Subungual amelanotic malignant melanoma

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ABSTRACT

We report a 61-year-old, male patient complaining from prolonged lesion on his great toe that has been previously treated surgically. Histopathological examination of toenail specimen revealed the presence of nests of atypical tumor cells that led to the diagnosis of amelanotic malignant melanoma. Four years ago, he was diagnosed as gout due to extreme erythema and edema in the same toe. He has been taken to surgical treatment and chemotherapy and is still undergoing. As this disease is seen very rarely, it can be misdiagnosed. This situation also has poor prognosis. We presented a case of subungual amelanotic melanoma, as it is rare disease, early and correct diagnosis is very important.

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It has been well recognized that the incidence of malignant melanoma, in which early diagnosis is significantly important, and has been increasing for the last 50 years. There are several different types of malignant melanoma of which the subungual form is rare (1-3%) and it constitutes 10-31%, of all cases of melanomas in Caucasian and in other races.[1] Its incidence in recently reported cases was estimated to be 0.18-2.8%.[2] Similarly, amelanotic malignant melanoma is a rare disease, and constitutes approximately 2% of all malignant melanoma cases.[3]

Subungual malignant melanoma may appear in 20-80 years of age, but mostly observed in 6th and 7th decades of life. Although, ultraviolet radiation has been considered to be the most important risk factor for many types of malignant melanoma, etiology of subungual form has not been known yet. Ultraviolet radiation, which hardly penetrates the nail plate, may play a minor role in subungual melanoma. However, trauma has been shown to be the major responsible factor as it is usually found in great toe.[2] Supporting this idea is an observation that blacks have relatively increased frequency of subungual melanoma as whites, but significantly lower incidence of melanoma elsewhere.[4] Amelanotic subungual melanoma is usually misdiagnosed as a benign disease, and this leads to a delayed diagnosis (**Table 1**).[5] It is known that 5 years survival is generally poor, ranging from 20-60%.[4] In this report, we presented a case of subungual amelanotic malignant melanoma, as it is a very rare disease, and can be easily misdiagnosed. Therefore, early and correct diagnosis can lead to an improved prognosis of the disease.

Case Report. A 61-year-old male patient, Fitzpatrick's skin type III, was admitted to our dermatology clinic with the complaints of prolonged bleeding of his lesion in his right great toenail for 9 months that was not healed despite an operation 2 months ago in a private clinic. In his dermatological examination, there was an edema at the right great toenail and a verrucous mass (bleeding at scattered sites, mildly watery, in yellow-skin color) was observed which involved entire distal and almost half of the toe, particularly the tips, and demonstrated various radius sizes between 0.5-2 cm with well-

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Table 1 - Differential diagnosis of subungual malignant melanoma.

Cases of clinical misdiagnosis	
Onychomycosis	Subungual nevus
Paronychia	Subungual exostosis
Pyogenic granuloma	Mucous cyst
Chronic ingrown nail	Subungual fibroma
Subungual hemangioma	Keratoacanthoma
Hemorrhage	Bowen's disease
Glomus tumor	Subungual squamous cell carcinoma
Subungual warts	Kaposi's sarcoma

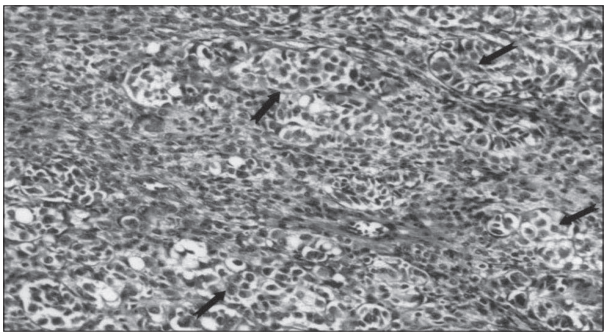

Figure 2- A micrograph of a histopathologically stained biopsy from the affected toenail shows nests of atypical tumor cells (arrows) with variation in size and shape (hematoxylin & eosin x 20).

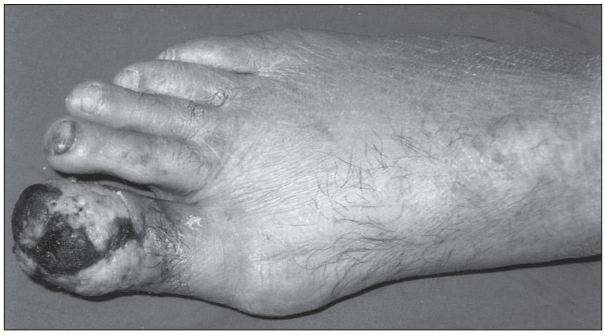

Figure 1- A photograph of the patient's big toe demonstrates black necrotic tissues at the side of amelanotic verrucous mass.

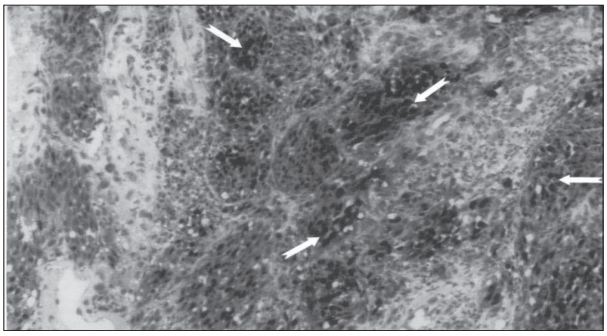

Figure 3 - A micrograph of immunohistochemically stained biopsy from the affected toenail demonstrates the presence of HMB-45 positive tumor cells (arrows) (x 20).

defined black necrotic regions. No plaque of nail was observed (**Figure 1**). Systemic examination revealed a mass in the right inguinal region suggesting a mobile, solid lymphadenopathy. Four years ago, he was diagnosed of having gout due to pain, redness and swelling. He was on oral administered 300 mg/day allopurinol treatment at the time of examination. Routine laboratory tests including lactic dehydrogenase, and the liver function tests had no abnormal result except a slight increase in serum uric acid. The x-ray photography of the foot was in normal appearance. Punch biopsy was taken on the suspects of pyogenic granuloma, squamous cell carcinoma, amelanotic malignant melanoma, deep fungal infection, verruca, or cutaneous leishmaniasis. Histopathological analysis revealed a tumor structure, which formed sockets and spread into whole tissue while presenting round and oval shaped nucleus with marked nucleolus, and mitosis in places (**Figure 2**). Immunohistochemical staining of biopsies with S-100 and HMB-45 antibodies were positive (**Figure 3**). Based on these findings, the patient was diagnosed as having Clark level IV amelanotic malignant melanoma and operated on by a plastic and reconstructive surgeon, after consultation. The toe was applied first ray amputation and placed graft, right inguinal lymph nodes dissection was performed by lazy S incision. Operated material revealed the same histopathological findings with sound surgical contours. One of 8 lymph nodes extracted was found to be metastatic. The cranial, chest and abdominal CT scans did not show any suspected metastatic foci. The disease was assessed as T_{4b} N_{1a} M_0, stage III_b according to the American Joint Committee on Cancer classification. He was referred to an oncology clinic and still undergoing treatment with cisplatin and nitrous urea.

Discussion. Subungual melanoma was first defined in 1834 as a painful, inflammatory nodule in a fingernail develops gradually over 2 years. Characteristic features were first defined in 1886 and the diseases is mostly misdiagnosed in its early phase.[2] His statement is currently valid and poor prognosis of the disease has been attributed to misdiagnosing.[5] Ungual invasion is a localization rarely observed in Caucasians with 2 major signs: melanonychia striata and Hutchinson's sign. Initial change observed in

subungual melanomas was pigmentation developed in nail bed in approximately 76% of the cases. Only one third of the cases are detected during this phase. In most of the cases, changes of the nail bed, secondary infection or ulceration along with a granulation tissue in nail bed are observed.[2] It was reported by a study that in cases of subungual melanoma, the rate of misdiagnosis was 52% by clinicians who carried out the initial examination. This rate was even higher as 85% if the initial examination was performed by clinicians not specialized in dermatology.[6] Thus, the tumor is often more advanced at the time of diagnosis and most of the cases are usually detected at Clark level 4 or 5.[7] Like in other forms, the most important prognostic factor in subungual forms has been considered to be the thickness of tumor.[8]

Amelanotic form, a very rare form of malignant melanoma, usually has an ulcerated nodule or an appearance of a vascular lesion. It may be presented as erythematous macula, depigmented patch, inflammatory plaque or dermatitis-like plaque.[9] On the other hand, amelanotic form of subungual melanoma is relatively more frequent and constitutes15-25% of subungual form.[2,7] In such cases the diagnosis really becomes difficult, and its differential diagnosis from benign diseases is possible by biopsy analysis only.[2] Such cases do not show pigmentation of the lesion. Histopathological diagnosis is based on the presence of ribbon- or socket-shaped atypical melanocytes in dermis, as well as the detection of S-100 and HMB-45 antigens in immunohistochemically stained biopsies, which may further substantiate the diagnosis.[10]

Treatment of this form of melanoma is similar to the other forms of malignant melanomas. The initial phase in the treatment of subungual melanoma usually involves digital amputation beginning with distal or proximal region. However, such surgical management may cause functional and cosmetic problems. Therefore, new functional surgical methods are being investigated.[8] Most clinicians have suggested elective or radical lymph nodes dissection followed by surgical therapy as a standard procedure. Advanced cases may require adjuvant chemotherapy with certain agents such as dacarbazine, vincristine, nitrous urea, cisplatin, interferon-2α^2. We do not know regarding the effects of gout disease, diagnosed during its first attack on the same digit 4 years ago, on the development and course of subungual malignant melanoma. Unfortunately, we have not found any report on such association in the literature. We think that this association may be coincidental. Frequent exposure of the great toe to trauma led to efforts to make an association with trauma; however, its low incidence requires to consider other factors that may effect its development. Thus, we believe it is beneficial to report such an association, even we have no idea whether it is coincidental or not, for its etiology. However, difficulties involved in the diagnosis of malignant melanoma led to increasing number of studies toward ensuring early diagnosis. However, early detection of amelanotic form is rarely possible. Furthermore, the diagnosis of subungual melanoma can be very difficult due to anatomical position. Thus, most patients are diagnosed with the advanced stage and the tumor is metastasized or spread to the lymph nodes or distant organs. This affects the patient's survival negatively. Furthermore, our patient was operated by a surgeon who made the initial examination without considering malignant melanoma or even consulting a dermatologist. Malignant melanoma should have to be considered at any age after puberty in subungual and periungual pigmented, and non-pigmented lesions those gradually grow and spread into one digit. We believe it is absolutely imperative to refer such patients to a specialized dermatologist before attempting to make any kind of surgical intervention, as this will avoid unnecessary future complications and poor prognosis.

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