

Nodular Melanoma-Like Superficial Spreading Melanoma Arising from Intradermal Unna Nevus-Can Incomplete Oncogenic-senescence be Responsible for Non-hierarchical Melanomagenesis?

Betul Tas^{1*}, Ozgur Pilanci², Yazgi Koy³ and Umit Seza Tetikkurt³

¹Department of Dermatology Bagcilar Research and Training Hospital, Turkey

²Department of Plastic Aesthetic and Reconstructive Surgery, Bagcilar Research and Training Hospital, Turkey

³Department of Pathology, Bagcilar Research and Training Hospital, Turkey

Abstract

We report a 70-year-old woman who presented a superficial spreading malignant melanoma with a nodular melanoma appearance, located on her leg. Most common clinicopathological types of malignant melanoma are lentigo maligna, superficial spreading, nodular, and acral lentiginous melanoma. Unusual variants of melanoma are rare but important. These are amelanotic melanoma, neurotropic melanoma, desmoplastic melanoma, metastatic melanoma, invisible melanoma, balloon cell melanoma, melanoma arising within a benign nevus and pedunculated melanoma. The lesion of our patient simulated a nodular or a pedunculated melanoma clinically, but its histopathological examination showed a superficial spreading melanoma arising from the surface of an Unna nevus. To the best of our knowledge, such misleading nodular appearance of a superficial melanoma arising from an intradermal nevus of Unna which seems to be a unique finding has not been reported previously.

Keywords: Malignant melanoma, Intradermal nevus, Unna nevus, Superficial spreading melanoma, Nodular melanoma, Polypoid melanoma, Pedunculated melanoma

Introduction

Malignant Melanoma (MM) is an aggressive tumor of melanocytes, and its incidence has been increasing worldwide over recent decades [1]. It can arise from either benign melanocytic skin lesions, or melanocytes within the other regions of the body including skin, mucosa and uvea, as de nova [2]. MM incidence is less than 5% among all skin cancers, but it is responsible for around 95% of skin cancer deaths [3]. Location of the MM lesions is more prevalent on the trunk in men, and more prevalent in the lower extremities in women [3,4]. The most common clinicopathological type of MM in Caucasians is superficial spreading melanoma (SSM) and the second is nodular melanoma (NM) [3-5].

Case

A 70-year-old female patient was admitted to our clinic complaining of a gradually growing mass on her right thigh for 1 year. According to the patient history, she noticed the lesion when she was 10 years old. Formerly, the lesion was a small and colorless papule which had a few hairs. The lesion began to grow in size 1 year ago, and color started to appear from 6 months ago. The patient has Fitzpatrick skin type-III. Dermatological examination showed an eroded and black-colored pedunculated nodule approximately 2.4 × 1.5 cm in size which was located on the back of the right thigh. It looked like a muffin with chocolate sauce poured on top (Figure 1a). When palpated, the lesion was non-tender, and elastic in consistency. On the other examinations including rest of the skin, scalp, mucous membranes and nails, no additional pathological finding was detected. With dermatoscopy, an eroded, hemorrhagic, little hairy whitish center which was surrounded by a white crescent, a dark-black area on one side of the nodule, and a black-brown background of the eroded nodule were seen. In the periphery of the background pigmentation, there were three, brown, asymmetric pseudopods. In the pseudopods, atypical pigment networks were seen. Satellite pigmentation was not seen around the nodule (Figure 1b). The patient had no other complaints, and there were no regional or systemic enlarged lymph nodes, hepatomegaly or splenomegaly. Routine laboratory examinations including total blood cell count, blood biochemistry, blood sedimentation rate, urinalysis,

as well as serum levels of lactate dehydrogenase (LDH) and chest radiogram showed no pathology. Cancer markers were negative. With the prediagnoses of NM or pedunculated melanoma (PM), the lesion was totally excised with a 3 cm safety margin. The histopathological examination of the excised tissue revealed mild acanthosis, multiple elongated rete ridges, which give a labyrinth-like image by merging together in epidermis as well as mitotic, multinucleated, hyperchromatic and pleomorphic atypical melanocytes in sheets and nests which were mostly located along the dermal-epidermal junction and papillary dermis. The nest sizes and counts of the melanocytes decreased toward the reticular dermis, but did not reach the subcutaneous fatty tissue. In the lesion, microsatellite, lymphovascular or perineural invasion, and

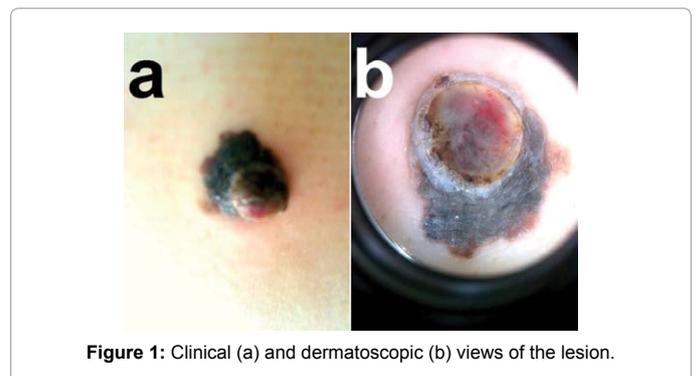


Figure 1: Clinical (a) and dermatoscopic (b) views of the lesion.

*Corresponding author: Betul Tas, Department of Dermatology, Bagcilar Research and Training Hospital, Atakoy 7-8. Kisim, Marti Sitesi, 14/105, Bakirkoy/Istanbul, Turkey- 34156, Tel: (+90) 212-4404000; Fax: (+90) 212-4404000; E-mail: betulavc@yahoo.com

Received April 06, 2015; Accepted April 17, 2015; Published April 25, 2015

Citation: Tas B, Pilanci O, Koy Y, Tetikkurt US (2015) Nodular Melanoma-Like Superficial Spreading Melanoma Arising from Intradermal Unna Nevus-Can Incomplete Oncogenic-senescence be Responsible for Non-hierarchical Melanomagenesis? Pigmentary Disorders 2: 179. doi:10.4172/2376-0427.1000179

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tumor regression were not seen. Growth phase was vertical. Tumor-infiltrated lymphocyte score was (++). Breslow thickness was 4.375 mm in the thickest part of the lesion. Clark level was IV. Mitotic index was 2/per mm². Histological type of the tumor complied with SSM (Figure 2a, b). Immunohistochemically, the tumoral region (mostly junction and papillary dermis) showed diffuse and strong immunopositivity with Human Melanoma Black (HMB45) (Figure 2c). However, in the some regions of upper and mid-dermis of the nodule, dense, isomorphic and homogeneous nevus nests were noticed, and these portions did not stain with HMB45. The morphological structure of the nodular lesion was consistent with an intradermal nevus of the Unna type. With the histopathological and immunohistochemical findings, the diagnosis of SSM arising from upper parts of an Unna nevus was confirmed. After the diagnosis of the nodule, regional lymph nodes were marked with methylene blue, and sentinel lymph node was excised from the inguinal region. Its histopathology showed reactive hyperplasia and a few melanin laden macrophages but no atypical cells. Immunohistochemical examination of the lymph node with Melan-A antibody did not show any evidence of atypical melanocytes. No regional or systemic metastases were seen on computer tomography, and the available clinical and laboratory investigations, did not show any alternative primary source for the lesion. Based on this evidence, the stage of the disease was identified as Stage-IIB (pT3b,N0,M0). Therefore, additional therapy was not given to the patient. The patient was checked monthly for three months, and every three months for the following six months, and after that every six months. In the 21-month follow up period, no evidence of locoregional recurrence or metastasis was observed.

Discussion

The most common clinicopathological types of MM are lentigo maligna (LM), SSM, acral lentiginous melanoma and NM [1-3]. SSM is the most common clinicopathological subtype and accounts for 60-70% of MM cases in Caucasians, followed by nodular subtype. NM is the second most frequent subtype with 10-15% incidence in light-skinned people [4]. Besides these common presentations, MMs sometimes may show unusual clinical expressions. One of them is PM (or polypoid melanoma [PoM]), and this variant can be confused with other skin lesions with pedunculated or polypoid appearance including intradermal nevus, fibroepithelial polyp, or pyogenic granuloma [1,6].

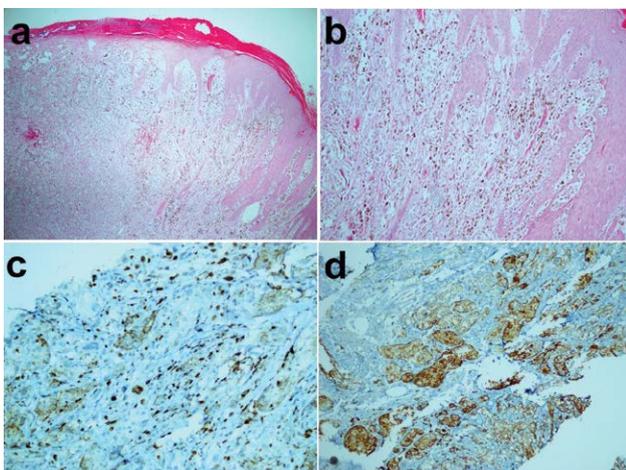


Figure 2: Histopathological (a. HEX40, b. HEX100) and immunohistochemical (Ki-67X200, HMB45X 100) views of the lesion.

Before the histological examination, since the clinical appearance of our patient's lesion was nodular in shape, we first thought the lesion could be a NM. However, our patient stated that the lesion began on a preexisting non-pigmented and little-hairy nevus which was first noticed when she was 10 years old. The nodular-shaped MM usually expresses a nodular type of melanoma. Rarely, the nodular appearance can result from a PM or PoM [1,6,7]. However, our lesion was SSM, and it arose from a preexisting intradermal benign hairy nevus. Therefore, this pedunculated (or polypoid) appearance of our lesion was a misleading feature. On the other hand, PM was first described by Vogler et al. in 1958 as an exophytic form of the NM in which most of the tumor lies above the skin surface [8]. This variant often appears ulcerated but not necessarily pigmented. It has been reported that the incidence of PM ranges from 2 to 43% [1]. Clinically, it evolves with rapid growth. In the histopathology, higher degree of melanocytic atypia, nuclear and cellular pleomorphism, and higher mitotic index are usually found. The reason for this pedunculated form is that it shows a rapid vertical growth pattern without radial growth [1,6]. When it was first described, it was indicated as the most aggressive form of NM with the worst prognosis [1]. In 1983, McGovern et al. classified PoM into pedunculated or sessile types [9]. The pedunculated form is defined as a lesion wholly above an unaltered cutaneous surface with which it is connected by a pedicle. The sessile form usually has at least 50% of the tumor above the skin surface [1,9,10]. Up until 1980s, only a few PM cases had been reported. Siminovitch et al. reported 26 cases in 1980. Although most of the reported PM cases were nodular types, other histopathological types of pedunculated (or polypoid) form were rarely published [11]. For example, Southerland et al. reported an amelanotic PoM in 1991 [12], and Belgaumi et al. reported a case of oral pedunculated desmoplastic MM [2]. On the other hand, in MM development, the most accepted theory is a "stepwise malignant transformation concept" which means the tumor develops from a common nevus to a dysplastic nevus and, finally, to melanoma in situ, in a hierarchical manner [13]. The development of MM from preexisting benign intradermal nevus is exceptionally rare. A certain proportion of MMs may arise from large congenital melanocytic nevi. The risk of MM development from small congenital nevi and acquired nevi is exceedingly low. Annual transformation rate of a single nevus into melanoma has been reported as low as approximately 1/200,000-300,000 [14]. However, Tsao et al. suggested that the individual risk of a nevus transforming into MM increases with the "older age of the nevus" [15]. Indeed, underpinning new insights into nevocarcinogenesis is increasingly important role of senescence, meaning the arrest of proliferation with preservation of metabolic activity. It has been suggested that there are some different pathways in the process of nevi senescence. One of them is known as "replicative senescence" which causes an intrinsic limitation on the number of divisions [16,17]. Second pathway is "oncogen-induced senescence (OIS)" which runs through some pro-oncogenes such as BRAF, HRAS and NRAS which play crucial roles in melanocyte growth and proliferation. Interestingly, a delicate balance between the BRAF activity level at which proliferation is stimulated and the threshold for BRAF activity at which OIS is induced, has been detected [18]. Furthermore, activating mutations of the BRAF gene have been found in up to 82% of acquired nevi [19]. On the other hand, OIS may trigger stress-induced senescence, which also include DNA damage and other cellular stresses [20]. Similar to our case, Lallas et al. reported a case of LM which arose from overlying banal-appearing intradermal nevus of the Miescher type. Their patient was 58-years old, and her preexisting nevus was noticed when she was 20 years of age. Therefore, similar to the suggestion of Tsao et al., the authors speculated that, the reason for the MM development from an intradermal nevus could be related to advances age of patients [14].

Tajima et al. reported another case of MM within a preexisting intradermal nevus. In contrast to our lesion, their lesion was composed of an intradermal nevus in the upper portion of the dermis, and a deeper nodule composed of malignant neoplastic cells that extended into the reticular dermis, and only these deeper cells were positive for HMB45 while upper ones were not [21]. In another report, Benisch et al. reported two NM lesions originating from intradermal nevi [22]. Our lesion was a SSM. SSM usually begin as a slightly elevated pigmented papule. When the vertical growth pattern begins, the lesion turns into a papule followed by nodularity, and sometimes an ulceration develops on the surface [23]. In the histopathology of early stage, junctional activity of the malignant cells is predominant, while in tumorigenic vertical growth phase, at least one, although often more than one, clusters of melanoma cell are found in the dermis [24]. Contrastingly, NM starts as a slightly raised, variably pigmented papule that increases in size quite rapidly to become a nodule, and often undergoes ulceration. Therefore, in the development of NM, it has been stated that an in situ component might be lacking. When the lesion is first diagnosed, a tumorigenic vertical growth pattern is usually seen due to the fleet antecedent radial phase [25,26]. Although the clinical appearance of our lesion was similar to NM and PM (or PoM), due to its histopathological features which were attributed to SSM, and typical history of our patient, our lesion was differentiated from both NM and PM (or PoM). Additionally, despite our lesion arose from a preexisting intradermal nevus, the histopathological type of our lesion was different from the previously reported cases developing from intradermal nevus. SSM is believed to be associated with acute intermittent rather than chronic continuous ultraviolet radiation (UVR) exposure, and usually occurs on lower legs, especially in women [27]. Our lesion was also located on the upper leg which was an unexposed area, however our patient was very old. For aforementioned reasons, we think that the concept of "older age of the nevus" may be a valid theory for etiopathogenesis of our lesion. BRAF may play an important role in MM development [28]. UVR exposure leads to an acquired BRAF mutation, but high rates of BRAF mutations have been found in nevi from non-UVR-exposed skin, as well [29]. Therefore, we also think that during the OIS process, a proliferation-prone imbalance in activation levels of pro-oncogens, with the contributions of unfavorable metabolic and immunological factors, may lead to incomplete senescence processes, and could be responsible for melanomagenesis in cases such as our patient. In conclusion, to the best of our knowledge, the presented case is the first example of SSM arising from a preexisting intradermal nevus of Unna type. We hope that the pathogenesis of development of MM originating from intradermal nevi, which develop in non-hierarchical way, will be enlightened in the future, through the understanding of exact roles of some molecular mechanisms.

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