

Cutaneous melanoma arising on pre-existing nevi – case reports

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Abstract

Skin cancer is a common healthcare issue that affects millions of people worldwide. Only a small part of that population is suffering from melanoma and an even smaller proportion has melanoma developed on a pre-existing nevus. This paper illustrates five such cases, diagnosed over an 18-month period, with their histological particular aspects. Among the total number of patients diagnosed and treated in the Department of Plastic and Reconstructive Surgery, University Emergency Hospital, Bucharest, Romania, over approximately one year, of which half for melanoma in general or for benign nevi, only a small fraction had developed melanoma on a common or dysplastic nevus. These patients, as well as those with *de novo* developed melanoma, are a reason for concern since most of the lesions were diagnosed in a locally advanced stage of the disease. Though efforts are being made to screen and diagnose early, there are still a lot to be done in order to lower the mortality and morbidity rates for this pathology.

Keywords: cutaneous melanoma, nevi, dysplastic, immunohistochemistry.

☐ Introduction

Among all malignancies, skin cancer is by far the most frequent. Currently, between 2 and 3 million non-melanoma skin cancers and 132 000 melanoma skin cancers occur globally each year [1]. There are more new cases of skin cancer each year [2] than the combined incidence of breast, prostate, lung and colon cancer [3]. Only 4% of all cancers [4] and 1% of all skin cancers [3] are melanomas; out of these, very few develop on pre-existing pigmented nevi. According to a study by Tsao *et al.* [5], it was estimated that the lifetime risk of any selected nevus transforming into melanoma by the age of 80 years old (for a 20-year old individual) was about 0.03% for men and 0.009% for women.

Nevertheless, mortality from cutaneous melanoma is significant. The estimated five-year survival rate for patients with localized disease is about 98% in the U.S. This rate falls to 62% when the disease reaches the lymph nodes and 18% when distant metastases are present [3]. In addition, response to neoadjuvant treatment, such as chemotherapy or radiation therapy, is far from satisfactory, especially in advanced stages of the disease. Thus, it represents a major public health concern, especially among fair-skinned Caucasians who are predisposed for developing skin lesions, benign or malignant, throughout

their lives. Recently, targeted genetic therapy is being researched and implemented for locally advanced and metastatic disease, in patients with B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) and tyrosine-protein kinase Kit (*c-Kit*) gene mutations, with promising results [6–9].

The aim of this study was to recognize and better apprehend melanocytic lesions with malignancy risk, as well as report the one-year incidence of the Department of Plastic and Reconstructive Surgery, University Emergency Hospital, Bucharest, Romania.

☐ Case presentations

Taking into account the patients admitted in the Department of Plastic and Reconstructive Surgery, University Emergency Hospital, Bucharest, Romania, between January 2016 and July 2017, 26 of them were diagnosed with melanoma following surgery. Out of them, only five (19.23%) cases presented melanoma developed on a pre-existing nevus.

Case No. 1

The first patient, a 63-year-old woman, presented with a large skin lesion located on the abdomen, approximately 20/20 mm, heterochromatic and irregular in shape, which bled spontaneously or after minimal trauma (Figure 1).

The lesion was clinically suspicious; therefore, a wide-margin resection was performed *per primam intentionem*. Microscopic examination revealed Clark level III, Breslow of 1.06 mm melanoma developed on a common compound nevus with a mitotic rate of 2 mitoses/mm², without ulceration, regression, emboli or perineural invasion. Resection margins were negative. Given these results, the patient was subsequently advised to undergo a lymphoscintigram in order to assess lymph node status. Bilateral inguinal nodes showed increased activity. The patient was informed and she opted for a surgical excision of the reactive nodes. Histological examination revealed pigmented cells in the nodes. Immunohistochemical (IHC) staining was performed to provide a positive diagnosis, and results were negative for malignant melanocytes. Following a brief recovery period, the patient was discharged without complications and is currently being monitored by her oncologist.

Case No. 2

The second patient is a 35-year-old woman who presented with a 10/9 mm pigmented lesion on the helix and superior crus of her left ear (Figure 2). She was

referred to a specialist by her family physician, who was concerned by the size of the lesion and the fact that it had constantly grown in the previous three months. The lesion was again excised with safety margins, including ear cartilage. The microscopic examination revealed melanoma developed on a dysplastic nevus with Clark level III, Breslow of 1.1 mm, 1 mitosis/mm² and negative for ulceration, regression, emboli or perineural invasion (Figure 3, a and b). Margins were also negative, including the excised cartilage. Histologically, atypical nests of malignant melanocytes were present in the center of the lesion and at the dermoepidermal junction, whereas, at the periphery, we can see nests of nevocytes typically for a dysplastic nevus. IHC results confirmed the diagnosis.

Since Breslow thickness was over 1 mm, and the lesion was localized at the head, the patient was a good candidate for sentinel lymph node biopsy. However, the exam was not readily available at the moment and in order to avoid further delays, the patient was offered the option of a lymphoscintigram, which she accepted. The result showed no reactive lymph nodes and the patient was discharged with similar recommendations as the first patient in our case reports.



Figure 1 – Melanoma developed on a dysplastic nevus.

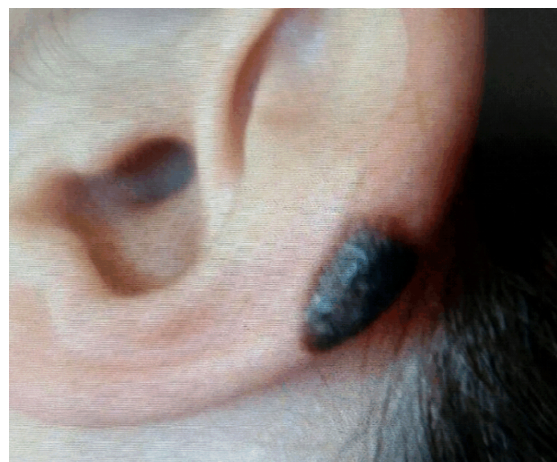


Figure 2 – Melanoma developed on a common nevus localized on the abdomen: ear – gross aspect.

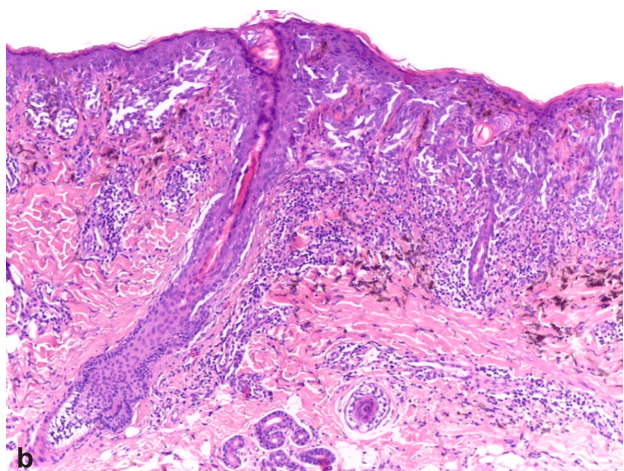
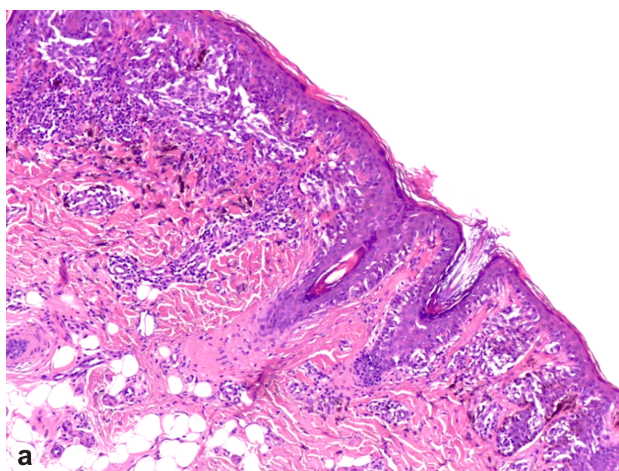


Figure 3 – (a) Melanoma developed on a dysplastic nevus – in the lower-right corner, there are nests of dysplastic melanocytes arranged at the dermoepidermal junction, whereas in the upper left corner, the lesions are characteristic of a melanoma; (b) Melanoma developed on a dysplastic nevus – on the left part of the image, there are nests characteristic for dysplastic nevus. Hematoxylin–Eosin (HE) staining: (a and b) $\times 100$.

Case No. 3

The third patient, a 40-year-old woman, was referred to the Department of Plastic Surgery by a dermatologist. He had noted an abnormal looking lesion on the patient's posterior thorax, a lesion that had been growing constantly and was recently traumatized. Physical examination revealed a 10/12 mm dark brown lesion. It was surgically excised and the results showed *in situ* melanoma developed on a pre-existing nevus. The results were confirmed by IHC staining. She was advised against UV exposure, and is seen periodically by her dermatologist for recurrences or new lesions.

Case No. 4

The fourth patient in our group was a 31-year-old woman. She had seen her family physician when she had accidentally traumatized a pigmented skin lesion on her left hip. He referred her to our Department and the skin lesion was excised. It was a 12/10 mm heterochromatic skin lesion with uneven borders. The results revealed Clark level III, Breslow 0.9 mm melanoma developed on a nevus, noting 1 mitosis/mm² and negative for ulceration, regression, emboli or perineural invasion. The resection margins were negative. Given that she had a Breslow depth of less than 1 mm, but a mitotic rate of 1 mitosis/mm², performing a lymphoscintigram was discussed with the patient. She agreed to the investigation, and the results were negative. She is under oncological supervision and returns to our Department periodically for follow-up visits.

Case No. 5

The fifth patient is a 34-year-old female, referred to the Department of Plastic Surgery by her dermatologist, who noticed an abnormal looking pigmented lesion on her posterior thorax. The lesion was about 8/6 mm, with heterochromatic aspect and irregular surface (Figure 4).

In our Department, given the macroscopic aspect of the lesion and the dermatologist's consult, the lesion was excised with wide safety margins and the histopathological result showed a malignant melanoma developed on a nevus with Clark level III and Breslow depth of 0.7 mm. Margins were negative. It presented no atypical mitoses, ulceration, necrosis, regression, emboli or perineural invasion. The staining presented malignant nests in the middle of the lesion and matured, uniform nevocytes, without atypia, in

the deeper portion of the tumor (Figure 5, a and b). The inflammatory infiltrate was predominant lymphocytic. IHC staining was also performed to confirm the diagnosis, and it revealed S100, melan A and pan-melanoma cocktail 2 [melanoma antigen recognized by T-cells 1 (MART-1) and tyrosinase] positive in the tumor cells, and Ki-67 positive in 30% to 40% of the tumor cells nuclei (Figure 6, a–d).

Considering treatment guidelines, for patients with melanomas less than 1 mm thickness, with no ulceration, mitotic rate <1 mitosis/mm² and no adverse features (stage I, IA or *in situ*), the recommended treatment is wide-excision surgery. Thus, this patient was discharged from our Department and was advised to return for periodic follow-up visits, to avoid prolonged exposure to UV radiation and to register with an oncologist in her hometown.

Discussions

Melanoma is a rare form of skin cancer, with a high mortality rate if left untreated. However, its incidence has grown in the past decades, partly due to environmental risk factors, such as thinning of the ozone layer, partly due to more accurate diagnostic methods and better reporting systems. The general population now knows, throughout skin cancer awareness programs in the media that melanoma can frequently develop on pre-existing benign nevi that turn malignant. While the information is true and any skin lesion that changes in shape, size and color should be investigated by a specialist, only a small part of all melanomas developed on previously-existing, benign nevi.



Figure 4 – Melanoma developed on a common nevus; posterior thorax – gross aspect.

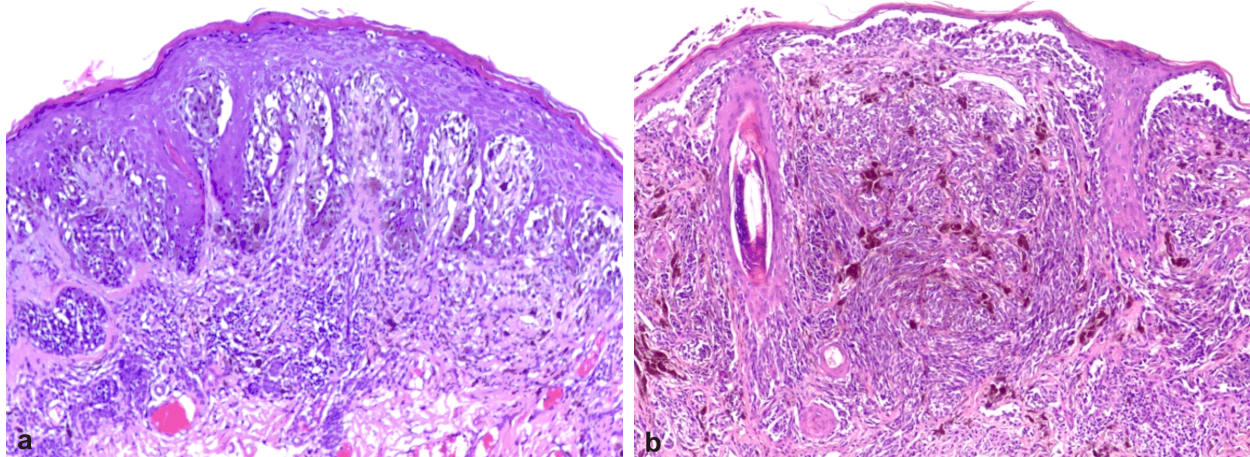


Figure 5 – (a) Melanoma developed on a common nevus, with nests of nevocytes in the lower left corner of the image; (b) Melanoma developed on a nevus. Hematoxylin–Eosin (HE) staining; (a and b) ×100.

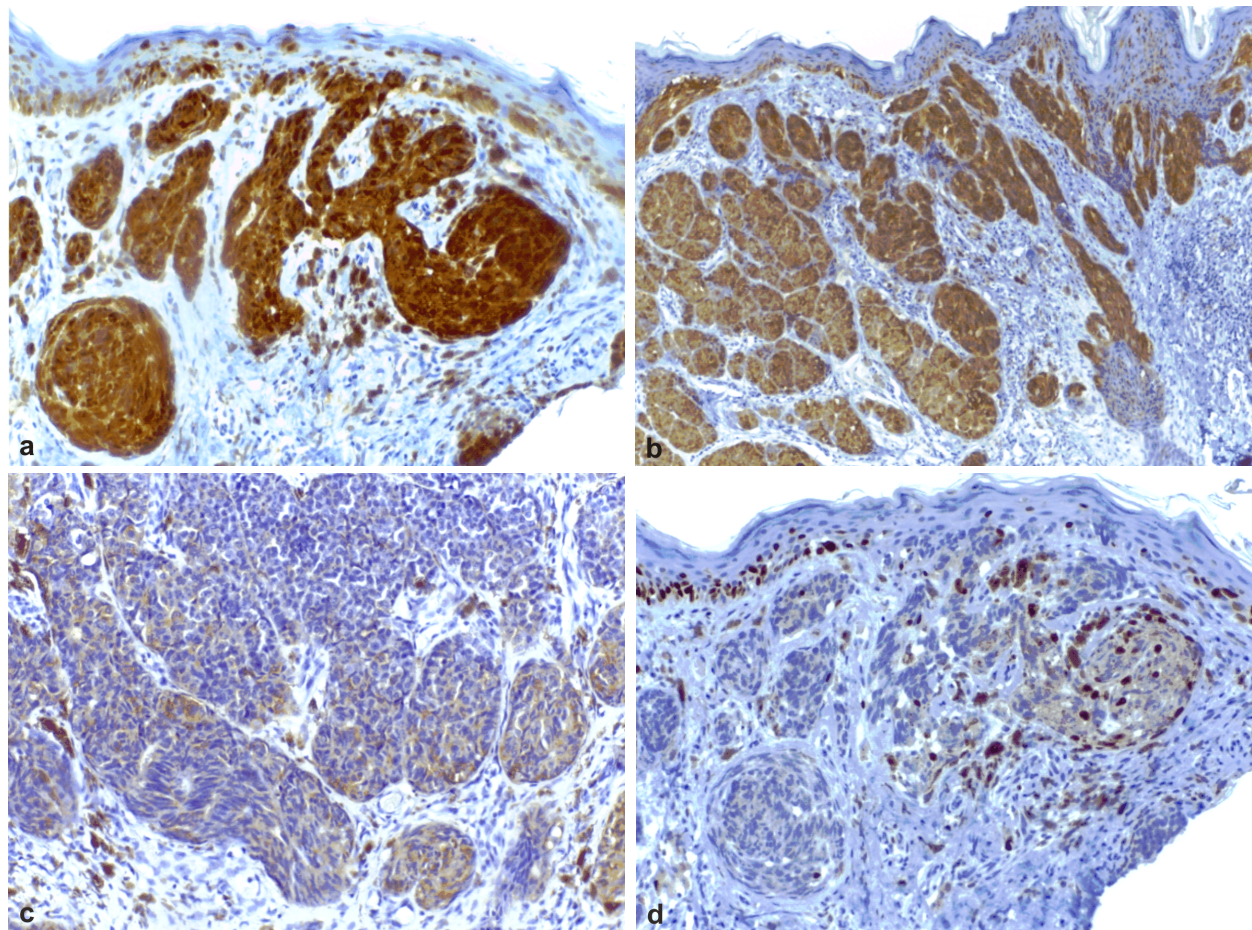


Figure 6 – Melanoma developed on nevus: (a) Anti-S100 antibody immunostaining, $\times 100$; (b) Anti-melan A antibody immunostaining, $\times 100$; (c) Anti-HMB-45 antibody immunostaining, $\times 200$; (d) Ki-67 antibody immunostaining, $\times 100$. HMB-45: Human melanoma black-45.

In the Department of Plastic and Reconstructive Surgery, during the time frame mentioned, 103 patients had benign pigmented skin lesions surgically excised. Sixty-one (59.22%) patients had one or multiple nevi and 21 (20.38%) had dysplastic nevi. Because our Department is a surgical department, simple observation of the development of skin lesions over time is not always applicable. Though the cohort of patients treated and studied in our Department is not significant for a general assessment of the risk of benign skin lesions turning into melanomas, it is worth mentioning that only one patient in that time period had a melanoma developed on a dysplastic nevus.

Dysplastic or atypical nevi are considered to be precursors of melanoma, mainly because their histological characteristics, such as architectural disorder and cytological atypia, are similar to both benign proliferations and melanoma [10, 11]. In a large meta-analysis conducted by Gandini *et al.* [10, 12], dysplastic nevi were overall shown to be a prominent risk factor for developing melanoma. It is estimated that about 20% of melanomas arise from dysplastic nevi, while most are *de novo* lesions [10, 13]. Little is known and studied about melanoma developing from other types of nevi. Another study, conducted by Tucker *et al.* [10, 14], followed families with high risk of developing melanoma and found that most of their dysplastic nevi remained stable over time. This was also true for patients without familial history [15].

There are other studies which suggest a much higher rate of melanoma developing on a pre-existing nevus, as opposed to *de novo* occurrences. A study by Haenssle *et al.* [16] reported remnants of melanocytic nevi in 54.2% of melanoma patients examined. A larger meta-analysis conducted by Pampena *et al.* [17] that reviewed case control and cohort studies, summing 20 126 melanomas indicated that 29% of melanomas were nevus-associated, although mentioning heterogeneity between studies. They also noted a much lower average Breslow thickness in these cases as opposed to *de novo* melanomas. This finding is similar to the cases in our studies, where despite macroscopic size, and delayed presentation, the tumors were relatively thin, compared to similar, *de novo* melanomas. That was also a factor that contributed to the favorable prognosis of the patients. Another study, conducted in Brazil [18] reports similar findings, with one-third of melanomas developing on pre-existing nevi. This study also reported a higher occurrence rate of this kind of malignancy on the trunk than on the head. Out of the five cases presented, four were located on the trunk and one on the head. The study also found a higher rate of nevus-associated melanoma in areas intermittently exposed to the sun. Such was the case in four of our patients, who developed melanomas on their posterior trunk, abdomen and hip, all areas without constant sun exposure, especially in women.

There is also research that indicates a better prognosis for melanoma developed on nevi than *de novo* tumors [19]. They reveal that *de novo* tumors have a higher Breslow score upon examination (over 1 mm) and a higher rate of adverse features (ulceration, nodular subtype) as opposed to melanomas developed on nevi. Such is the case of the patients presented, three of whom, despite having rather high Breslow scores and adverse signs (mitotic rate higher than 1 mitosis/mm²) had no lymph node involvement at the time they were investigated. They were free of recurrences at the time this paper was written. This and other studies [19, 20] correlate nevus-associated melanoma with younger age. This is also relevant for our patient's group, only one of the five patients being over 40 years of age at the time of the diagnosis.

From the clinician's perspective, the moment of diagnosis is important in these cases along with the reasons why patients see a physician in the first place. Two of the patients had been sent by a physician (dermatologist in one case or family physician in another) who noted abnormal lesions that had not concerned the patient. Another two had seen a specialist after accidentally traumatizing skin lesions, while one had presented without prior examination. Literature reports [21] show that half of melanomas detected were observed by a dermatologist and had not been part of the initial complaint. This only stresses the importance of regular supervision of pigmented skin lesions, especially in patients with family history or conditions such as multiple nevus syndrome [22]. It is perhaps also interesting to note that only one out of the five patients who noticed a skin lesion alter in size and shape had seen a physician and had the tumor excised while still *in situ*. Although a lot of effort has been made to encourage the population, especially fair-skinned Caucasians with a history of sun exposure, to practice self-examination and have all suspicious skin lesions checked by a professional as soon as possible after detection, many patients are still admitted with ulcerated or infected lesions, both indicating locally advanced disease. In more fortunate cases, patients are directed to dermatology or surgery after a routine check-up by the general physician or a physical examination by other specialists, for other pathologies. This concern is not limited to our geographical area. Xavier *et al.* [23] analyzed 211 cases of melanoma and observed that the lesions were self-discovered in 41.7% of the patients; healthcare providers detected 29.9% and 27% were discovered by others. The main component in delay was patient-related. Only 31.3% of the patients knew that melanoma was a serious skin cancer, and most thought that the pigmented lesion was not important, thus causing a delay in seeking medical assistance. 36.4% of the patients reported a wait interval of more than six months from the onset of an observed change in a pigmented lesion to the first visit to a physician. On the other hand, we highlight the fact that all melanomas presented in this paper, although most of them invasive, did not had any poor prognosis factors such as emboli, perineural infiltration, regression or ulceration.

Prospectively, new screening and diagnostic methods using modern technology are tested. There have been computer algorithms developed in order to distinguish

between benign and malignant skin lesions using macroscopic images obtained with a digital camera, with promising results [24, 25]. Such software, although it has limitations, could be a useful tool for clinicians to encourage larger numbers of people to have their skin lesions examined.

As far as the resection margins are concerned, recommendations and definitions vary [26]. Narrow resection margins vary from 1–2 cm, and wide margins between 3 and 5 cm [26, 27]. Deep excision margins are also subjected to debate, and not included in many studies. As far as our patients were concerned, the tumors were excised with margins between 1 and 2 cm, according to local anatomy. As for depth, tumors were excised to the fascia, in the truncal lesions, and to the cartilage in the case of the melanoma developed on the ear. All resection margins were microscopically negative and the patients presented no local recurrences.

✎ Conclusions

Skin cancer has been steadily increasing in incidence in the past decades, with melanoma still leading the mortality rates. Therefore, it is only natural for health care providers to strive to improve early diagnostic and treatment options for these patients. Nevertheless, there is little consensus among specialists regarding screening protocols, regular check-ups, targeted population, even the appropriate surgical excision margins. To this day, self-examination and early presentation to a specialist remain the patient's best tools for an early diagnosis. From a clinician's point of view, it is highly recommended that any growing skin lesion should be dermatoscopically examined and excised with safety margins, since the only certain diagnosis is the histopathological examination result. While melanoma is a rare occurrence, even more so when it is developed on a pre-existing nevus, its impact on the individual and on the healthcare providers is undeniable.

Conflict of interests

The authors declare that they have no conflict of interests.

Ethical standards

We undersign, certificate that the procedures and the experiments we have done respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2000 (5), as well as the national law.

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