CLINICAL CASE

EARLY DETECTION AND MANAGEMENT OF MELANOMA: A CASE REPORT

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ABSTRACT

Melanoma stands as the most lethal variant of skin malignancies. During its incipient stages, surgical intervention alone can yield successful treatment outcomes, resulting in high survival rates. However, once metastasis occurs, the survival rates substantially decline. In this case study, we present the journey of a 42-year-old woman with thalassemia minor and a benign breast nodule, highlighting the critical role of early detection and specialized medical care in securing the most favorable prognosis for patients. Upon presentation to the Dermatology department, a thorough evaluation unveiled a unique tumor formation on the patient's skin, approximately 2.5 cm in diameter, with irregular margins. Importantly, the dermatoscopic examination showed a polymorphic appearance with atypical pigment network and central regression, findings that immediately raised concerns. Subsequent surgical excision, coupled with histopathological and immunohistochemical assessments, confirmed a superficial spreading melanoma with a Clark level IV invasion. The development of this malignancy has occurred concurrently with a preexisting intradermal melanocytic nevus. This study underscores the value of early detection and specialized medical intervention in melanoma cases, showcasing the transformative impact of timely medical attention on treatment outcomes and patient well-being.

KEYWORDS: *superficial spreading melanoma; dermatoscopy; immunohistochemistry; early detection*

INTRODUCTION

Melanoma represents 4% of all newly diagnosed cancer cases and is responsible for 1.3% of all cancer-related fatalities, which places it as the fifth most prevalent cancer and ranks it among the top 15 leading causes of cancer-related deaths in the European Union [1,2]. In contrast to other cutaneous malignancies such as squamous cell carcinoma and basal cell carcinoma, which predominantly manifest in sun-exposed regions of the body, melanomas have the capacity to emerge in diverse anatomical locations along the skin's surface [3,4]. These may encompass areas such as the palms of the hands and soles of the feet, as well as the mucous membranes that line the oral,

nasal, and genital regions. If melanoma remains untreated, it has a notably increased tendency for metastatic dissemination to distant anatomical sites compared to other cutaneous malignancies. Fortunately, the early detection of melanoma often enables efficacious intervention, thereby diminishing the likelihood of disease dissemination [5-8].

Various clinical factors significantly influence the prognosis of melanoma patients, encompassing age, gender, skin complexion, tumor pigmentation status, and the location of the primary tumor [9]. Advanced age is associated with a less favorable prognosis in contrast to younger patients, and male individuals tend to face a less advantageous prognostic outlook than their female counterparts [8-10]. Other notable risk factors contributing to an individual's susceptibility to developing melanoma include a prior history of melanoma, the presence of a substantial number of nevi, the existence of large or atypical (unusual-looking) nevi, a family history of melanoma indicating a genetic predisposition, immune-suppressive conditions or treatments, light or fair skin complexion, skin that is prone to burning and resistant to tanning, and the use of sunbeds or tanning salons [11,12]. High-risk anatomical regions for melanoma development include the back, upper arm, neck, and scalp. Acral sites are also often associated with a more challenging prognosis [13,14].

Superficial Spreading Melanoma (SSM) stands as the most prevalent subtype, accounting for approximately 70% of all cutaneous melanomas [15]. It is most frequently diagnosed in areas intermittently exposed to the sun, especially affecting the lower extremities in women and the upper back in men [15,18]. Its classic clinical presentation aligns with the ABCD criteria, characterized by irregular borders and pigmentation [16,17]. Notably, SSM is the melanoma subtype most frequently linked to preexisting nevi [19].

Dermatoscopy plays a pivotal role in enhancing the sensitivity and specificity of clinicians when diagnosing melanoma. It facilitates the identification of melanomas that may not exhibit clinical conspicuousness during their earlier stages, while also aiding in distinguishing benign lesions that could appear concerning from a clinical standpoint [15,20]. The dermatoscopic criteria used to assess melanoma are a consequence of its asymmetric growth and can vary among different subtypes of the disease. These criteria include several positive features such as the presence of a blue-white veil, multiple brown dots, pseudopods, radial streaks, scar-like depigmentation, peripheral dots/globules, the presence of multiple colors (typically five or six), multiple blue-gray dots, and a broadened network [8,21].

This study presents the case of a 42-year-old patient who underwent a significant medical course that highlights the importance of early detection and specialized care. The patient's delayed medical attention, despite acknowledging visible changes in the nevus, highlights the importance of raising awareness. In the context of melanoma research, the interplay between pre-existing nevi and melanoma development remains a subject of active investigation, with varying perspectives [19]. This study aims to comprehensively analyze this case, emphasizing the significance of early detection and specialized care in achieving successful treatment outcomes, offering insights relevant to the broader scientific and medical community. Regular dermatoscopic monitoring is a valuable tool for tracking the patient's progress and detecting any potential issues at an early stage [15,16].

CASE PRESENTATION

We present the case of a 42-year-old woman, known with thalassemia minor and a benign breast nodule, who presented herself at the Dermatology department with a cutaneous tumor located on her posterior chest, seeking specialized diagnosis and treatment. The lesion's evolutionary timeline spanned approximately one year. Intriguingly, despite being recommended to seek a specialist consultation in the previous year, the patient chose to delay seeking medical attention and did not pursue any treatment. However, she later recognized the urgency and finally presented herself at the Dermatology department for a comprehensive evaluation and specialized treatment. The local skin examination unveiled a solitary tumor, approximately 2.5 cm in diameter (Figure 1). The lesion exhibited irregular margins and a distinctive dermatoscopic appearance, characterized by chromatic polymorphism, an

atypical pigment network, blue-white veil with a central regression area, uneven dots and globules (Figure 2).

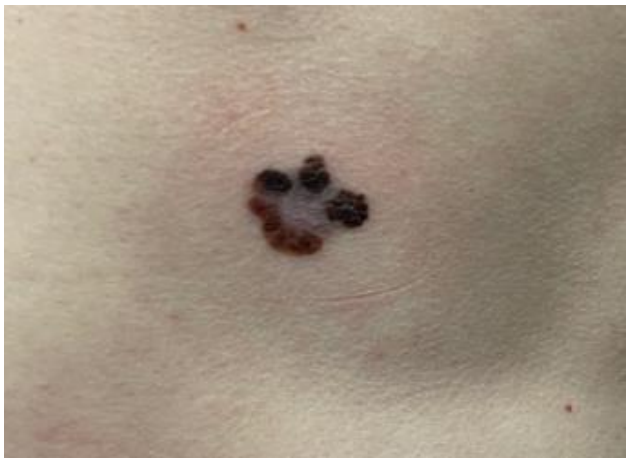

Figure 1 - A solitary tumor, around 2.5 cm in diameter, was revealed during the skin examination

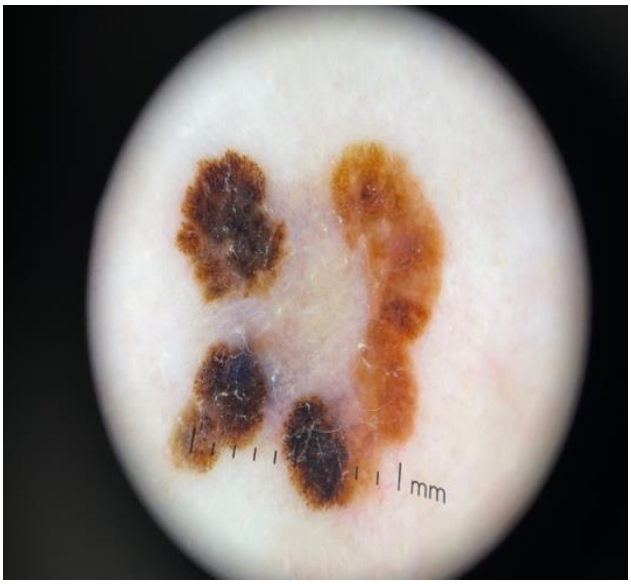

Figure 2 - Dermatoscopic image of the lesion, showing irregular margins and a distinctive dermatoscopic appearance: chromatic polymorphism, an atypical pigment network, blue-white veil with a central regression area, uneven dots and globules; those findings are suggestive of melanoma.

Recognizing the need for thorough evaluation, the medical team promptly performed surgical excision under local anesthesia with 1% xylocaine. The procedure involved a 0.5 cm safety margin, extending to the muscular fascia (Figure 3). This approach preserved the possibility of sentinel lymph node examination, in response to histopathology and immunohistochemistry (IHC) results. The wound was meticulously sutured with non-absorbable 3-0 polypropylene thread and compressively dressed.

The histopathological examination provided valuable insights. The patient's skin excision specimen revealed a melanocytic tumor marked by asymmetry, significant size, and indefinite borders. The tumor was primarily composed of atypical, epithelioid melanocytes, arranged at the dermo-epidermal junction. Within this intricate architecture, melanocytes formed anisomorphic, unevenly spaced confluent nests with a distinctive pagetoid ascent. This combination of features, though diagnostically complex, is characteristic of melanoma. Further exploration into the papillary and reticular dermis uncovered an invasive tumor component. This segment was characterized by atypical epithelioid cells, displayed individually, in nests or clusters. These cells exhibited variable pigmentation and a mitotic index of 1 mitosis per square millimeter. The histopathological assessment indicated a Breslow thickness of 1.3 mm, qualifying the lesion as a Clark level IV melanoma. The tumor displayed no signs of ulceration, lymphovascular invasion, perineural invasion, or microsatellite lesions. Interestingly, this melanocytic proliferation was intricately associated with a pre-existing intradermal melanocytic nevus.

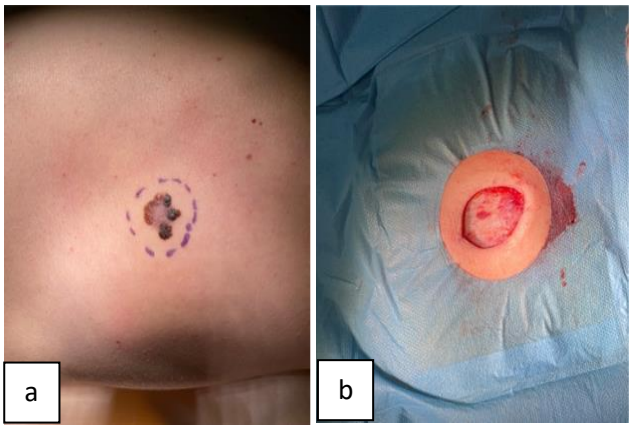

Figure 3 - Surgical excision involved a 0.5 cm safety margin (a), extending to the muscular fascia (b)

Immunohistochemical examination and optical microscopy added depth to the diagnostic process. SOX10 demonstrated nuclear positivity in tumor cells, emphasizing disorganized intraepidermal growth with pagetoid epidermal and dermal invasion. PRAME (PReferentially expressed Antigen in MElanoma) exhibited nuclear positivity within the tumor proliferation

but was conspicuously absent in adjacent, monomorphic melanocyte groups, affirming the pre-existence of a melanocytic nevus. Notably, p16 displayed weak, focal positivity within the tumor proliferation, indicative of abnormal expression, and intensely positive with a "checkerboard" pattern in nevus cells (normal expression).

In essence, the histopathological examination painted a complex portrait of superficial spreading melanoma, non-ulcerated, with a Breslow thickness of 1.3 mm (pTa2). This melanoma had developed in association with a pre-existing intradermal melanocytic nevus.

The post-surgery recommendations included topical treatment, to ensure proper healing. The patient was advised to return for a follow-up appointment in two weeks to remove sutures and discuss the HP results in the clinical context. Furthermore, dermatoscopic monitoring every three months was recommended to ensure early detection of any potential recurrence. The patient was further referred to an oncologist as part of a comprehensive and proactive approach to monitor and manage her melanoma, in order to diligently detect any potential recurrence or metastasis.

DISCUSSION

Numerous studies have consistently shown that women tend to exhibit higher survival rates than men, even when accounting for factors such as tumor thickness and the location of the melanoma. Furthermore, as patient age increases, a less favorable prognosis is observed in terms of overall survival rates [15]. Other several factors have been demonstrated to have a significant influence on the prognosis of patients with melanoma: Tumor (Breslow) thickness, primary tumor ulceration, microsatellites, regional lymph node metastasis, extranodal extension [10]. Prognostic factors necessary for the staging of melanoma include the primary tumor's mitotic rate, the level of invasion (anatomical or Clark level of invasion), tumor-infiltrating lymphocytes, lymphovascular invasion, neurotropism, tumor burden, the status of margins [10,24].

The groundbreaking research conducted by Alexander Breslow established that the most important predictor of clinical outcomes for individuals with localized primary cutaneous melanoma is the vertical measurement of tumor thickness [10]. This measurement extends from the upper boundary of the epidermal granular layer to the deepest point where invasive melanoma cells are found [22]. In cases where the lesion is ulcerated, the measurement is taken from the ulcer's base to the deepest point of tumor invasion. As outlined in the 8th edition of the American Joint Committee on Cancer (AJCC) Melanoma Staging System, tumor thickness remains the primary criterion upon which the staging of patients with clinically localized primary melanoma is based [23]. Ulceration is characterized by the complete absence of an intact epidermis over any part of the primary tumor, accompanied by a host reaction indicated by a histopathological examination, which typically reveals a fibrinous and acute inflammatory exudate located above the primary tumor, and it has adverse prognostic implications [24]. A microsatellite is described as a microscopic cutaneous or subcutaneous metastatic lesion located near or beneath a primary melanoma, as determined by a pathological examination of the primary tumor site. If the diagnostic biopsy reveals the presence of one or more microsatellites, without any clinically affected lymph nodes or readily visible satellite or in-transit metastases, it necessitates the clinical designation of Stage III [10, 23]. The condition of the nearby lymph nodes holds the highest predictive value for survival in melanoma, where the presence of regional lymph node metastasis indicates a more unfavorable prognosis [15].

The mitotic rate is a continuous prognostic variable and serves as a robust independent predictor of patient outcomes. Therefore, it should be evaluated and documented in all primary melanomas, both in the initial biopsy and the excision biopsy [10]. Numerous studies have emphasized the significance of the tumor mitotic rate as a stand-alone predictor of survival, indicating that a higher mitotic rate is associated with reduced survival [15]. Furthermore, the presence of any mitotic activity in the dermis, often referred to as "mitogenicity," not only forecasts survival outcomes but also serves as a predictor of sentinel lymph node positivity [10,23]. Back in 1969, Clark et.al identified a link between

melanoma prognosis and the depth of invasion, categorizing it into five distinct anatomical levels. However, the assessment of Clark levels tends to have lower reproducibility among pathologists when compared to the measurement of tumor thickness [25]. Another significant prognostic factor is lymphovascular invasion, which is associated with a heightened risk of disease relapse, lymph node engagement, distant metastases, and mortality [15]. The existence of neurotropism has been connected to a higher likelihood of local recurrence, and in certain situations, it may necessitate more extensive excision margins and/or supplementary radiotherapy as part of the treatment approach [23].

In our case, the histopathological evaluation indicated a superficial spreading melanoma with a Breslow thickness of 1.3 mm, qualifying the lesion as Clark level IV. Importantly, there were no signs of ulceration, lymphovascular invasion, perineural invasion, or microsatellite lesions. The mitotic index of the tumor was of 1 mitosis per square millimeter. The Breslow thickness of 1.3 mm is considered a favorable prognostic factor. The Clark level IV indicates that the melanoma has invaded the reticular dermis but has not yet reached the subcutaneous tissue or lymph nodes. The absence of ulceration, lymphovascular invasion, perineural invasion, or microsatellite lesions also contributes to a more favorable prognosis. A mitotic index of 1 is considered relatively low, suggesting a lower rate of cell division within the tumor.

While molecular testing holds significant promise and enjoys strong support for its advancement, at present, when it comes to the routine diagnosis of melanocytic lesions, immunohistochemical studies are still the most practical and commonly used method [26]. Given this information, immunohistochemical examination added depth to the diagnostic process of our patient's tumor. SOX10 demonstrated nuclear positivity in tumor cells, emphasizing disorganized intraepidermal growth with pagetoid epidermal and dermal invasion. PRAME (PReferentially expressed Antigen in MElanoma) exhibited nuclear positivity within the tumor proliferation but was conspicuously absent in adjacent, monomorphic melanocyte groups, affirming the pre-existence of a melanocytic nevus. Notably, p16 displayed weak, focal positivity within the tumor proliferation, indicative of abnormal expression, while demonstrating intense positive expression with a "checkerboard" pattern in nevus cells, signifying normal expression.

PRAME immunohistochemistry is a valuable tool for assessing margin status in melanoma, with its frequent expression in neoplastic melanocytes, absence in normal tissues, and a correlation with histologic margin clearance assessment that may surpass H&E or immunostains for melanocyte differentiation antigens, particularly in challenging cases involving inflammation or background melanocyte hyperplasia [27,28]. Compared to SOX10 immunostains, PRAME IHC provides a clearer microscopic delineation of lesion boundaries [27]. In cellular senescence, particularly within melanocytes, the importance of p16 lies in its role as a crucial barrier against tumorigenesis or the progression of melanoma [29]. Evaluation of human melanocytes indicated that cells lacking p16 exhibited heightened proliferation and an elongated replicative lifespan in the context of replication-associated DNA damage [30]. Sry-related HMg-Box gene 10 (SOX10), a nuclear transcription factor essential for melanocytic cell differentiation, acts as a sensitive marker for melanoma [31]. SOX10 proves particularly valuable in assessing junctional melanocytic proliferations on sun-damaged skin, dysplastic nevi, and in the examination of sentinel lymph node biopsies [32]. In sentinel lymph node biopsies, SOX10 is a highly dependable marker for detecting metastatic malignant melanoma, according to studies [33].

Regarding treatment, surgical excision remains the main approach for melanoma. For localized melanoma, the recommended treatment involves surgical excision with margins corresponding to the microstate of the primary lesion [34]. For melanomas with a tumor thickness exceeding 1 mm, sentinel lymph node biopsy is essential for accurate staging, and in the event of a positive finding for metastases, it should be succeeded by a complete lymphadenectomy of regional lymph nodes [35]. In our case, the surgical excision was performed with a 0.5 cm safety margin extending to the muscular fascia, to preserve the opportunity for

sentinel lymph node examination. Surgery has the potential to cure 75 percent of patients with melanoma, but recurrences are possible, with 50 percent happening in the first year, 75 percent within the first 3 years, and 90 percent within the initial 5 years. In cases without lymph node dissection, over 75 percent of recurrences manifest in the regional lymph node basin; however, with complete lymph node dissection, regional recurrence drops to less than 20 percent [36]. Additionally, the prognosis for individuals with primary cutaneous melanomas is significantly influenced by the histopathological condition of the sentinel lymph node [37]. Survival rates are high for those without sentinel lymph node (SN) involvement (~90%), but individuals with metastasis face higher risks of recurrence and mortality, as the majority of morbidity and mortality related to melanoma are attributed to its metastasis, as an adverse prognosis in melanoma is often associated with the presence of metastasis to visceral sites [38-40]. Recent advancements in adjuvant immunotherapies and targeted therapies using anti-CTLA-4 antibodies, anti-PD-1 antibodies, or BRAF/MEK inhibition have enhanced recurrence-free survival in melanoma patients with completely removed nodal metastases [15,38].

Post-diagnosis follow-up for melanoma serves two main purposes: the early detection of any recurrence and the timely diagnosis of an unrelated new primary melanoma. Approximately 5-10% of melanoma patients experience a second invasive melanoma, while over 20% develop an unrelated melanoma in situ [34] . Regular surveillance is crucial to address these concerns and improve overall patient outcomes. In our case, the patient was recommended to undergo dermatoscopic surveillance at three-month intervals for timely detection of potential recurrence, accompanied by a referral to an oncologist as an integral component of a proactive strategy to vigilantly oversee and address melanoma, with the objective of identifying any potential recurrence or metastasis.

CONCLUSION

In conclusion, this case study reinforces the transformative impact of early detection and specialized medical intervention on melanoma treatment outcomes. Through meticulous examination, histopathological assessment, and immunohistochemical analysis, clinicians can tailor proactive management strategies, offering patients the best prospects for favorable prognosis and long-term well-being. Regular follow-up and surveillance remain integral components of comprehensive melanoma care, ensuring the timely identification of recurrences and unrelated primary melanomas, thereby improving overall patient outcomes.

REFERENCES

[1] P. Koczkodaj, U. Sulkowska, J. Didkowska, P. Rutkowski, and M. Mańczuk, "Melanoma Mortality Trends in 28 European Countries: A Retrospective Analysis for the Years 1960-2020," Cancers (Basel), vol. 15, no. 5, p. 1514, Feb. 28, 2023. doi: 10.3390/cancers15051514.

[2] H. Sung et al., "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwde for 36 Cancers in 185 Countries," CA Cancer J Clin, vol. 71, no. 3, pp. 209-249, 2021. doi: 10.3322/caac.21660.

[3] U. Leiter and C. Garbe, "Epidemiology of melanoma and nonmelanoma skin cancer--the role of sunlight," Adv Exp Med Biol, vol. 624, pp. 89-103, 2008. doi: 10.1007/978-0-387-77574-6_8.

[4] D. S. Rigel, "Cutaneous ultraviolet exposure and its relationship to the development of skin cancer," J Am Acad Dermatol, vol. 58, no. 5 Suppl 2, pp. S129-32, 2008.

[5] H. Kittler et al., "Standardization of terminology in dermoscopy/dermatoscopy: Results of the third consensus conference of the International Society of Dermoscopy," J Am Acad Dermatol, vol. 74, no. 6, pp. 1093-1106, 2016. doi: 10.1016/j.jaad.2015.12.038.

[6] D. E. Elder et al., "The 2018 World Health Organization Classification of Cutaneous, Mucosal, and Uveal Melanoma: Detailed Analysis of 9 Distinct Subtypes Defined by Their Evolutionary Pathway," Arch Pathol Lab Med, vol. 144, no. 4, pp. 500-522, 2020. doi: 10.5858/arpa.2019-0561-RA.

[7] J. R. Marsden et al., "Revised U.K. guidelines for the management of cutaneous melanoma 2010," Br J Dermatol, vol. 163, no. 2, pp. 238-256, 2010. doi: 10.1111/j.1365-2133.2010.09883.x.

[8] M. A. Bobonich and M. E. Nolen, Dermatology for Advanced Practice Clinicians. LWW, 2015, pp. 94-112.

[9] U. Leiter, U. Keim, and C. Garbe, "Epidemiology of Skin Cancer: Update 2019," Adv Exp Med Biol,

vol. 1268, pp. 123-139, 2020. doi: 10.1007/978-3-030-46227-7_6. PMID: 32918216.
[10] M. Bobos, "Histopathologic classification and prognostic factors of melanoma: a 2021 update," Ital J Dermatol Venerol, vol. 156, no. 3, pp. 300-321, 2021. doi: 10.23736/S2784-8671.21.06958-3.
[11] J. U. Bertrand et al., "Melanoma Risk and Melanocyte Biology," Acta Derm Venereol, vol. 100, no. 11, p. adv00139, Jun. 3, 2020. doi: 10.2340/00015555-3494.
[12] R. Darp and C. Ceol, "Making a melanoma: Molecular and cellular changes underlying melanoma initiation," Pigment Cell Melanoma Res, vol. 34, no. 2, pp. 280-287, 2021. doi: 10.1111/pcmr.12950.
[13] F. Tas and K. Erturk, "Acral Lentiginous Melanoma Is Associated with Certain Poor Prognostic Histopathological Factors but May Not be Correlated with Nodal Involvement, Recurrence, and a Worse Survival," Pathobiology, vol. 85, no. 4, pp. 227-231, 2018. doi: 10.1159/000488457.
[14] S. S. Bernardes et al., "More than just acral melanoma: the controversies of defining the disease," J Pathol Clin Res, vol. 7, no. 6, pp. 531-541, 2021. doi: 10.1002/cjp2.233.
[15] S. Kang et al., Fitzpatrick's Dermatology, 9th ed. McGraw Hill, 2019, pp. 1982-2017.
[16] N. G. Marghoob, K. Liopyris, and N. Jaimes, "Dermoscopy: A Review of the Structures That Facilitate Melanoma Detection," J Am Osteopath Assoc, vol. 119, no. 6, pp. 380-390, 2019. doi: 10.7556/jaoa.2019.067.
[17] D. S. Cassarino et al., Diagnostic Pathology: Neoplastic Dermatopathology, 2nd ed. Elsevier, 2016.
[18] D. C. Whiteman et al., "Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma," J Natl Cancer Inst, vol. 95, no. 11, pp. 806-812, 2003. doi: 10.1093/jnci/95.11.806.
[19] A. H. Shain et al., "The Genetic Evolution of Melanoma from Precursor Lesions," N Engl J Med, vol. 373, no. 20, pp. 1926-1936, 2015. doi: 10.1056/NEJMoa1502583.
[20] S. E. Rose, G. Argenziano, and A. A. Marghoob, "Melanomas difficult to diagnose via dermoscopy," G Ital Dermatol Venereol, vol. 145, no. 1, pp. 111-126, 2010.
[21] G. Ferrara, "The Histopathological Gray Zone," in Cutaneous Melanoma: A Pocket Guide for Diagnosis and Management, A. Argenziano, A. Lallas, C. Longo, E. Moscarella, A. Kyrgidis, and G. Ferrara, Eds. London, UK: Academic Press, 2017.
[22] A. Breslow, "Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma," Ann Surg, vol. 172, no. 5, pp. 902-908, 1970. doi: 10.1097/00000658-197011000-00017.
[23] M. B. Amin et al., Eds., AJCC Cancer Staging Manual, 8th ed. Springer, 2017.
24. J. E. Gershenwald et al., "Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual," CA Cancer J Clin, vol. 67, no. 6, pp. 472-492, 2017. doi: 10.3322/caac.21409.
[25] W. H. Clark Jr. et al., "The histogenesis and biologic behavior of primary human malignant melanomas of the skin," Cancer Res, vol. 29, no. 3, pp. 705-727, 1969.
[26] S. S. Koh and D. S. Cassarino, "Immunohistochemical Expression of p16 in Melanocytic Lesions: An Updated Review and Meta-analysis," Arch Pathol Lab Med, vol. 142, no. 7, pp. 815-828, 2018. doi: 10.5858/arpa.2017-0435-RA.
[27] C. Lezcano et al., "PRAME Expression in Melanocytic Tumors," Am J Surg Pathol, vol. 42, no. 11, pp. 1456-1465, 2018. doi: 10.1097/PAS.0000000000001134.
[28] G. Cazzato, "Histopathological Diagnosis of Malignant Melanoma at the Dawn of 2023: Knowledge Gained and New Challenges," Dermatopathology, vol. 10, no. 1, pp. 91-92, 2023. https://doi.org/10.3390/dermatopathology10010013.
[29] L. Ha, G. Merlino, and E. V. Sviderskaya, "Melanomagenesis: overcoming the barrier of melanocyte senescence," Cell Cycle, vol. 7, no. 13, pp. 1944-1948, 2008. doi: 10.4161/cc.7.13.6230.
[30] C. Fung, G. M. Pupo, R. A. Scolyer, R. F. Kefford, and H. Rizos, "p16(INK) (4a) deficiency promotes DNA hyper-replication and genetic instability in melanocytes," Pigment Cell Melanoma Res, vol. 26, no. 2, pp. 236-246, 2013. doi: 10.1111/pcmr.12062.
[31] A. Mohamed, R. S. Gonzalez, D. Lawson, J. Wang, and C. Cohen, "SOX10 expression in malignant melanoma, carcinoma, and normal tissues," Appl Immunohistochem Mol Morphol, vol. 21, no. 6, pp. 506-510, 2013. doi: 10.1097/PAI.0b013e318279bc0a.
[32] T. Ferringer, "Immunohistochemistry in dermatopathology," Arch Pathol Lab Med, vol. 139, no. 1, pp. 83-105, 2015. doi: 10.5858/arpa.2014-0075-RA.
[33] B. C. Willis, G. Johnson, J. Wang, and C. Cohen, "SOX10: a useful marker for identifying metastatic melanoma in sentinel lymph nodes," Appl Immunohistochem Mol Morphol, vol. 23, no. 2, pp. 109-112, 2015. doi: 10.1097/PAI.0000000000000097.
[34] N. Emiroglu, F. Pelin Cengiz, and R. Hofmann-Wellenhof, "Dermoscopic and clinical features of trunk melanomas," Postepy Dermatol Alergol, vol. 31, no. 6, pp. 362-367, 2014. doi: 10.5114/pdia.2014.47119.
[35] R. Dummer, A. Hauschild, M. Guggenheim, L. Jost, and G. Pentheroudakis; ESMO Guidelines Working Group, "Melanoma: ESMO Clinical

Practice Guidelines for diagnosis, treatment and follow-up," Ann Oncol, vol. 21, Suppl 5, pp. v194-v197, 2010. doi: 10.1093/annonc/mdq188.
[36] W. W. Dzwierzynski, "Managing malignant melanoma," Plast Reconstr Surg, vol. 132, no. 3, pp. 446e-460e, 2013. doi: 10.1097/PRS.0b013e31829ad411.
[37] D. M. Bello and M. B. Faries, "The Landmark Series: MSLT-1, MSLT-2 and DeCOG (Management of Lymph Nodes)," Ann Surg Oncol, vol. 27, no. 1, pp. 15-21, 2020. doi: 10.1245/s10434-019-07830-w.
[38] L. Kretschmer et al., "The sentinel node invasion level (SNIL) as a prognostic parameter in melanoma," Mod Pathol, vol. 34, no. 10, pp. 1839-1849, 2021. doi: 10.1038/s41379-021-00835-5.
[39] F. Sandru, R. C. Petca, M. Costescu, M. C. Dumitrașcu, A. Popa, A. Petca, and R. G. Miulescu, "Cutaneous Mastocytosis in Childhood-Update from the Literature," J Clin Med, vol. 10, no. 7, p. 1474, 2021. doi: 10.3390/jcm10071474.
[40] C. M. Balch, S. J. Soong, J. E. Gershenwald, et al., "Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system," J Clin Oncol, vol. 19, no.16, pp. 3622-3634, 2001. doi: 10.1200/JCO.2001.19.16.3622.