesion periphery there was the scar tissue of the skin.

Surgery was carried out, excision of a pigmented neoplasm (Fig. 1).

The general condition of the child normalized; on March 29, 2019 the outpatient treatment of the patient was discontinued.

Histological conclusion dated on March 29, 2019: among the reticular fibers around the dense unstructured lesion, the cyst with the lining of multilayered squamous epithelium was formed. It was surrounded by the chronic inflammation zone. Parakeratosis was determined, the presence of pigment in the epidermis stratum corneum , dilation of the dermis vessels with ulceration of the latter and the phenomena of fibrosis were determined. Conclusion: morphological features were typical for a target-like hemosidereal nevus.

The correlation analysis between clinical manifestations and the results of dermatoscopic examination revealed that the visually the recurrence had no characteristic features of the corresponding type of previously removed nevus, which made it impossible to apply the basic criteria of benign melanocytic lesion according to the ABCDE principle.

Morphological features of recurrent melanocytic nevi.

The analysis of histological specimens made it possible to identify the following histological variants of recurrent melanocytic nevi (RMN) (Tab. 4).

Discussion

During morphological study of RNM biopsies, in the absence of data on primary pigment lesion, it was found that using the histological structure of recurrent (continued growth) melanocytic object is almost impossible to determine the type of primary nevus. 3 clinical cases were an exception when there were residual structures of melanocytic lesions, with their "non-radical (incomplete) removal" due to traumatic scarification.

Unfortunately, the histological method can't be considered as the basic objective verifier of the diagnosis in all patients with recurrent pathology. The primary morphological characteristics of the removed objects were known only in half (9)numbers of the removed nevi, which did not allow to identify completely the associative series of certain morphological features with an increased risk of recurrence (Tab. 5).

The importance of the primary morphological

Fig. 1. Patient Sh., Age 12. Diagnosis: Nevus on the back. A – general view of the pigment formation during hospitalization; B – type of tumor while dermatoscopy; C – removed PN (macropreparation); D – postoperative wound (general view). 1 – fragments of scar tissue.

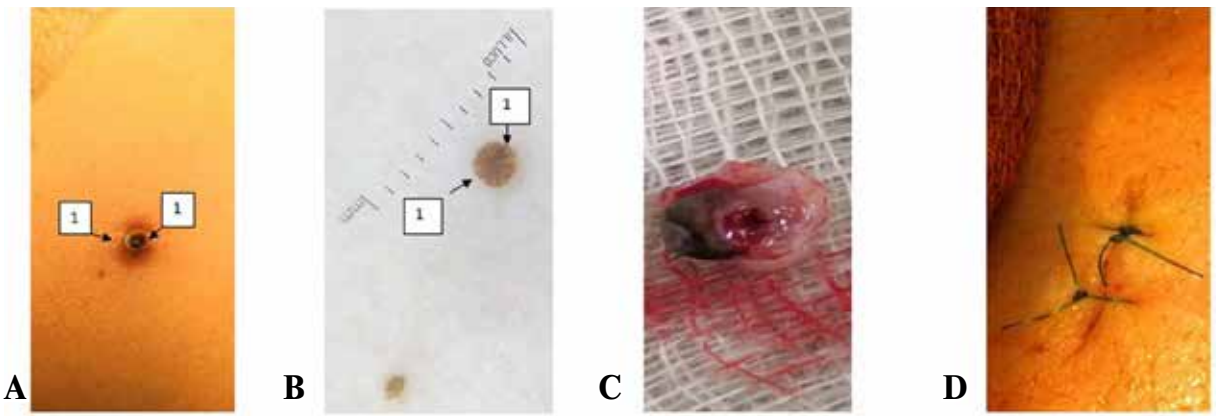


Table 4

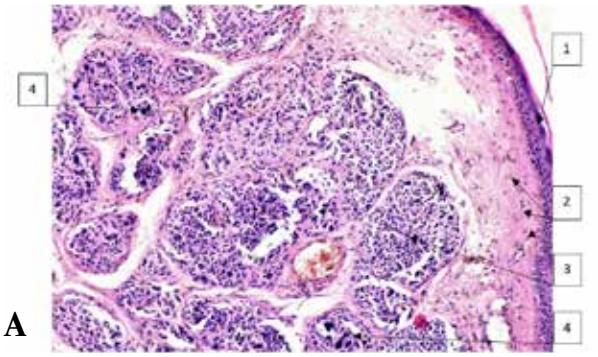
Histological variants of recurrent melanocytic nevi

Histological variants of recurrence melanocyte nevi	Features of the Histological building of recurrence melanocyte nevi
I (epidermal)	Atrophy of the epidermis, proliferation of atypical melanocytes in the epidermis with the formation of nests, the presence of scar tissue in the dermis, melanophages and possible inflammatory infiltration (Fig. 2).
II (dermal)	Atrophy of the epidermis, proliferation of atypical melanocytes in the dermis with the formation of scar tissue, the presence of melanophages and inflammatory infiltrates (Fig. 3).
III (mixed)	Atrophy of the epidermis, proliferation of atypical melanocytes in the epidermis and dermis with the formation of nests, the presence in the dermis of scar tissue, melanophages and residual infiltrates (Fig. 4).
IV (residual)	Atrophy of the epidermis, hyperpigmentation of the basal layer of the skin, in the dermis - melanophages, inflammatory reaction and scar tissue, sometimes residual complexes of the primary nevus (Fig. 5).

Table 5

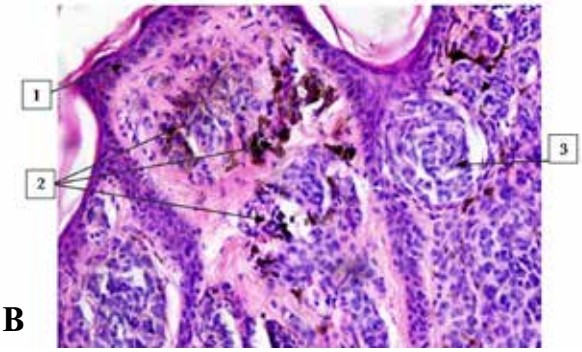
Data on the histological diagnosis of primary melanocyte formation.

Histological conclusion	Number of cases	
	Absolute value	%
Intradermal nevus	5	27.78
Dysplastic nevus	4	22.22
Histology is unknown	7	38.89
No histological studies have been performed	2	11.11
Total	18	100.0



A

Fig. 2. The first variant. Primary morphological diagnosis: intradermal nevus. Hematoxylin and eosin staining. Magnification ×200. Atrophy of the epidermis with proliferation of atypical melanocytes (1) and extracellular accumulation of melanin (2), the existance of solid nests of non-oral cells containing melanin in the dermis (3) and multinucleated Tuton cells (4).



B

Fig. 3. The second variant. Primary morphological diagnosis: intradermal nevus. Hematoxylin and eosin staining. Magnification ×400. Atrophy of the epidermis (1). Extracellular and intracellular accumulation of melanin (2), the formation of nests in separate areas by neural cells in the form of concentric figures (3).

verification of the diagnosis at the initial PN removal is illustrated by the following clinical example.

Clinical example. Patient Z., age 11, hospitalized in the surgical department on January 21, 2019 with a preliminary diagnosis: nevus on the back. According to the anamnesis of the disease it is known that the pigmented neoplasm on the back has been present since birth, with a gradual tendency to increase in size with the age of the child. About 9 months ago, during a sports competition, a complete mechanical scarification of the nevus part protruding above the skin surface took place.

The site of skin damage healed on its own without visible to the naked eye signs of hyperpigmentation of the causal area. However, 3 months ago, in the projection of the nevus (scar) localization , two fragments of hyperpigmentation of dark brown color with diameters of 5.0 – 6.0 mm appeared at the level of the skin. The parents sought medical help, and after the clinical and laboratory examination on January 22, 2019, the patient underwent surgery – removal of the nevus. Under general anesthesia after treatment of the operating field three times with betadin solution, edging the pigmented lesion with a sharp (scalpel) a piece of the skin measuring 20.0 × 12.0 mm

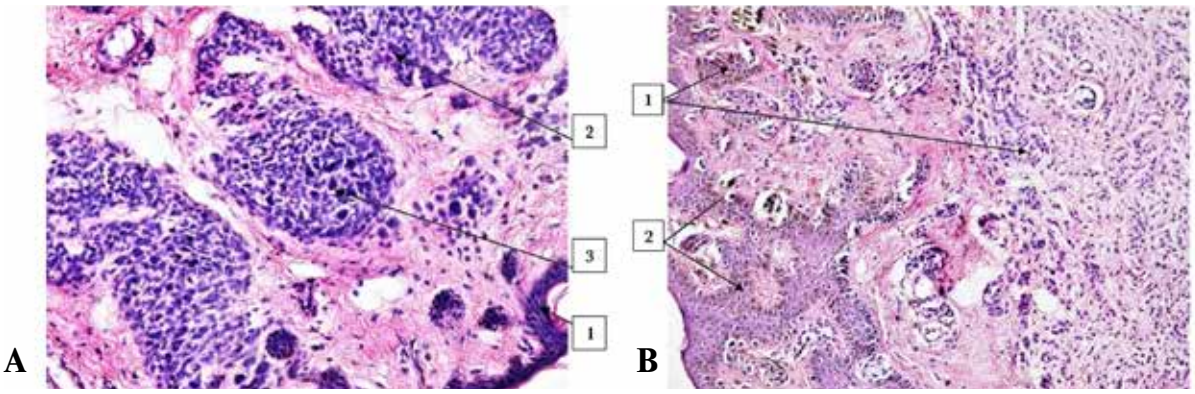


Fig. 4. The third variant. A. Primary morphological diagnosis: intradermal nevus. Hematoxylin and eosin staining. ×400. Atrophy of the epidermis with proliferation of atypical melanocytes (1), solid nests of non-oral cells in the dermis, individual nevocytes containing melanin (2), large Tuton cells (3). B. Primary morphological diagnosis: mixed nevus, Hematoxylin staining and eosin. ×200. Against the background of atrophy of the epidermis, nesocyte nests and individual cells loaded with melanin (1), small nests of non-oral cells in the dermis and individual nevocytes containing melanin (2).

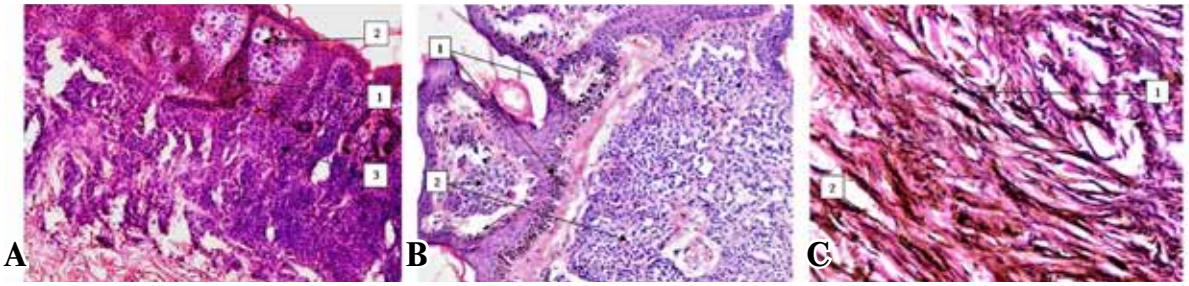


Fig. 5. Variant IV. A. Primary morphological diagnosis: intradermal nevus. Hematoxylin and eosin staining. Magnification ×200. Accumulation in the basal layer of the epidermis of melanin (1), the existence in the upper parts of the dermis, along with normal melanocytes (2), light balloon-like cells (3). B. Primary morphological diagnosis: mixed nevus. Hematoxylin and eosin staining. ×200. Atrophy of the epidermis, hyperpigmentation of the basal layer of the epidermis (1), fields of neocytes (2). C. Primary morphological diagnosis: blue nevus. Hematoxylin and eosin staining. Ч 400. Accumulation of elongated melanocyte-filled process melanocytes in the upper part of the reticular layer (1) and the basal level (2) of the skin.

and subcutaneous fat were removed, followed by hemostasis, suturing the skin. The removed soft tissue fragment was sent for histological examination.

Histological description of the micropreparation: the morphological picture of the biopsy resembled the structure of an intradermal Spitz nevus with a pronounced reactive lymphoid infiltration against the background of the epidermis atrophy. In the dermis, solid nests of non-oral cells containing melanin were identified, and sometimes large multinucleated Tuton cells were found; in some areas, the neural cells form concentric shapes; extracellular accumulations of melanin, pigment content in the cells of the basal layer of the epidermis, the presence of keratin cysts were observed in the upper parts of the dermis (Fig. 6).

Due to the use of destructive methods of removal of melanocytic lesion in patients , which do not allow to save biopsy material for preliminary histological examination, there are significant clinical difficulties in differential diagnosis in cases of recurrent (continued growth) MCN, as the lack of material for comparison makes it impossible to assess biology of the primary melanocytic lesion[13].

However, the presence of the MCN recurrent phenomenon (prolonged growth) after their removal makes it necessary to carry out such a differential diagnosis, especially in the skin melanoma, particularly in cases of the recurrent dysplastic nevi, which is primarily characterized by atypical structure and cytology, exacerbated in relapses.

In addition, in the process of performing this stage of the study, it must take into account the existing fact that the presence of any periodic or prolonged exposure to physical (mechanical, thermal, radiation, wave, etc.) stimuli, certain age categories (pre- and pubertal age) increases the likelihood of activation of malignant melanocytic skin lesion.

Confirmation of this postulate is the fact that in the process of morphological studies a low frequency (11.1%) of coincidence of clinical and histological diagnoses of RMN was determined which is explained by the existing variety of different histological variants of the course of PN pathology. Also, the low percentage of coincidences of clini-

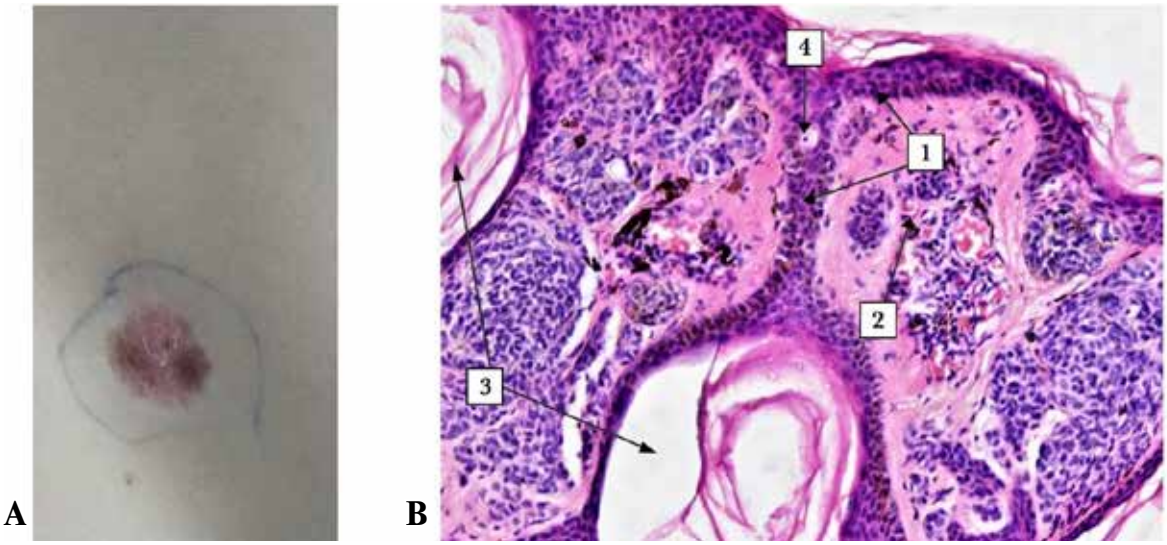


Fig. 6. Patient Z., age 11. Diagnosis: nevus on the back. A – General view of the pigment formation of the back; B – histological structure of the biopsy: proliferation of spindle-shaped nevus cells without atypia in the form of their clusters, with low content of intracytoplasmic melanin (1), Tuton cells (2), keratin cysts (3), large light goblet cells (4). Hematoxylin and eosin staining. ×200.

cal and morphological diagnoses of RMN and the possible presence in biopsy specimens of active cells of melanocytic origin in the scar area necessitates a differential diagnosis with possible onset of the skin melanoma, especially in cases without histological verification of the primary biopsy.

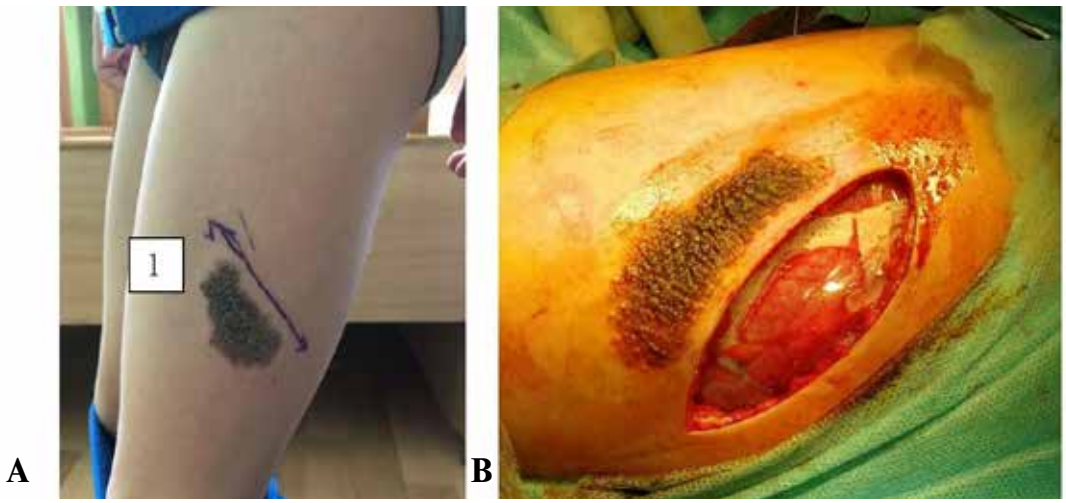
In order to illustrate this situation a clinical example is presented..

Patient D., age 8 years 18.02.2019, was hospitalized for the left thigh pigmentation inpatient treatment. On the basis of the disease anamnesis it is known that the child has been ill since birth. His mother said that in recent months the pigment formation tended to increase rapidly in size and change color to darker tones. Locally: on the outer surface of the left thigh in the middle third was determined by the pigment lesion measuring 11.0 × 6.5 cm, dark brown, the surface of the nevus was velvety, bumpy. The lesion protruded above the skin up to 3 – 4 mm, the surface was without hairs. On February 19, 2019, an operative procedure was performed: subcutaneous expander (Fig. 7).

During re-hospitalization, on May 29, 2019, surgery was carried out: removal of the pigmented formation of the left thigh, removal of the subcutaneous balloon, skin grafting. Histological conclusion of melanocytic formation was the dysplastic nevus. It was recommended to review the results of biopsy in the State Research Institute of Research in Kyiv, where after immunological examination of histological preparations the final diagnosis was made: the skin melanoma of the left thigh T1N0M0 1clinical group.

On July 11, 2019, in accordance with the

Fig. 7. Patient D., age 8 years. A – the outward of the pigment formation: 1 – marking the line of operative access; B – stage of surgery – setting the subcutaneous expander.



recommendations of the State Research Institute of Research in Kyiv, surgery was performed: the radicalization of the postoperative scar with a gap of 1.5 cm within healthy tissues. Histological conclusion of removed skin biopsies was as follows: the skin with dermis scarring and the presence of foci of granulomatous inflammation around the elements of the suture material; fibrous adipose tissue with marginal standing of leukocytes in blood vessels.

Conclusion

It has been determined that regardless of the histological type of melanocytic nevus, the phenomena of epidermal atrophy with hyperpigmentation of the basal layer, melanophages, inflammatory reaction and fibrous scar tissue in the dermis are observed. The difference in the morphological structure is only in the localization of foci of atypical melanocytic proliferation or in their absence.

The present difference in the morphological structure of different types of melanocytic nevus explains the low frequency of clinical and histological diagnoses of recurrent pathology in childhood, the possibility of the atypical cells presence of melanocytic origin in the scar area necessitates differential diagnosis in the recurrent skin melanoma, especially in cases of absence of histological verification of primary melanocytic formation.

Taking into consideration possible diagnostic difficulties in verifying the diagnosis, it is necessary to give preference to surgical methods of the nevus tissue excision with the mandatory histological examination of the biopsy material.

Information about the source of support in the form of grants, equipment, drugs

The work was carried out in accordance with the plan of scientific research of the National Pirogov Memorial Medical University, Vinnytsia, Ukraine. The authors did not receive any financial support from drug manufacturers.

Conflict of interest

The authors declare that there is no conflict of interest.

Ethical aspects. Ethics committee approval

The study was approved by the ethical committee of the National Pirogov Memorial Medical University, Vinnytsia, Ukraine.

When describing clinical cases, information on the consent of patients is indicated. Agreement

The patients agreed to the publication of the data and the publishing on the Internet of information about the nature of their disease, the treatment carried out and its results for scientific and educational purposes.

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