GEORGIAN MEDICAL NEWS


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"THE DANGEROUS BRASSIERE" AND THE NEVUS ASSOCIATED POLYPOID MELANOMA: CONNECTION SEEMS PLAUSIBLE?

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Abstract.

The development of cutaneous melanoma of the skin based on dysplastic nevus is not uncommon. The causes of the progression of nevi to melanomas are numerous and not well understood at present. Certain genetic and epigenetic factors have a major influence on this evolution. We describe a 46-year-old female patient with multiple dermal melanocytic nevi who developed a polypoid melanoma in one of them. After a carefully performed anamnesis, the mole that developed into melanoma was found to be localized in the dorsal area adjacent to the brassiere and underwent permanent and daily mechanical irradiation during the last 6-7 years. Around this mole there were 5 other moles with similar clinical and dermatoscopic morphology, which did not transform into melanomas and were not subjected to mechanical irritation.

The patient had a dermatological examination 6 years ago and it was suggested that this lesion has to be surgically removed, which she declined.

The patient was treated surgically and the lesion suspicious for cutaneous melanoma was removed in two stages according to the generally accepted AJCC/EJC recommendations.

In parallel, 5 additional melanocytic nevi were removed, which histologically had features of dysplastic dermal melanocytic nevi but no signs of progression to melanoma.

This article discusses the causes of nevus-associated melanomas and emphasizes the thesis of potential malignant transformation through mechanical irritation - in this case that of the brassiere. The moles localized in this area, although clinically and dermatoscopically apparent, should be treated surgically. This painless, short-term manipulation has a preventive effect on the future development of cutaneous melanomas.

Key words. Nevus associated melanoma, irritated nevus, polypoid melanoma, surgery, brassiere.

Introduction.

Melanocytes are pigment-producing cells, derived from the neural crest, which can be found in the skin, eyes, bones, inner ears and leptomeninges [1]. From pathogenetical point of view, cutaneous melanoma (a malignant skin cancer), melanocytic nevi (benign skin formations) and dysplastic nevi (a form between the nevi and melanoma) have a common ancestor – the melanocyte [1].

Atypical moles, Clark nevi, B-K moles are all synonyms found in the literature for dysplastic nevi [2]. However, only a few of the atypical moles have a “microscopic appearance” of a dysplastic nevus [2]. On a clinical examination, the dysplastic nevi share visual similarity to the melanoma lesions, often even described with the ABCDE morphological characteristics for melanoma [2].

Genetic alterations are the probable main cause for the development of both benign and malignant melanocytic tumors [3].

Acquired nevi are a result from several mutations in the melanocytes, which have already extended to the epidermis, and are often associated with a mutation in the BRAF gene [3]. Although BRAF mutations were found to be prevalent (with 66% estimated rate) in cutaneous melanoma [4], Uribe et al. [4] suggests that some mutations alone are not enough to induce a malignant transformation of a benign lesion.

Over the last four decades with a constant increase in incidence rates, cutaneous melanoma is presented as one of the fastest developing malignancies worldwide [5]. Being on the lower part of the Fitzpatrick scale (type 1&2), having different lifestyle factors cooperated in your everyday life such as the use of indoor tanning beds, excessive sun exposure, not wearing enough or any sun protection and etc. are all very well-known risk factors for developing melanoma [5].

However, even with the genetic understanding of the disease and the above-mentioned risk factors, there are still a few missing pieces from the puzzle called “melanoma”. After a thorough search of the literature, we found scarce information about one of the most commonly seen but poorly described triggering risk factors – chronic mechanical irritation.

We present a case with a 46-year-old female with a history of chronic mechanical irritation due to the use of a brassiere (a piece of woman’s underwear), which developed in our observation a nevus associated polypoid melanoma alongside multiple dysplastic nevi. The dermatosurgical approach was demonstrated once again as the most efficient method when dealing with skin malignancies. A short review of the existing literature will be done regarding the relationship between dysplastic nevi and melanoma, contributing risk factors of cutaneous melanoma.

Case report.

A 46-year-old female came to the dermatology department with primary complaints of multiple pigmented lesions located on the back and the waist areas both dating from 20 years (1a-1c). Six years ago, the patient reported three nevi being removed in the abdominal area, with a recommendation for the removal of another pigmented lesions located on the back, which she refused. The patient came to the department 6 years later with a request for physical examination of the lesions on the back and further therapeutic approach to be established if necessary.
The patient reported no comorbidities or skin malignancies in any family member. The routine blood tests showed slight abnormalities in the Gran% - 77.8%, squamous cell – 41.0/ul, LDL – 3.6 mmol/l and urea 2.6 mmol/l. CT scan of the thorax, abdomen and pelvis was ordered. An abnormal finding in the uterus was found – it had a CT characteristic of a myoma nodule, an inhomogeneous hyperdense oval lesion was visualized in the uterine wall in the left lateral area with axial dimensions - 2.58/3.91 cm.

The dermatological examination showed six very distinguishable pigmented lesions located on the back, clinically and dermatoscopically suspected for dysplastic/irritated melanocytic nevi (Figures 1a-1c) One of them has been suspected of nevus associated cutaneous melanoma- the number 1 on picture 1b (Figures 1a-1c).

The patient was recommended surgery for the suspected lesions.

After disinfection, under local anesthesia with lidocaine, the melanoma-suspicious tumor formation as well as the five pigmented lesions suspicious for dysplastic nevi were removed by elliptical excision with resection margins of surgical security of approximately 0.3 cm in all directions. The remaining defects were closed by single interrupted sutures. Daily dressings with povidone iodine were performed. The histopathology results (Figures 1d-f) came positive for five dysplastic nevi and the histology for lesion 1 (polypoid lesion) was represented by atrophic epidermis, compact melanocytic proliferation of large, epithelioid an isomorphic cells with marked pleomorphism, centrally located large nuclei with scattered chromatin and 1-2 large nucleoli, abundant cytoplasm forming a dense conglomerate in a richly vascularized stroma. Lympho-vascular and perineural invasion were absent; clear resection lines, Breslow 4.3mm. The histological picture corresponded to a nevus associated polypoid melanoma (Figures 2-4).

The patient was referred to the oncology department for a SPECT/CT. Sentinel lymphoscintigraphy was performed in planar and SPECT/CT mode after intradermal application of 99mTc-Nanocol at four sites around the operative cicatrix on the skin on the back, scintigraphic SPECT/CT data of lymphatic drainage to both axillary regions with delineation of one sentinel lymph node in each (with greater intensity on the right), their projection site is marked on the patient's skin. Lymphatic drainage to inguinal areas is not established. The patient was recommended a re-excision for the melanoma lesion with a surgical safety margin of 2 cm in all directions and removing of the sentinel lymph nodes. She agreed and a second surgical intervention was planned with: a re-excision of the primary cicatrix (Figure 5a), and the detection and performance of the sentinel lymph node – one in the left (Figure 5b) and one in the right (Figure 5c) axillar regions. A 2 cm resection of the cicatrix from the primary tumor was performed in the lumbar region (Figure 5a). A layered suture with one drain was placed. Histology was not indicative for the availability of tumour cells. Melanoma was staged as : stage 2C (pT4bN0M0).

Discussion.

Melanocytes are pigment-producing cells located mainly in the skin [6]. Their main function is to protect the epidermal layer of the skin by producing a pigment (melanin), which absorbs the UV radiation and thus protecting the layers below from further DNA damage [6].

Melanocytic lesions can be simply divided into several categories: benign nevi , dysplastic nevi, and malignant melanoma [7]. The benign lesions are symmetrical, evenly pigmented and the edges of the nevus are usually well-defined [7].

Moles with atypical clinical features (atypical moles, dysplastic nevi), such as variation in size, irregular borders and in homogenous pigmentation, were described for the first time as B-K mole syndrome (“B” and “K” being the families acknowledged) [8] and as FAMMM (familial atypical multiple
mole melanoma syndrome) [9] in families with an unusual increased incidence rate of melanoma [10].

Acquired atypical mole syndrome (or FAMMM syndrome) is a rare cutaneous disease characterized by a development of numerous dysplastic nevi and melanoma on the skin [11]. Some studies suggest that patients with the FAMMM syndrome have an estimated risk of nearly 100% for melanoma development by the age of 70 [10,12,13].

Melanoma development is also possible in patients with the so-called “sporadic” dysplastic nevus syndrome [14].

Dysplastic nevi (DN) are often referred to as an intermediate form between common benign lesions and melanomas [15]. It should be noted that patients with dysplastic nevi might have insufficient DNA repair or overexpression of pheomelanin which may result in further DNA damage and tumor progression [15]. In the literature they are often described as potential precursors for melanoma or as markers for an increased risk for developing one [15] and thus should be kept in mind when examining atypical moles. An increased 10-fold risk for melanoma development was found in patients with more than five dysplastic nevi [16].

Despite DN being classified as “mild,” “moderate” and “severe”, other collectives have linked the melanoma risk only with the dysplastic nevi showing high grade histological atypia [17].

A consensus seems to be impossible because the only way to identify if the melanocytic nevus is indeed dysplastic, we would have to perform a biopsy and further observation on the evolution of the lesion would be impossible [18].

Cutaneous melanoma is the most aggressive type of skin cancer responsible for about 90% of skin cancer-related deaths [19]. With a worldwide increase in incidence rate over the years for melanoma – 25 new cases per 100,000 population in Europe and 60 new cases per 100,000 in Australia [20], as clinicians we must inform our patients about the importance of regular skin examinations and frequent follow-ups in terms of lowering these numbers in the future.

Phototypes (types 1&2), a high number of acquired melanocytic nevi, UV radiation and damage, painful sunburns in childhood and excessive sun exposure in adulthood contribute to the melanoma formation [20]. These are all very well-known risk factors among the population.

However, different risk factors contribute differently to melanoma development. For example, the melanin found in the melanocytes, is considered a protective agent from UV light and that explains why some phototypes on the Fitzpatrick’s scale (types 1&2) have an increased risk for developing skin cancer [20].

Mechanical injuries are linked with the development of acral melanoma and melanoma located on the extremities [21]. A retrospective study with 369 melanoma patients performed by Kaskel et al. [21] concluded that 32 of the patients considered an association between the melanoma and past trauma, 22 patients reported single traumatic event, 10 a persisting irritation and two reported an irritation to a pre-existing melanocytic nevus (later on confirmed as melanoma on acquired or congenital...
Since most of the patients with melanoma on the extremities were also reporting a traumatic event, we should consider more often a history of trauma in these anatomical locations [21].

According to Holm et al. [22] the human dermis can undergo malignant transformation due to several risk factors, including chronic injury [22].

Chronic irritation as a potential risk in terms of skin cancer development has been discussed since 1828 [23].

A case report presented by Nakai et al. [24] showed a patient with chronic irritation due to sewing resulting in hyperpigmentation on the thumb which clinically resembled a malignant melanoma. The patient had no history of systemic, inherited disease or exposure to chemicals thus leaving mechanical irritation as the only explanation for the hyperpigmentation [24].

According to a paper by Morales Suarez-Varela et al. [25], 73% of the patients had no family history of malignancy and thus concluded that the malignancy was a result from rather environmental than genetic factors.

In the case presented by our team, the patient’s malignant lesion was under a lot of irritation due to a constant wear of a brassiere in her everyday life (patients anamnestic data).

Keeping in mind that she denied having skin malignancies in the family or comorbidities, we can conclude that the mechanical irritation during the years could have been one of the main risk factors for developing nevus associated polypoid melanoma.

A systemic meta-analysis by Gandini et al. [26] have found that one of the most important risk factors for melanoma development are the number of the common and/or atypical nevi with an estimated relative risk (RR) = 6.89;95% [26].

The relationship melanocytic nevi-melanoma isn’t one sided and should be further investigated [27]. A systemic review by Dessinioti et al. [27] stated that the presence of nevi in histological correlation with melanoma (also called nevus-associated melanoma or NAM) is an interesting side to the theory on malignant transformation of nevi to a nevus-associated melanoma.

Evidence provided from different collectives on the matter has stated the different nature, in terms of genetics, histology and etc. of the NAM and the de novo occurring cutaneous melanomas [28,29].

Clinicopathological differences were found between the de novo developing melanomas and the nevus-associated melanomas, proving the possibility of different origin of both type of lesions [29].

“Dermatoscopic clues” for NAM such as negative pigment network, tan areas without structure and areas without identifiable structures were provided by Reiter et al. [30].

The carcinogenic evolution proposed by Clark et al. [8] in 1978 suggests that in patients with history of melanoma, the dysplastic nevi is the precursor for melanoma.

A systematic review by Dessinioti et al. [27] suggests that 65% of the nevus-associated melanomas develop within a dysplastic nevus.

In the cohort study by Bosch-Amate [28] with 2,227 patients, the nevus-associated melanomas were 22.86% and the patients which developed them were younger, with a fairer phototype, had higher nevus count and the tumors were located on the trunk in comparison with the de novo melanomas.

A retrospective study performed by Lin et al. [31] showed no prognostic implication on the overall survival rate of patients with de novo versus nevus-associated melanoma. Despite this, we should acknowledge these two lesions as different subtypes in the melanoma family [28].

Polypoid melanoma is a rare type of nodular cutaneous melanoma in which the tumor is directly connected to the skin by a pedicle [32]. It has young onset development (20-39 years), with predisposition sites such as the back area and a survival rate of 5 years [32]. Clinically, it is presented with exophytic growth and ulceration [32]. This type of melanoma has a poor prognosis due to thickness and ulceration and a possible risk of vascular embolization [33].

Although cutaneous melanoma is an aggressive disease with a high mortality rate, if diagnosed early it is curable [34].

When examining the skin lesions, we must consider the relationship between clinical findings, risk factors and family history as a whole [34].

Cutaneous melanoma is diagnosed based on a physical examination of the skin [35].

The ABCDE (asymmetry, border, color, diameter, evolution) and “ugly duckling” sign (moles that doesn’t look normal or stand out from the rest on the body) are used in the daily practice as diagnostic criteria [35].

Dermoscopy remains the classical method used in the everyday clinicians practice [35]. New horizons may be set with the current technological development in the medical field, such as artificial intelligence-driven image analysis, 3D body imaging, reflectance confocal microscopy (RCM), optical coherence tomography (OCT) and much more, providing more precision in the diagnostic world [35,36].

Surgical management is currently the best option for localized, invasive melanoma with approximately 5-year survival rate [37,38]. The standard procedure for localized cutaneous melanoma is the wide local excision [37].

After the initial staging, the evaluation for sentinel lymph node biopsy remains very important [36]. Lymph node metastasis impacts the prognosis of the disease and the further treatment [39]. A less invasive alternative than traditional dissection is the sentinel lymph node biopsy [38]. This step provides further information about the following treatment options [38].

Conclusions.

Early detection, prevention and eradication of malignancies seem to be a never-ending topic in the dermatology field.

With the current innovations in the diagnostic area, the diagnosis of skin cancer seems faster, more precise, and less time-consuming.

In the early stages of melanoma development, the survival rate is much higher than those in the later stages. Therefore, the patients must realize the importance of regular physical examinations, and we as clinicians should improve our skills and knowledge.

We present a case with a 46-year-old female with a history of chronic mechanical irritation due to the use of a brassiere (a piece of woman’s underwear), which developed on the back
a nevus associated polyoid melanoma alongside multiple dysplastic nevi. Dermatosurgery was once again proved as the most efficient way of eradication of skin malignancies.

REFERENCES
