An unusual cutaneous malignant melanoma arised de novo: a case report

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Abstract
Malignant melanoma is a type of skin cancer with accelerated evolution and a high metastatic potential, thus being the most aggressive type of skin tumor. Its origin resides in the epidermal melanocytes, which multiply chaotically, therefore becoming malignant cells. The main objective of this study was represented by the clinical, histological and also immunohistochemical analysis of a peculiar case of malignant cutaneous melanoma arised de novo. Patient M.H., age 54, was admitted due to concerns regarding a cancerous growth on the right scapula. Deroscopy revealed an asymmetrical, polymorphic and polychromatic lesion; therefore, a surgical intervention was scheduled. The histological exam showed a microscopic structure resembling an epithelioid cell malignant melanoma, with inflammatory reaction and central ulcerations. Immunostaining with melanocytic differentiation markers revealed the presence of pagetoid-disseminated cancerous cells into the epidermis, in addition to deep dermis invasion and the extension of cancerous cells in and around the hair follicles. In most cases, malignant melanoma develops on pre-existent nevi, but it can also appear de novo with accelerated evolution, mainly at phototype I young people. The importance of this particular case consists in the fact that the tumors presented some unusual particularities: appearing on healthy skin tissue, with slow evolution, at an age when this pathology is rarely encountered; the patient was phototype III and the cutaneous territory had been rarely exposed to ultraviolet radiations. Therefore, the case has proven interesting and worthy of being taken into consideration by the appropriate literature.

Keywords: cutaneous malignant melanoma, dermoscopy, immunohistochemistry, tumor markers.

Introduction
Cutaneous malignant melanoma (CMM) continues to be a current matter in dermatologic pathology, since it poses significant diagnostic, evolution and, especially, treatment issues [1, 2]. As long as, currently, healing is not insured by any therapy schema [3], combination of chemotherapy and/or immunomodulators [4], by themselves or in combination with other physiotherapeutic or surgical methods, CMM will continue to represent a prime subject of oncological research [5, 6].

We consider this case as much as instructive as it is interesting, because, on one end, of the de novo debut, on apparently healthy tegument, at a patient over 50, and, on the other, of the position, on a cutaneous area seldom exposed to UV radiation.

In this study, we presented the clinical, histological and immunohistochemical analysis of a peculiar case of malignant cutaneous melanoma arised de novo.

Case report
The case concerns a patient, M.H., age 54, living in urban environment, which has been admitted on July 2015 to the Department of Dermatology, Emergency County Hospital of Craiova, Romania, on account of noticing a highly pigmented cancerous lesion of 1 cm in diameter, with irregular borders, located on the right scapula. From the patient’s declaration, the tumor slowly grew in size and changed shape and color in over two years.

Amongst the risk factors, the patient was a heavy smoker (over one pack of cigarettes/day) and overweight, with a BMI (body mass index) of 26.8 kg/m². The patient was included in phototype III. The medical history revealed second-degree arterial hypertension.

On examination, the tumor was of normal coloration, with thigh folliculitis and impalpable superficial lymph nodes. A cancerous lesion has been observed on the right scapula, locally. It had irregular edges, brown-to-black coloring with chromatic polymorphism, and slightly overhung (3–4 mm), with a diameter of approximately 1 cm (Figure 1). The edges of the tumor presented a small degree of infiltration, and the swollen surface was not painful on palpation.

Clues pointing to malignant melanoma were suggested by the clinical aspect of the tumor; chromatic polymorphism, tumescent surface and irregular edges.

The dermoscopic examination was carried out with a Heine Delta 20 dermoscope, which revealed an asymmetrical lesion with polymorphism and polychromatism with atypical pigmentary network and the presence of the “veil” characterizing the malignant melanoma (Figure 2).

The surgical intervention was decided, excising the
tumor in toto, with oncological safety borders and per primam suture, then the sample was sent to the Laboratory of Pathology for a pathological analysis.

The excised tissue fragments were fixed in 10% buffered formalin and they were processed using the classical paraffin-embedding technique. The paraffin blocks were sectioned at 3–4 μm thick segments, which were initially stained with the usual Hematoxylin–Eosin (HE) staining. Subsequently, serial sections were performed and displayed on glass slides coated with poly-L-Lysine for the immunohistochemical examination.

The immunohistochemical approach was the two-step technique with Streptavidin–Biotin–Peroxidase as secondary antibody (LSAB plus kit, DakoCytomation, Denmark), and the substrate chromogen used for visualizing the immunoreactions was AEC (3-amino-9-ethylcarbazole). The primary antibodies used were: S100 protein (polyclonal, DakoCytomation, 1:500 dilution), HMB45 (clone HMB45, DakoCytomation, 1:50 dilution), Tyrosinase (clone T311, Novocastra, 1:40 dilution) and Ki-67 (clone MIB1, DakoCytomation, 1:100 dilution).

The histopathological exam confirmed the suspicion invoked by clinical tests, revealing a microscopic structure of malignant melanoma, intensely pigmented, with epithelioid cells, central ulceration and moderate inflammatory reaction. It presented a Clark III level and a Breslow Index less than 1 mm (663 μm) (Figures 3 and 4).

The immunohistochemistry revealed an intense and also diffuse marking of S100 protein in the cancerous cells, with the help of melanocytic differentiation markers. HMB45 (Figure 5), Tyrosinase (Figure 6) and Melan A (Figure 7) immunostaining showed intense cytoplasmic marking in cells from the dermis limit of the tumor, without increased representation when scaling with depth, and also the immunoexpression presented a patchy pattern. Likewise, these markers revealed pagetoid-disseminated cancerous cells into the epidermis and cancerous cell invasion in and around the hair follicles. Ki-67 cellular proliferation marker (Figure 8) was scarcely found into cells, suggesting a low proliferation activity of the cancerous cells.
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Figure 5 – Intense HMB45 immunostaining in the deep layers of the lesion, with a patchy pattern, ×40.

Figure 6 – Tyrosinase immunostaining is intense in the deep layers, ×40.

Figure 7 – Melan A immunostaining is intense in the deep layers, with a patchy pattern (pagetoid diffusion of malignant melanocytes in the epidermis and hair follicle), ×40.

Figure 8 – Low level of Ki-67 nuclear immunostaining, ×100.

Discussion

The malignant melanoma is the most aggressive melanocytic tumor, showing rapid evolution and a high metastatic capacity [7, 8]. The classical specialty literature and modern research show that CMM usually appears on a pre-existent nevus, but it can also develop on tegument, which seems to be normal [9, 10].

The frequency has increased in the last decades due to prolonged exposure to type B UV (UV-B) radiation [11, 12] and it represents 1–3% of the total number of malignant tumors and 7–8% of the cutaneous tumor cases [13, 14]. In spite of the latest progress in the therapy process, CMM has an ill prognosis, statistic showing that the survival rate rests between six to eight months, survival rate up to five years is lower than 5%, emphasizing that metastatic CMM is still without any cure [15, 16].

In most cases, malignant melanoma develops on a pre-existent nevus, but it can also appear de novo, mostly on young patients, with rapid evolution. Phototype I and II individuals are predisposed, and the prime risk factor is prolonged exposure to UV radiation. Published clinical statistic data, cumulated with the clinical experience, reveals the necessity of new monitoring rules, spanning on longer periods and over a wider, high-risk population (dysplastic nevi, sporadic or hereditary, people with occupations that involve prolonged exposure to artificial or natural UV radiation, phototype I individuals or personal/family history of CMM, etc.).

Today’s youth shows a tendency to disregard dangers posed by UV radiation, which proves extremely risky and imposes a certain level of health education concerning proper clothing, as well as rational and effective usage of sunscreen products. From the aforementioned data, CMM is revealed to represent a main concern for clinical and biological research and, as long as there is no true-standard treatment, metastatic cases should be included in clinical studies and trials.

Therapy management has significantly improved for the affected patients, but no combination of chemotherapy and/or immunomodulators has shown promise, even with additional physiotherapy or surgery [17–19].

The case we are presenting, with a Clark III prognosis index and a Breslow of 663 μm, for which a tumor excision was performed later on, raises similar uncertainties regarding the therapy schema. This stems from the fact that the patient developed de novo CMM, on apparently normal tegument, which was seldom exposed to the sun,
on an age at which this certain pathology rarely occurs. Also, the slow evolution (exceeding two years) is uncommon for CMM [20, 21]. All these occurrences served only to delay the diagnosis, with all the following consequences.

Immunostaining with melanocytic differentiation markers (S100 protein, HMB45, Tyrosinase and Melan A) revealed a pagetoid dissemination in the epidermis of the cancerous cells, combined with depth in the dermis and cancerous extension inside and around the hair follicles.

HMB45 expression showed the absence of cell maturation throughout the deep layers of the lesion, therefore the expression of this marker never decreased with depth in the dermis. On the contrary, cancerous cells in the deep layers of the lesion expressed this marker intensely, in a patchy pattern. A similar immunoeexpression was noticed when using Tyrosinase and Melan A markers, therefore supporting the lack of cancerous cell maturation in the deep levels of the lesion.

A series of studies have demonstrated the function of melanocytic differentiation antigens (S100 protein, HMB45, Melan A and Tyrosinase) in the distinction between malignant melanomas and common or dysplastic melanocytic nevi [22, 23]. HMB45 is particularly helpful in detecting the pattern of nevi “maturation”, the decreasing expression of this marker with increasing depth in the dermis or diffuse expression throughout the lesion is suggestive of benign diagnosis, i.e., nevus. In contrast to nevi, primary cutaneous melanomas usually express HMB45 in a patchy pattern, with isolated or clustered cells throughout the dermis. Tyrosinase expression is very similar to HMB45 labeling [22].

Ki-67 cellular proliferation marker showed low expression in the melanocytes located in the dermis, relative to proliferative keratocytes from the basal layer of the epidermis. This aspect could undermine the malignant melanoma diagnosis, but the lack of cancerous cell maturation in the depth of the lesion guided to malignant melanoma. Low proliferative activity, revealed with Ki-67, correlates with the slow evolution that the lesion presented on one end, and on the other, it suggests low aggressiveness and a brighter outcome.

High Ki-67 expression in primary cutaneous melanoma, correlated with both Breslow thickness and the presence of ulceration, has also been reported in other studies [24, 25]. However, no significant relationship was found with patient prognosis. Although other immunohistochemical studies have shown a correlation between Ki-67 expression and melanoma patient outcome [26], these have mainly been concerned with thicker tumors [27]. In the study of Witold Kycier in 2006, Ki-67 antigen was detected in the nuclear area of primary melanoma tumor cells, in 70% melanoma cases, and showed a statistical correlation with the probability of survival or death. Possibly, expression levels for Ki-67 would prove helpful in determination of aggressiveness and metastatic potential of melanomas [28]. Melanocytic differentiation marker immunostaining provides a support in the differential diagnosis of dysplastic melanocytic nevi with cutaneous malignant melanomas, whilst Ki-67 cellular proliferation marker immunostaining is proving useful in asserting the aggressiveness and metastatic potential of cutaneous malignant melanomas developed de novo.

Conclusions

The importance of this case consists in the fact that the tumor presented a few characteristics: formed on seemingly healthy skin, with slow evolution, the patient was over 50 and fit in phototype III, and the region on which the lesion appeared has been seldom exposed to UV radiation. With all this data, the case has proved to be of great interest and worthy to take into consideration by further studies. A very important factor in predicting the patient’s outcome in the case of a patient with clinically node negative disease is primary tumor ulceration that was not present in our case.

Conflict of interests

The authors declare that they have no conflict of interests.

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References

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Demierre MF, Sabel MS, Margolin KA, Daud AI, Sondak VK. State of the science 60th anniversary review: 60 Years of advances in cutaneous melanoma epidemiology, diagnosis, and treatment, as reported in the journal Cancer. Cancer, 2008, 113(7 Suppl):1728–1743.


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