NIEMCZYK, Anna, MIŁEK, Magdalena, ŚLUSARCZYK, Monika, STAWSKA, Weronika, FORYŚ, Angelika, KWAŚNIAK, Ksenia, MAGIERSKA, Agata, BANACH, Mariola, BOLLA, Patrycja and STAŚ, Magdalena. Subungual melanoma - what you need to know about it. A literature review. Journal of Education, Health and Sport. 2024;73:51811. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.73.51811
https://apcz.umk.pl/JEHS/article/view/51811

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).**© The Authors 2024;**
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 25.04.2024. Revised: 10.05.2024. Accepted: 22.05.2024. Published: 05.06.2024.

Subungual melanoma-what you need to know about it. A literature review.

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Abstract

Introduction and objective:

Melanoma is one of the most malignant skin cancers originating from pigment cells, accounting for 5–7% of all skin cancers. The prognosis, especially in case of late diagnosis, is poor. The aim of the study is to systematise information on subungual melanoma. To raise awareness among the public and professionals working in the skin care sector of the diagnosis, early detection and treatment of subungual melanoma.

Brief description of the state of knowledge:

Subungual melanoma originates from subungual melanoma lentigines and constitutes from 0.7% to 3.5% of all malignant melanomas. Among dark-skinned populations, this subtype accounts for up to 30% and is the most common subtype of malignant melanoma among African Americans, Asians, and Latinos. Subungual melanoma occurs asymmetrically, most often affecting the big toe or thumb. In this disease, the starting point are melanocytes, which undergo malignant transformation within the nail matrix. A symptom of the disease may be melanonychia, a streak of pigment or irregular discoloration, eventually it takes the form of a triangle. This symptom indicates an advanced stage of the disease. The basis for making the diagnosis is dermoscopy and biopsy. Grazzini et al. suggest conducting a biopsy in each case where one nail plate is affected and the lesion persists for more than 6 months. An important element of diagnostics that helps diagnose of subungual melanoma is the ABCDEF algorithm.

Knowledge of the above-mentioned helps to detect disturbing symptoms at an early stage of the disease, which improves the prognosis and increases the chances of cure.

Summary:

Early detection of melanoma gives a better chance of cure, reduces mortality and complications of the disease, therefore any action to increase public knowledge and awareness on the subject is important.

Keywords: melanoma, subungual melanoma, dermoscopy, melanocytic lesions

Introduction and Description of Current Knowledge

Melanoma is one of the most malignant skin cancers originating from pigment cells, accounting for 5-7% of all skin cancers. It arises in either unchanged skin or within pigmented moles. Melanoma tends to metastasize relatively early and untreated invariably leads to the patient's death. The prognosis for this diagnosis is poor, heavily dependent on lymph node involvement[1]. Prognosis is also dependent on the location of the lesion, the thickness of the invasion, and the presence of ulceration[2]. The stage of the disease also matters. The earlier the detected lesion and initiated treatment, the higher the five-year survival rate[3]. Melanomas are tumors with a high cure rate when the disease is localized only to the skin. The ten-year survival rate in patients with melanoma thickness ≤1 mm and no ulceration is 97% [4]. Early detection of melanoma provides a better chance of cure, reduces mortality, and complications of the disease and therapy [5]. High societal awareness and knowledge of warning signs among people working in skincare and nail services can contribute to earlier detection of the disease in its early stage. In Poland, the number of melanoma cases is constantly rising, both among women and men [6]. In 2020, the number of malignant melanoma cases in Poland was 3272, with 1430 deaths [4].

The types of malignant melanoma include superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), and acral lentiginous melanoma (ALM) [7]. Subungual melanoma (SM) is a rare subtype of malignant melanoma classified among melanomas located on the extremities originating from lentigo maligna. The course of ALM progresses faster than LMM and SSM, lasting from several months to several years, and it can metastasize earlier [8]. Subungual melanoma accounts for 0.7% to 3.5% of all malignant melanomas worldwide [1,9].

Etiology

Subungual melanoma originates from melanocytes, which undergo malignant transformation within the nail matrix. This does not seem to be correlated with sun exposure, which is one of the main factors in malignant skin melanoma [9,28].

Epidemiology

Lentigo maligna melanoma is the rarest form of melanoma among the white race population, accounting for up to 3%, while in populations with darker skin, this subtype represents up to 30%. Subungual melanoma is the most common subtype of malignant melanoma among African Americans, Asians, and Latinos, accounting for up to 75% of malignant melanomas in the African population [9]. The disease affects men and women equally. Women are often diagnosed earlier.

Localization

Subungual melanoma occurs asymmetrically, most commonly affecting the thumb or big toe but can affect any nail on the fingers or toes. These locations represent 75-90% of subungual melanoma occurrences [9].

Appearance

Subungual melanoma develops slowly, initially manifesting as brown-black discolorations within the proximal nail fold. It can appear as a pigment streak or irregular discolorations. This symptom is called longitudinal or striated melanonychia [10,11]. Over time, the pigmented band widens and may be visible along the entire length of the nail plate. The shape of the band often takes the form of a triangle with a wider base at the proximal nail fold and its apex at the free edge of the nail. The extension of pigmentation from the nail to the surrounding soft tissues (periungual tissue) is called Hutchinson's sign [12]. The presence of this sign indicates an advanced stage of the disease. Advanced stages often lead to destruction of the nail plate and the appearance of ulceration. Hutchinson's sign is an important indicator of subungual melanoma.

Algorithm ABCDEF by Levit et al.

In 2000, Levit et al. developed the ABCDEF algorithm, which facilitates the diagnosis of subungual melanoma. Although each letter of the ABCDEF algorithm is important, to

improve the detectability and survival of individuals with subungual melanoma, all letters should be considered together.:

A - age - peak incidence between 50-70 years of age, mainly affecting Asians, African Americans, and Native Americans.

B - band - pigment band - the lesion appears brown-black, has an irregular and jagged border, with a band width above 3 mm.

C - change - change in the nail streak or lack of change despite presumably appropriate treatment.

D - digit - finger - the lesion most commonly locates on the thumb, big toe, or index finger, appearing asymmetrically.

E - extension - spreading - indicates extension of pigment to the proximal and/or lateral nail fold (i.e., Hutchinson's sign).

F - family - indicates familial or personal occurrence of dysplastic nevi or melanoma [13,14]

Diagnostics

Dermoscopy is an essential diagnostic tool for evaluating melanocytic lesions. It allows for in vivo assessment of structures within the epidermis and dermis[8,15]. It is a diagnostic technique that involves examining and assessing pigmented skin lesions. Its advantage is simplicity and low cost. Handheld dermoscopes can provide a 10x magnification [8]. Dermoscopy was initially used to differentiate between melanoma and melanocytic lesions. Currently, it is used for diagnosing hair diseases, inflammatory dermatoses, ectoparasitic infestations, microcirculation assessment [8], and differential diagnosis of lesions located under the nail plate (onychoscopy) [16]. It is an effective method for diagnosing melanocytic lesions, characterized by high sensitivity and specificity compared to examination with the naked eye [15]. Dermoscopic examination of lesions located under the nail plate requires experience [15].

Disturbing dermoscopic features suggesting subungual melanoma include [15,17,18]:

- wide pigment streak, above 6 mm
- presence of multicolored, irregular pigment bands
- pigment streak with irregular, jagged edges
- triangular shape of the lesion
- presence of residual pigment granules

- occurrence of "micro-Hutchinson's sign" - pigment spread to the soft tissues around the nail [16]
- presence of cracks or fissures within the nail plate

Figure 1 depicts the external structure of the nail.

Figure 2 illustrates dermoscopic features suggestive of subungual melanoma

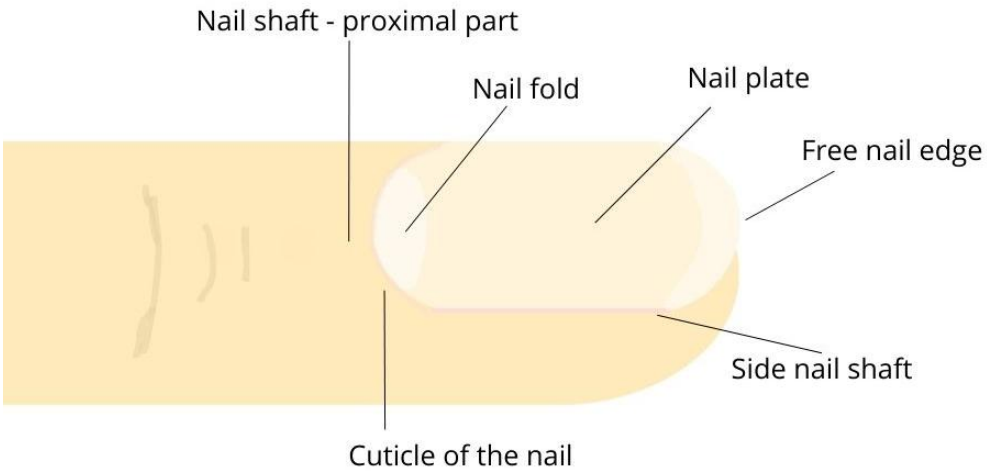

Figure 1

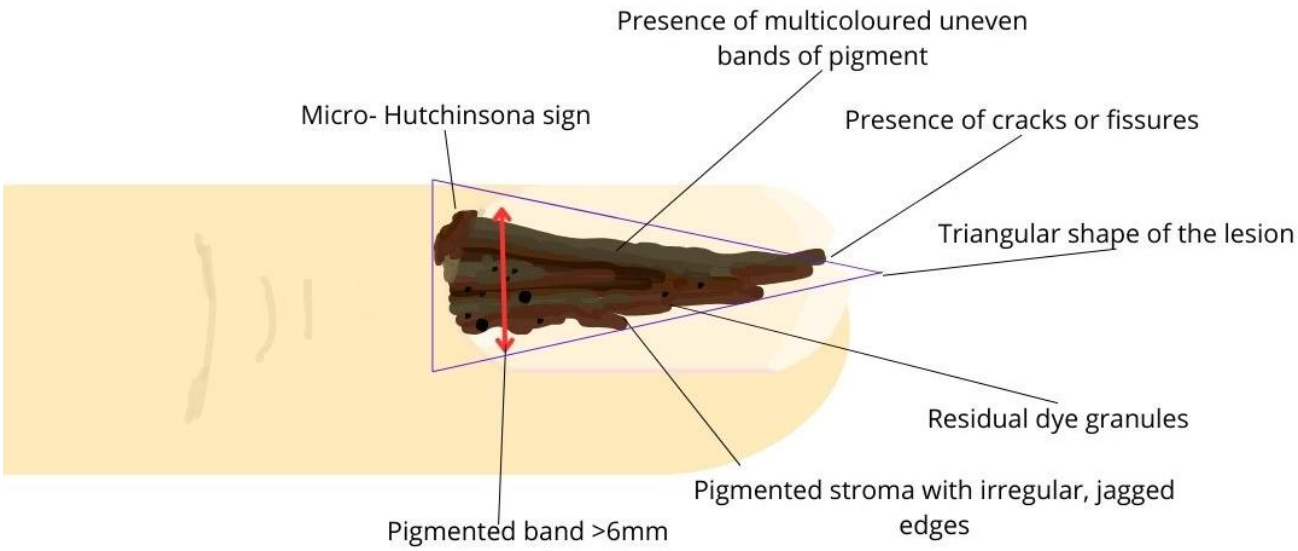

Figure 2

If features suggestive of subungual melanoma are observed, the patient should be referred to a dermatologist. Dermoscopic assessment by a qualified person is essential for diagnosis. It should be remembered that the definitive diagnosis of subungual melanoma is made based on full-thickness biopsy of the nail matrix or complete excision of the lesion [19,20]. This is the only method to establish a correct diagnosis in the case of a tumor lesion. Grazzini et al. [21] suggest performing a biopsy in every case of involvement of a single nail plate and the persistence of the lesion for more than 6 months. The excised lesion should be macro- and microscopically examined. Macroscopic examination should pay attention to features such as: the size of the excised lesion with the skin in three dimensions, the size of the lesion in two dimensions, coloration, border of the lesion, presence of nodules, lateral and depth margins, and advancement degree. Microscopic examination should evaluate: Breslow's thickness of invasion, presence or absence of ulceration throughout the thickness, number of mitotic figures per 1mm2, growth phases, peripheral and depth margins, and advancement degree [22,25,26]. After excisional biopsy and diagnosis of melanoma, a sentinel lymph node biopsy should be performed to assess the presence of metastases in the regional lymph nodes. This biopsy helps determine the stage of advancement and the risk of melanoma metastasis. If

the examination confirms the presence of metastases in the excised sentinel lymph nodes, surgical removal of the remaining lymph nodes is necessary [22]. Subsequently, based on the histopathological results, further treatment plan is established, which most commonly involves complete surgical excision or even finger amputation.

Classification and Staging

In order to properly plan treatment for subungual melanoma and estimate a patient's survival time, it's necessary to classify this tumor, which helps assess its stage of advancement. Currently, the TNM classification [23], updated in 2016 by the American Joint Committee on Cancer and the Union of International Cancer Control, serves this purpose. It evaluates: T - primary focus, N - regional lymph nodes and the presence of metastases, M - distant metastases to internal organs. The primary tumor is assessed using the scale developed by Alexander Breslow, which defines the thickness of tumor infiltration and is a key prognostic factor for patients. The thickness is measured using a micrometer under a microscope and is used for TNM assessment.

In the 8th edition of the AJCC classification, the stages of primary melanoma are classified based on the T N M features [29,30]:

T - assesses the thickness of the lesion [mm] according to the Breslow scale and the presence of ulceration.

Tis - melanoma in situ, i.e., pre-invasive.

T0 - no primary lesion (e.g., unknown primary lesion, melanoma that has completely regressed).

TX - thickness of the lesion cannot be determined (e.g., fragmentation of biopsy material).

T1-

- T1a- thickness ≤0.8 mm, no ulceration
- T1b- thickness ≤0.8 mm and ulceration present or 0.8–1 mm with or without ulceration

T2-

- T2a- thickness >1–2 mm, no ulceration
- T2b- thickness >1–2 mm, ulceration present

T3-

- T3a- thickness >2–4 mm, no ulceration

- T3b- thickness >2–4 mm, ulceration present

T4-

- T4a- thickness >4 mm, no ulceration
- T4b- thickness >4 mm, ulceration present

N - assesses the number of regional lymph nodes with metastases and the presence of in-transit metastasis, satellite foci, and/or microsatellites.

N0- no metastases in regional lymph nodes

NX- cannot determine the state of regional lymph nodes

N1-

- N1a - metastasis in 1 sentinel node identified in sentinel node biopsy (micro-metastasis) - clinically asymptomatic. Presence of in-transit metastasis, satellite foci, and/or microsatellites: no
- N1b - metastasis in 1 lymph node clinically identified (macro-metastasis). Presence of in-transit metastasis, satellite foci, and/or microsatellites: no.
- N1c- without metastases in regional lymph nodes. Presence of in-transit metastasis, satellite foci, and/or microsatellites: yes.

N2-

- N2a - micro-metastases in 2 or 3 lymph nodes - clinically asymptomatic. Presence of in-transit metastasis, satellite foci, and/or microsatellites: no.
- N2b - metastases in 2 or 3 lymph nodes, of which at least 1 was clinically identified. Presence of in-transit metastasis, satellite foci, and/or microsatellites: no.
- N2c- metastasis in 1 lymph node (clinically identified or in sentinel lymph node biopsy). Presence of in-transit metastasis, satellite foci, and/or microsatellites: yes.

N3-

- N3a - micro-metastases in at least 4 lymph nodes - clinically asymptomatic. Presence of in-transit metastasis, satellite foci, and/or microsatellites: no.
- N3b - metastases in at least 4 lymph nodes, of which at least 1 was clinically identified, or lymph node package. Presence of in-transit metastasis, satellite foci, and/or microsatellites: no.

- N3c - metastases in 2 or more lymph nodes and/or lymph node package. Presence of in-transit metastasis, satellite foci, and/or microsatellites: yes.

M - evaluates the location of distant metastases and the concentration of lactate dehydrogenase (LDH) in peripheral blood.

M0- no distant metastases.

M1-

- M1a- skin, subcutaneous tissue, or extra-regional lymph nodes.
  - M1a0- LDH concentration within normal range
  - M1a1- elevated LDH concentration
- M1b- lungs.
  - M1b0- LDH concentration within normal range
  - M1b1- elevated LDH concentration
- M1c- other visceral organs except the central nervous system.
  - M1c0- LDH concentration within normal range
  - M1c1- elevated LDH concentration
- M1d- central nervous system.
  - M1d0- LDH concentration within normal range
  - M1d1- elevated LDH concentration

The Breslow scale [27] distinguishes 4 degrees:

- 1 depth of infiltration is less than 0.75 mm
- 2 depth of infiltration 0.76-1.5 mm
- 3 depth of infiltration 1.51-3.99 mm,
- 4 depth of infiltration is greater than 4 mm

Treatment

The primary treatment for subungual melanoma is surgical removal of the lesion along with a margin of healthy tissue [24]. Similar to other malignant tumors, it can metastasize to local lymph nodes via the lymphatic route or distant metastases via the bloodstream. In the case of diagnosed metastases to lymph nodes, lymphadenectomy, i.e., surgical removal of lymph nodes, should be performed, while if metastases are found in distant organs, various types of palliative treatment are applied, which prolong the lives of patients and often reduce

symptoms resulting from the disease. Radiotherapy has limited application in melanoma and should only be used in specific circumstances [9].

Differential diagnosis

Subungual melanoma should first be differentiated from subungual hematoma because it can present a very similar clinical picture. Therefore, a detailed medical history should be taken to determine if the patient has previously experienced trauma. The differential diagnosis of subungual melanoma also includes subungual nevi. Unlike melanoma, they usually appear in adolescence, remain uniformly colored, and usually occupy a narrow part of the nail, whereas congenital nevi can occupy the entire nail plate. Band-like discoloration within the nail also requires differentiation from changes associated with nail infections - mainly fungal and bacterial, mainly Pseudomonas aeruginosa.[20]

Summary

Early detection of melanoma provides a better chance of cure, reduces mortality, and complications of the disease, which is why all actions increasing knowledge and awareness in society about this topic are so important. Individuals involved in hand and foot care are among the first to detect initial symptoms of subungual melanoma and contribute to earlier detection of the disease and initiation of treatment.

Authors Contribution:

Conceptualization- AN, MS, MM; methodology- PB, KK; wirting- rough preparation- AN, MŚ, MB; supervision-AM,AF, writing- rewiev and editing- WS,PB,MM.

Founding Statement: This study didn't acquire external founding

Institutional Rewiev board Statement: Not applicable

Informed consent statement: Not applicable

Conflicts of interests: The autors declare no conflict of interest

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The drawings/figures were made independently.