CASE REPORT

Spitz nevus with an uncertain malignant potential

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Abstract

We present the case of 10-year-old girl who have had from birth a plane tumor, of tan color, 3–4 mm of diameter, localized on the face on the cutaneous part of the superior lip. This tumor has been stabile until 8-year-old. Then, after repeated sunlight exposures, the lesion has become more stark, hemispheric in shape, has increased in size becoming about 5–6 mm, with irregular borders, and after an accidental traumatism it began to bleed. We have performed the electroexcision of the lesion for diagnostic and therapeutic purpose. The histopathologic exam distinguished typical images of Spitz nevus on some of the histological sections but also of melanocytary tumor with uncertain malignant potential on the others where atypical mitoses localized in the deeper component of the tumor are being noticed. The immunohistochemical assessment of the tumoral cells showed positivity for the melanocytic markers HMB45 and Melan A, within junctional intraepidermic nevic cells and in the nevic cells from superficial dermis, and also for CD44 protein (belonging to the adhesion molecules family). However, cyclin D1 was positive in rare nevic cells, and the proliferation rate of the tumor was small, with a proliferation index for Ki67 lesser than 5%. The correlation between histopathological and immunohistochemical data conducive to final diagnosis of Spitz nevus with uncertain malignant potential. The clinical evolution confirmed the histopathological diagnosis by the fact that the patient did not presented clinical signs of local recurrences or metastasis at three years after the excision of the tumor.

***Keywords*:** Spitz nevus, malignant melanoma, child, neoplasia.

Introduction

A Spitz nevus or a nevus with pipe stems is a proliferation of melanocytes that usually appears during childhood. Initially, Sophie Spitz has described these lesions under the name of "juvenile melanoma" after the clinical behavior and the histopathological aspect [1].

Soon, many authors that have previously accepted the name of benign "juvenile melanoma" have confirmed the benignity of this kind of nevus. Because this is not a melanoma and is not exclusively the appanage of the child, being more frequently met in children and adolescents, but being able to appear on adults too, it has finally been accepted the simple name of Spitz nevus. The melanocytar nevi in children can be congenital or congenitally contracted, and the contracted ones are often Spitz nevi. Their incidence decreases progressively with age [2].

Spitz nevi are melanocytar neoplasias with distinctive pathological aspects. However, sometimes they can present some aspects that make the differential diagnosis with malignant melanoma very difficult. Spitz nevus can be diagnosed wrong as malignant melanoma and vice versa [3].

Patient and Methods

We present the case of 10-year-old girl who has had from birth a plane tumor, of brownish color, 3–4 mm in diameter, with smooth margins, localized on the face on the cutaneous part of the superior lip. After repeated sunlight exposures for two years, it has been noticed changes in shape, color and size, so the tumor has become more prominent, has increased in dimension (5–6 mm diameter), with anfractuous borders, of a brown-blackish color. After an accidental traumatism, the tumoral formation was broken, abundantly bleeding, this being the reason for the electroexcision of the lesion. The clinical exam performed initially, in the moment of hospitalization, and periodically during the monitorizing have not been high-lightened ganglionar loco-regional or at a distance modifications and the performed paraclinic investigations could not sustain a diagnosis of malignancy. The mentioned data have been sustained through a PET/CT exam (Budapesta – Hungary, 2007; Oradea – Romania, 2008).

The obtained resection piece has been worked in the Pathology Department of the Emergency County Hospital of Craiova, through the classical histopathological technique of inclusion in paraffin. There have been performed sections both for the usual

Hematoxylin–Eosin stain, as well as for the immunohistochemical exam. The immunohistochemical investigations have been realized both in the "Victor Babeş" National Institute for Research and Development in Pathology and Biomedical Sciences, Bucharest and in the Research Center for Microscopic Morphology and Immunology, University of Medicine and Pharmacy of Craiova. We have used the tristadial method based on the complex Streptavidine–Biotin (sABC Complex), and was performed the evaluation of the immunohistochemical expression of the following markers, using specific antibodies: anti-HMB45 (HMB45 clone, dilution 1:50, DAKO), anti-S100 protein (polyclonal, dilution 1:250, DAKO), anti-Vimentin (V9 clone, dilution 1:50, DAKO), anti-Melan A (A 103 clone, dilution 1:50, DAKO), anti-CD44 (DF 1485 clone, dilution 1:50, DAKO), and anti-Cyclin D1 (DCS-6 clone, dilution 1:40, DAKO). In order to evaluate the proliferation of the tumor, we have calculated the proliferation index Ki67 based on the nuclear immunomarking with antibodies anti-protein Ki67 (MIB 1 clone, dilution 1:50, DAKO). For each antibody have been used corresponding external check-ups.

Results

The fragment has been extracted from June 2007 and has been diagnosed histopathologically as a malignant Clark IV melanoma, Breslow 1.5, without borders of oncological security, being treated through chemotherapy within the period June 10th 2007–August 3rd 2007. The extension of the present disease evaluation has not determined metastases at a distance.

In July 2007 was performed a second surgical intervention practicing the excision of a 1.5 cm scar, that at the histopathological exam has highlighted a non-specific inflammatory process, without tumoral lesions. The lympho-ganglionar evaluation through PET was recommended.

After the PET investigations performed in September 2007, in Budapest, was noticed an accumulation of 6 mm in the right parajugular region, focal in a density of soft tissue, the accumulating structures being probably reactive. There have not been highlighted any pathological modifications in the head-neck, thymus, mediastinum, lungs, liver, spleen, suprarenal, kidneys region, and neither at the level of the osseous system. After the PET/CT exam from September 2008, in Oradea, there have not been highlighted any detectable morphological modifications or of FDG assignation of a malignant type.

The histopathological exam of the lesion offers typical images of Spitz nevus on some of the sections but also of melanocytary tumor with an uncertain malignant potential on some other sections (Figure 1).

In the sickness of the epidermis, there have been highlighted nests of fusiform/epithelioid cells grouped in a vertical position, perpendicular on the basal membrane, these being separated through gallants from the epidermic cells, aspect that does not appear in the malignant melanoma (Figure 2).

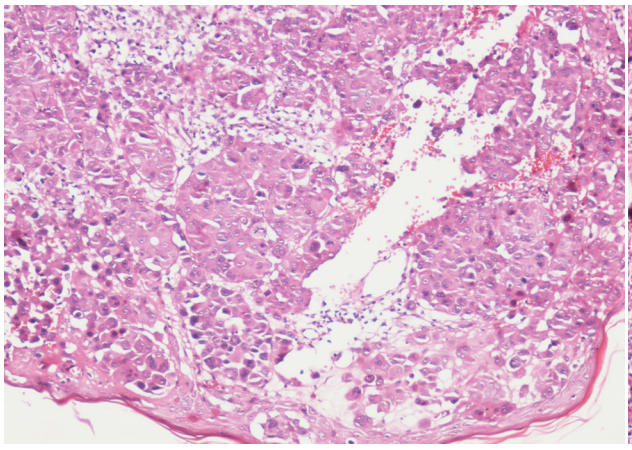

Figure 1 – ***Classical Spitz nevus, with features of tumor with uncertain malignant potential, rare atypical mitosis (H&E stain, 40×).***

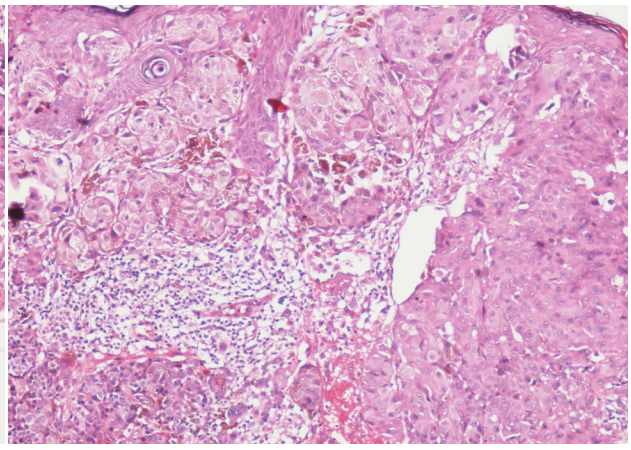

Figure 2 – ***Compound nevus: nests of intraepidermal nevic cells separated through gallants from the epidermal cells, rare cells with melanic pigment (H&E stain, 100×).***

Also, in other regions of the tumor there have been highlighted also in the derma nests of epithelioid cells, with an abundant cytoplasm, as well as multinucleated giant cells, but with nuclei of uniform shape and aspect – pleads for the Spitz nevus (Figure 3).

Another feature evidentiated on the examined sections in our case has been presented to the big nevic cells on the surface of the tumor (under-epithelial), with the progressive diminution of their dimensions towards the base of the tumor of the maturation of nevic cells from the epidermis to the profound dermis (big cells on the surface that become small at the base), aspect that is not noticed in a malignant melanoma (Figure 4).

Even if, globally the tumoral proliferated cells have presented monomorphic nuclei, though there have been areas in the tumor in which the cells were presenting polymorphic nuclei, with a heterogeneously condensed chromatin, and with macronucleoli (Figure 5). The mitotic activity has been low, presenting rare typical mitoses – it pleads for the Spitz nevus.

However, in some regions of the tumor there have been also highlighted very rare atypical mitoses and that

orient themselves towards a melanocytary tumor with uncertain malignant potential (Figure 5); the melanic pigment has been reduced quantitatively, present in rare tumoral cells or has been completely absent in some zones of the tumor, that pleads for the Spitz nevus (Figure 2). Tumoral stroma has been poorly represented, being constituted from thin fascicles of colagenous fibers that were surrounding the isles of nevic cells; the inflammatory lympho-plasmocytary infiltrate has been reduced in quantity. The modifications of the epidermis have consisted in atrophy, ulcerative zones, hyper-granulosis and hyperkeratosis.

In order to evidentiate the immunophenotype of the proliferated tumoral cells and for the differential diagnosis with a malignant melanoma, we have performed the immunohistochemical marking of the sections from the tumor with antibodies for melano-cytary markers (HMB45, Melan A), mesenchymal markers (S100, Vimentin), for the molecules of cellular adhesion (CD44), of tumoral growth (Cyclin D1), and of proliferation (assessing Ki67 proliferative index).

The immunostaining for HMB45 has been focal, heterogeneous, at the level of tumoral cells. Thus, this has been intensely positive cytoplasmic both at the level of the nests of nevic intraepidermic cells and focally at the level of some groups of tumoral cells from the dermis (Figure 6).

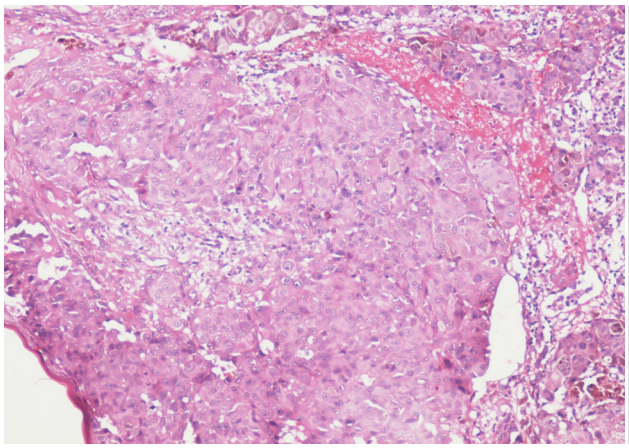

Figure 3 – S*pitz nevus: some epithelioid cells with abundant cytoplasm, with monomorphic nuclei with similar shape and size (H&E stain, 100×).*

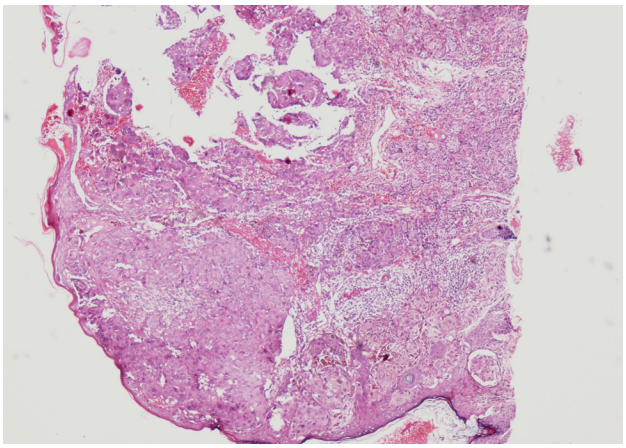

Figure 4 – *Spitz nevus: progressive decreased of the maturation of the nevic cells from the surface of the tumor (under-epithelial) towards the base of the tumor (H&E stain, 40×).*

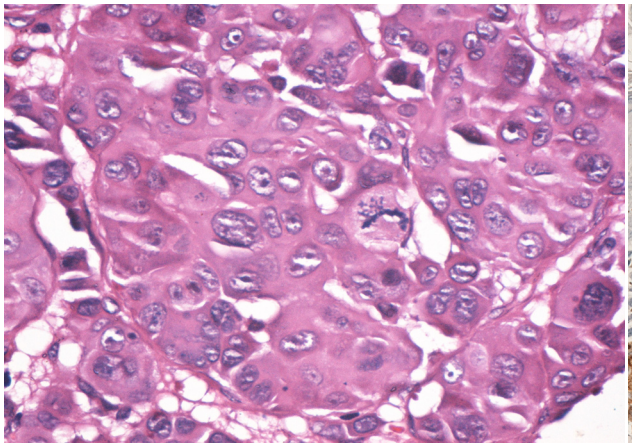

Figure 5 – *Spitz nevus with uncertain malignant potential: areas with pleomorphic nuclei and very rare atypical mitoses (H&E stain, 400×).*

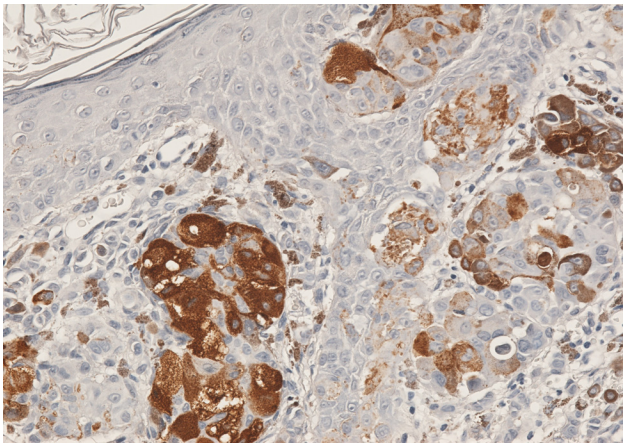

Figure 6 – *Spitz nevus: intensely positive immuno-staining for HMB45 in intraepidermal nevic cells and focally in the tumoral cells from the dermis (LSAB technique, 200×).*

As a completion of this staining, the expression of the Melan A marker has been also positive at the level of tumoral cells, being highlighted the same distribution in the tumor as in the case of the HMB45 marker but of wicker intensity (Figure 7).

The mesenchymal origin of proliferated tumoral cells has been highlighted through nuclear and cytoplasmic immunostaining intensely positive diffuse for S100 in all tumoral cells (Figure 8), as well as through diffuse moderately positive immunoreaction for vimetin at the level of tumoral cells and negative at the level of epithelial cells (Figure 9).

The immunohistochemical expression of CD44 marker has been positive at the level of nevic cells both in the intraepidermal nests and in those intradermal, being also positive at the level of epidermal cells (Figure 10).

The immunostaining for Cyclin D1 has highlighted a

positive nuclear reaction in rare tumoral cells, those being disposed especially in the superficial dermis, under the covering epithelium (Figure 11).

In order to evaluate the proliferative activity of the tumoral cells, a very important factor in the differentiation of an atypical Spitz nevus by a malignant melanoma, we have evaluated the proliferative Ki67 index, this being lower than 5% in the tumor (Figure 12), fact that leaded to the highlightening of a much-reduced proliferation of nevic cells.

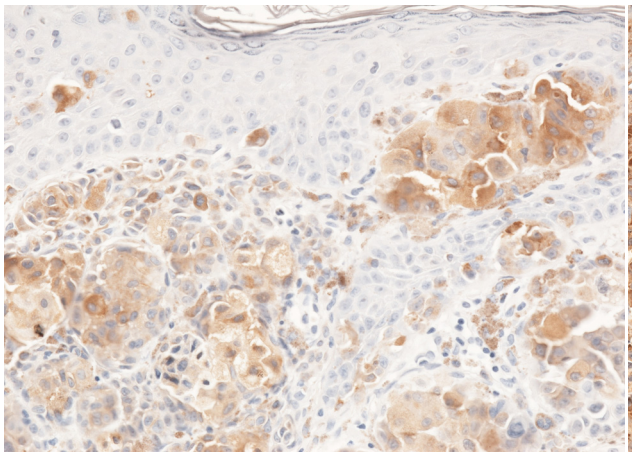

Figure 7 – ***Positive immunostaining for Melan A within tumoral nevic cells, with the same distribution as HMB45 marker but of wicker intensity (LSAB technique, 200×).***

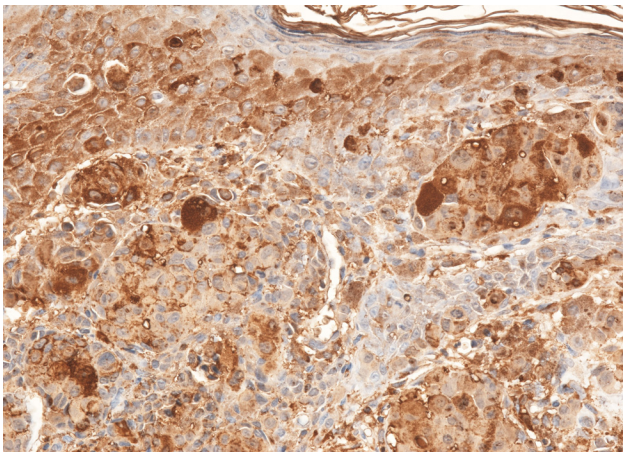

Figure 8 – ***Intensely positive nuclear and cytoplasmic immunostaining for S100, diffuse in all tumoral cells (LSAB technique, 200×).***

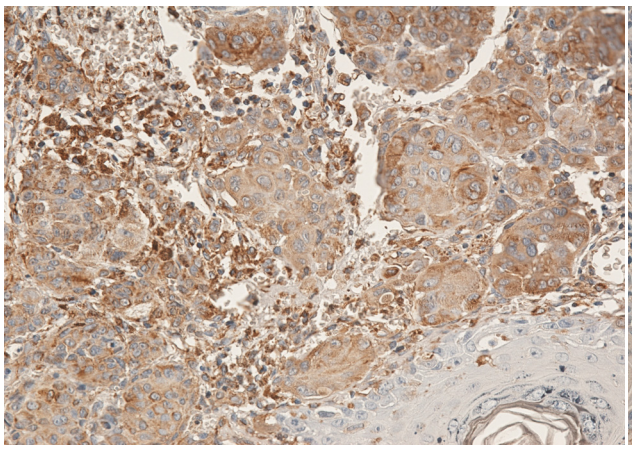

Figure 9 – ***Diffuse moderately positive immuno-reaction for vimetin at the level of tumoral cells (LSAB technique, 200×).***

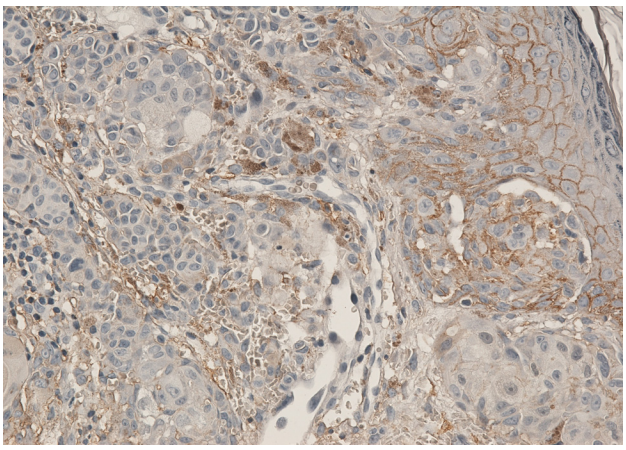

Figure 10 – ***Positive membrane immunohistochemical expression for CD44 in nevic cells, both in the intraepidermal nests and in those intradermal (LSAB technique, 200×).***

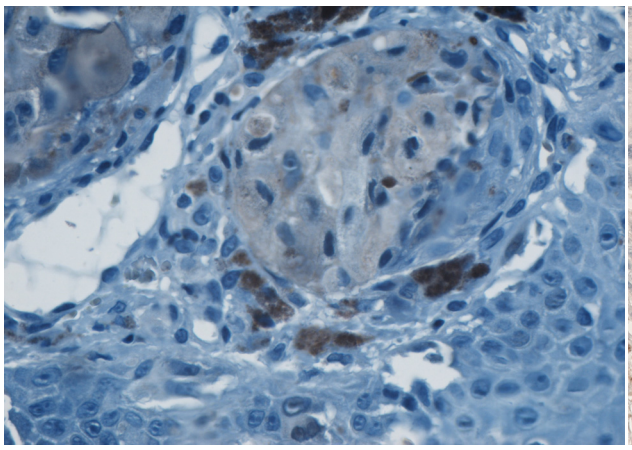

Figure 11 – ***Positive nuclear immunostaining for Cyclin D1 in rare tumoral cells, disposed especially in the superficial dermis (LSAB technique, 400×).***

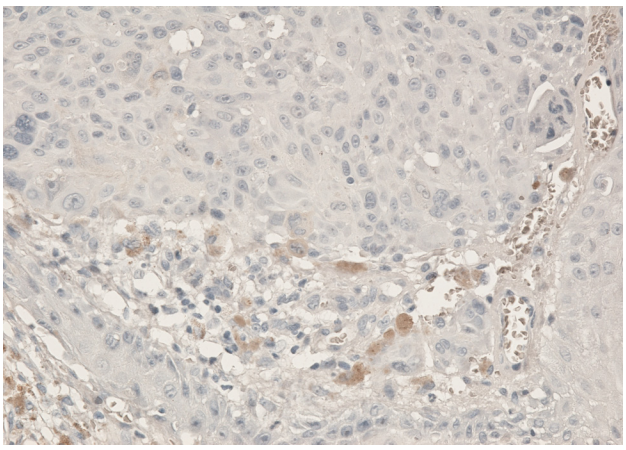

Figure 12 – ***Spitz nevus: the proliferative Ki67 index lower than 5% within the tumor (LSAB technique, 200×).***

Discussion

The Spitz nevus is a benign proliferation of melanocytes that seems sometimes very difficult or impossible to differentiate from the malignant melanoma through clinical and histopathological examination [4].

The tumor appears especially on children, but it can be found on adults as well; it has been communicated that it appeared before birth or frequently in the seventh decade of life. Both sexes are equally affected with a rare appearance in races Mongoloid and Negroid. It is impossible to estimate the prevalence of Spitz nevus, because the majority of the pathological surgical proofs have been in favor of an unusual lesion. Certain authors consider that it is likely to be less than 1% of melanocytary nevi in a child [5].

Clinically, the Spitz nevus appears in early childhood in the form of a head of a red-brown nodule; as compared to other gained nodules, this one increase rapidly reaching a dimension of de 6–8 mm at six months.

The lesions are highlighted, under the form of a dome, without hair and often firm on palpation. When a light pressure is applied over the surface of the lesion with a glass slide, a maneuver called diascopy, the pink coloration of the nevus will often disappear showing a tan-reddish pigmentation.

The erythema of the Spitz nevus results from the vascular component of this tumor that can even have a surface of telagiectasia. The surface may remain smooth and the epidermis is often thin and fragile. It is not unusual; after major lesions may appear bleedings and scalls.

The common areas for localization are the face, especially chicks and legs, but other area can be affected as well. After the initial increase, these can remain stationary for years [6]. Spitz nevus is usually solitary. The cases of Spitz nevi are rare, usually of a grouped form [7] or less common as Spitz nevus eruptive outspread [5, 8].

In the case described by us, this tumor has appeared from birth, being localized at the level of the superior lip as a plane formation, well delimited, of tan color that has then presented the above described modifications.

From a histopathological point of view, general architecture of the Spitz nevus usually is similar to that of a composed nevus, being formed either from fusiform cells that penetrate into the derma in twined fascicles or from epithelioid cells arranged in nests, with multinucleated giant cells among them.

In the case described by us, the tumor has consisted of nests of nevic epithelioid cells situated both intraepidermic, in the neighborhood of basal membrane and perpendicularly on this one, as well as within superficial and profound dermis.

After some authors, the histopathological examination has shown the following differences between the Spitz nevus according to age [9]: achantosis, parakeratosis, pagetoidal infiltration, and Kamino bodies (more frequent in children than in adults). In adults, the lesions are less pigmented, with a reduced cellular maturation and more desmoplasia [9].

The differential diagnosis of the Spitz nevus includes the juvenile xantogranuloma, the pyogenic granuloma or the malignant melanoma. The most problematic lesion in the differential diagnosis of Spitz nevus is malignant melanoma – in such a way that sometimes it can be clinically diagnosed wrong as a melanoma. In our case was also raised the problem of differential diagnosis with a malignant melanoma, both clinically and histopathologically, because the tumoral formation has been present since birth but with a rapid increase in the last year, being influenced by repeated sun exposures.

The malignant melanoma is a tegumentary cancer highly aggressive that develops in melanocytes unlike the Spitz nevus, which is a benign melanocytary lesion. The malignant melanoma is a black tumor that increases rapidly. Any new black macula or papule that extends should be biopsied in order to exclude the melanoma. Besides, certain forms of melanoma are apigmentary and appear clinically as pink papules extended rapidly. The melanoma on a child is very rare, being present on only 3% of the pediatric malignant tumors. Only 2% of all melanoma appear during childhood [10].

Clinically, it is impossible to make a distinction between a Spitz tumor and an achrome melanoma. Moreover, the majority of the melanomas diagnosed on a baby and that do not develop in congenital nevus are apygmentary. Early recognition of the melanoma is critical for survival because the prognosis depends on the depth of the penetration of malignancy into the derma [11].

On the *histopatological exam*, in our case the Spitz nevus has raised differential diagnostic problems with the malignant melanoma, because there have been highlighted some pleomorphic tumoral cells. The histopathological exam has revealed typical images of Spitz nevus on some of the sections, but also of melanocytary tumor with an uncertain malignant potential on others, where there have been noticed atypical mitosis localized in the dermal component.

Many authors have highlightened the fact that there is no single factor that could differentiate the Spitz nevus from the malignant melanoma, because virtually any histopathological aspect from this nevus has been also described in the melanoma [12, 13].

The differentiation is even more complicated in a case of atypical Spitz nevus with: large dimension, ulceration, extension up to the adipose hypodermic tissue and an increases mitotic activity. There is no consensus between dermatologists and dermato-pathologists in what the two lesions are concerned. Some consider that the Spitz nevus and the melanoma are part of a long sequence of lesions with the Spitz nevus benign at an end, and the malignant melanoma on the other end, between the two extremities existing different lesions with common aspects for them both [12, 14, 15]; others consider that there is no connection between the two lesions [16].

However, there are a few aspects that might help to the establishment of the differential diagnosis between the Spitz nevus and the malignant melanoma, that have

to be taken into consideration [17]. Thus, the junctional activity even though intense in the Spitz nevus, does not disorganize and do not wear down the epidermis, and the individual segregation "in the rain" of melanocytes from the basal stratum is discrete or absent. Lever insists so on the importance for the diagnosis of the artifactual split that partially isolates the nevic nests; these are present between the melanocytes in the superficial dermis and thicken the collagenous fascicles that divide the small nests [10]. Sometimes, rare atypical mitoses may be highlighted, especially in the cases of atypical Spitz nevus where a cellular pleomorphism may be present, these aspects being met in our case too.

Due to the limits of the classical clinic and histopathological exam in the differentiation of Spitz nevus (benign and atypical) from the malignant melanoma, many researchers have searched other methods in order to increase the accuracy of the diagnosis, namely the immunohistochemical exam and the techniques of molecular biology in order to find out the chromosomal abnormalities.

For the moment, the most accessible method is the immunohistochemical exam. Even though up to the present moment, a specific marker that could clearly differentiate between the Spitz nevus and the malignant melanoma, and as the used markers (melanocytary, mesenchymal, anti-apoptotic markers, molecules of cellular adhesion, markers for the tumoral growth) are positive in both types of lesions, however for the differential diagnosis is important to evaluate the intensity and the distribution of the immunostaining for these markers in melanocytary cells (melanocytes), as well as the degree of the tumoral proliferation.

HMB45 (*Human Melanosoma Black 45*) is a cytoplasmic antigen whose presence in the cells indicate the active formation of melanosomes and thus the differentiation is melanocytary. It is also being expressed in normal fetal melanocytes [18], but not in normal non-active melanocytes [19, 20].

The immunostaining for HMB45 in the melanocytary nevus depends on their localization at the level of the skin. The dysplastic nevi usually express HMB45 both in junctional cells as well as in nevic dysplastic cells from the superficial dermis; more the severity of the dysplasia is bigger, the most the nevic cells from the deeper dermis may focally express HMB45 [20, 21], the same aspect being also evidentiated in the case presented by us. This expression is suggestive for the diagnosis of dysplastic or atypical Spitz nevus, in the disservice of the diagnosis of malignant melanoma. Rarely, the melanocytary benign proliferations, such as nevi with fusiform cells, Spitz nevus and the atypical melanocytary hyperplasias express HMB45 [20, 22].

In the malignant melanoma, the cytoplasmic positivity for HMB45 is intense in a variable proportion of cells, the tumors that can reach to over 100%, exception making the desmoplasic malignant melanoma in which the expression of this marker may be completely negative [21, 23].

The immunostaining for markers **S100** and **Melan A** has been used frequently in the clinical studies in order to establish the diagnosis of malignant melanoma. In the case that we have presented, the immunoreaction for S100 has been intensely positive and diffuse at the level of all tumoral cells.

This expression of S100 is not specified for the Spitz nevus because the same distribution of the immunoreaction may be highlighted also in a malignant melanoma. However, the interpretation of the immuno-reaction for S100 does not have to be made isolate, but correlated to the immunostaining for the other melanocytary markers. From the data received from the specialty literature it was noticed that virtually all melanocytary benign lesions express S100 protein that is also present in over 95% of the malignant melanomas [21].

Melan A, isolated as a specific antigen for the melanoma, is a transmembranar protein having an uncertain function. In our case, the expression of the marker has been similar to that of HMB45, being evidentiated only at the level of tumoral cells from the superficial dermis and in rare isolated cells from the deeper dermis.

The assessment of the vimetin expression is useful in order to show the mesenchymal origin of the tumoral proliferated cells, but cannot differentiate between the benignant and malignant melanocytary tumors and between the Spitz nevus and the malignant melanoma. In our case, the expression of vimetin has been positively diffuse at the level of the nevic cells.

CD44 is a cellular adhesion protein expressed at a membrane level and has a role both in the regulation of intercellular interactions as well as in cellular migration [24]. It is considered that it has an important role in the tumoral invasion.

In our case, its expression has been homogenous in the tumor, CD44 being highlighted at the level of the membrane of nevic cells, as well as at the level of the epidermal cells. The data from the specialty literature showed that even in the malignant melanoma CD44 is present at the level of tumoral cells, but its expression is heterogenous in the tumor being correlated reversively proportional to the dimension of the tumor and the depth of the invasion [24, 25].

Cyclin D1 is involved in the regulation of cellular proliferation and in the cellular growth, being expressed also in the S phases of the cellular cycle. Its super-extension in the dysplastic nevi and in the Spitz nevus present an areal pattern, is highlighted at the level of nevic cells from the dermo-epidemic junction and less at the level of those from the papillary and reticular derma, being correlated to cellular maturation, while in the malignant melanoma this marker is expressed in a diffuse and intense manner at the level of cells in the tumor.

In our case, Cyclin D1 has been expressed focally in rare cells, disposed predominantly in the superficial derma. Thus, it can be concluded that an areal pattern of the expression of Cyclin D1 may offer useful information in the differentiation of the Spitz nevus from the malignant melanoma [26].

The analysis of the proliferative marker **Ki67** has a role in the differentiation of the malignant lesions from the benign ones. Often, its expression in dysplastic nevi and in the composed Spitz nevus is observed in less than 6% of the cells, usually at the level of the dermo-epidemic junction, being highlighted in very rare cells from the profound derma (average proliferative index of 3.2).

In exchange, the malignant melanoma contains multiple positive cells for protein Ki67, without a particular distribution but diffusely disseminated in the tumor (average proliferative index of 15.3%) [27, 28].

In our case, the Ki67-proliferative index has been less than 5% thing that was correlated to the slow clinical evolution and to the absence of any secondary determinations up to the present moment.

In what the evolution of the Spitz nevus is concerned, from the beginning to maturation is of about six months, and then it remains stationary. Very seldom, it can ulcerate without constituting a malignant sign; its coloring when is observable being due to rarefaction of the epidermis.

The lesion remains benign all over the evolution. There have been noticed, sometimes, some recidives after its removal, leading to the confusion with a melanoma.

The approach of the Spitz nevus is controversial. The majority of the Spitz nevi act in a benign manner. Sometimes, communications about Spitz tumors that are acting aggressively just as the melanoma has led to the uncertainty about the biological behavior. It has been described, also, the spitzoid melanoma (M). Many dermatologists have recommended the excisional biopsy of all Spitz nevi in order to allow the histological confirmation of the diagnosis.

Conclusions

Although, the clinical aspect pleaded for malignant melanoma, and the first histopathological exam was in favor of a malignant melanocytary tumor, the immunohistochemical examination and clinical evolution disjoint the diagnosis of Spitz nevus.

Regarding the evolutive potential to malignancy of the Spitz nevus, we consider that must become established a careful supervision of the patient presenting this type of a nevus, its excision being imposed with safety oncological margins.

The classical histopathological examination must be completed with an immunohistochemical exam, often capable to evidentiate differences to the malignant melanoma.

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