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Case Report

Acral Lentiginous Melanoma of the Thumb: Dermoscopy and Treatment

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Abstract: Melanoma affecting glabrous skin is a challenging entity that needs to be managed by an interdisciplinary team of dermatologists, oncologists, and surgeons. The thin subcutaneous layer of glabrous skin, which speeds up its metastatic spread, is one of the key elements that contributes to the aggressiveness of this form of cutaneous cancer when identified in this anatomical region. Acral lentiginous melanoma is a rare melanocytic malignancy that is usually associated with ominous outcomes, especially in those with dark skin. Moreover, more extensive research is needed to elucidate the puzzle of molecular drivers and their relationship with thermal injury. We reported our experience in order to highlight the value of timely diagnosis and treatment.

Keywords: melanoma; skin cancer; dermoscopy; surgical treatment

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1. Introduction

Glabrous skin melanoma is a difficult condition to manage, necessitating the collaboration of dermatologists, oncologists, and surgeons [1]. The thin subcutaneous layer, which speeds up its metastatic spread, is one of the key elements that contributes to the aggressiveness of this form of cutaneous cancer when identified in this anatomical region [1].

Early detection is crucial for the management of this tumor due to its high capacity for metastatic spread. Deng et al. [2] documented a 42-year-old woman whose lesion was initially mistaken for a verruca plantaris before being confirmed as a stage IIIC metastatic acral melanoma.

Acral melanoma most commonly affects elderly people and women, and it is more common in the lower extremities [3]. Furthermore, evidence in the medical literature shows that the survival of patients with acral melanoma is influenced by their socioeconomic circumstances [4]. Recent studies highlighted that non-nail acral melanomas are more common on the foot, whereas ungual melanomas seem to be more prevalent on the fingernails than on toenails [5].

A recently published hospital-based retrospective study by Tas et al. [6] found that melanoma of the finger is associated with dire outcomes compared to melanomas in other regions of the body. However, the histological subtype, and whether the lesion was on the hand or foot, did not seem to affect how the malignancy's clinical course developed [6].

Size, depth of infiltration, and clinical stages are the three key indicators of the prognosis for digital acral melanoma [7].

Although patients who are not of Caucasian origin seem to have acral melanoma diagnosed at later stages more frequently [8], a retrospective investigation by Asgari et al. [9] found no association between race or ethnicity and survival.

In this case report, we describe a patient with a history of thermal burn on the thumb who developed acral lentiginous melanoma on the same site and underwent surgical treatment.

2. Case Report

A 73-year-old woman came to the dermatology outpatient clinic complaining of a lesion on her right thumb. The patient reported having purposefully burned her thumb on the stove multiple times to relieve anxiety during the COVID-19 pandemic.

Upon clinical evaluation, two cutaneous lesions of a little over 1 cm in radius were evident. They presented central areas of discoloration and peripheral blackish contours (Figure 1). Their dermoscopic characteristics were the presence of multiple colors, especially in the central part, and irregular borders (Figure 2).

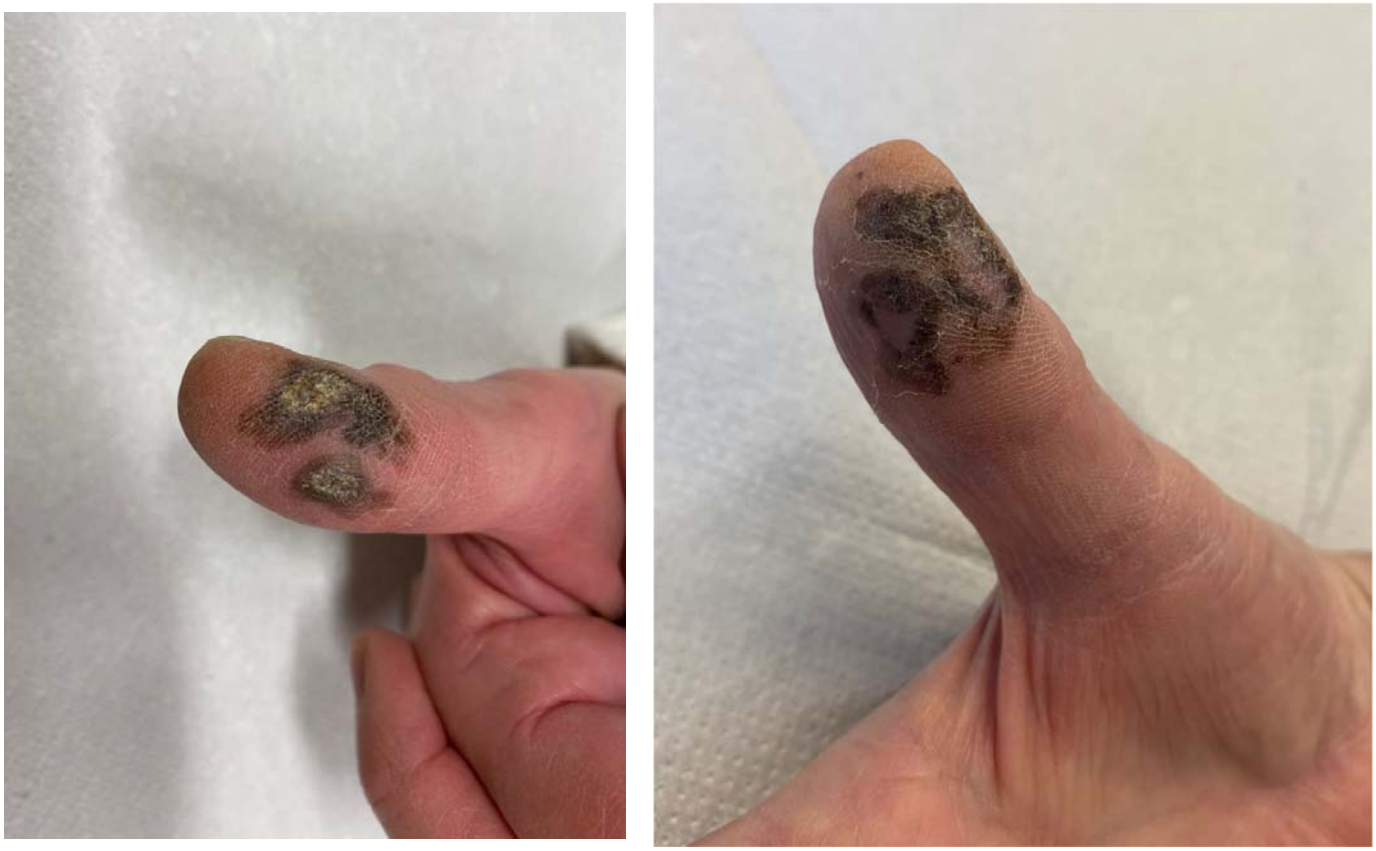
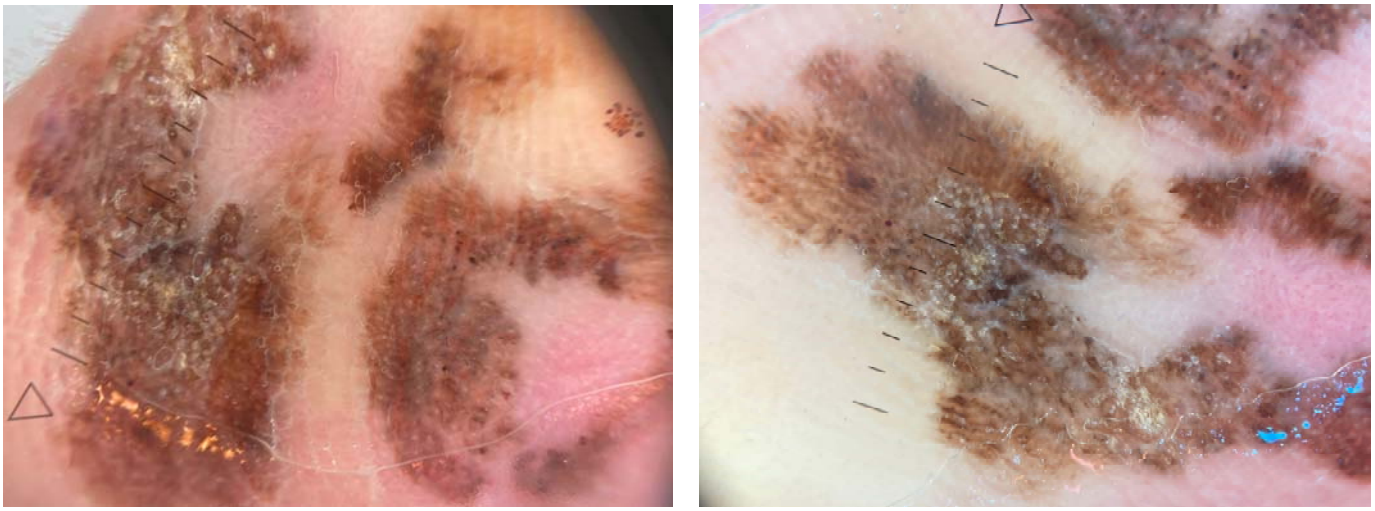


Figure 1. Acral lentiginous melanoma on the thumb of a 73-year-old female patient.

Given the constellation of signs and symptoms, the diagnosis of acral lentiginous melanoma was made.

After a digital nerve block of the thumb by means of mepivacaine 1%, a skin area of about 2.3 × 3.5 cm, including the pigmented neoformations, was removed from the ventral surface of the distant phalanx.

The surgical sample was sent for histopathological examination. A 5 × 3 cm skin lozenge was harvested from the left inguinal region to be used as a full-thickness graft to reconstruct the skin defect of the first right digit (Figure 3).



(**a**) (**b**)

Figure 2. Dermoscopy of the digital lesion of the patient. (**a**) The asymmetrical structure and multicomponent pattern of the lesion are evident. (**b**) Multiple colors are present.

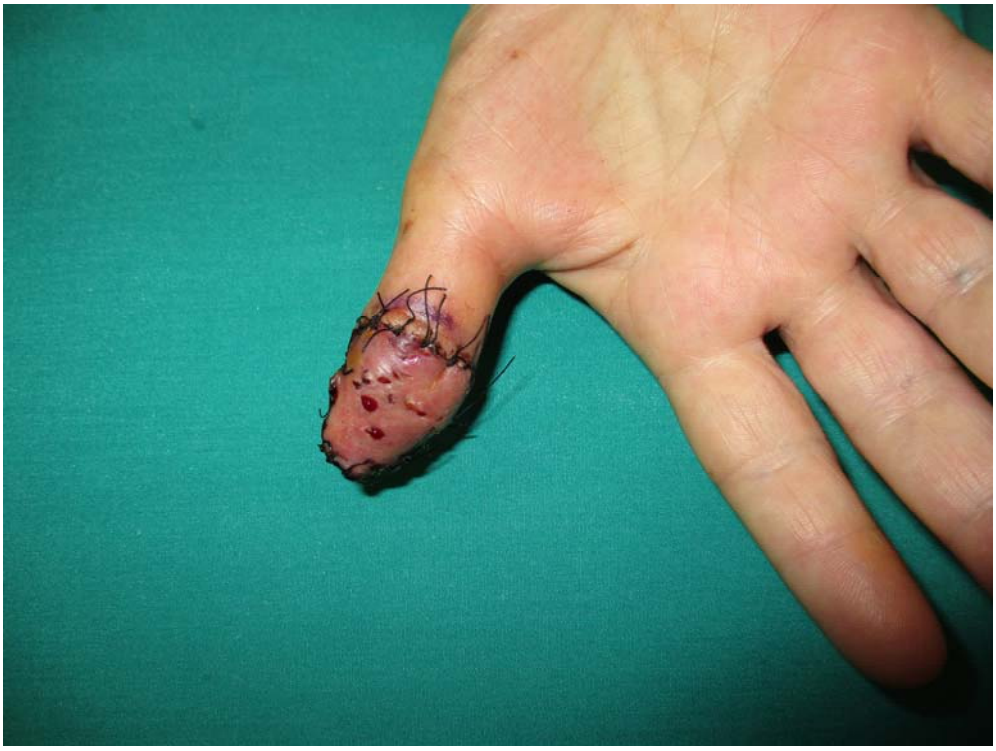


Figure 3. Finger of the patient after tumor excision and reconstruction.

The histological report confirmed the presence of acral lentiginous melanoma, Clark level III, and with a Breslow thickness of 0.4 mm. Junctional mitoses, a modest chronic intra- and peri-lesional inflammatory infiltrate, and signs of dermic regression, were present. There were no signs of vascular infiltration.

3. Discussion

Our case report raises the question of the involvement of previous trauma in the development of acral lentiginous melanoma, which is a controversial and poorly studied topic.

Thermal burns are known to increase the chance of developing squamous cell carcinoma, basal cell carcinoma, and malignant melanoma (it is thought that 2% of them turn malignant), but the average interval between an injury and a cancer diagnosis is between 23 and 27 years, which was not what happened with our patient [10,11].

In their study, Lee et al. [10] documented a 67-year-old patient who, 30 years after suffering a thermal burn from boiling water, acquired a metastatic nodular malignant melanoma on his right cheek. In another case report, a thermal burn scar that developed into melanoma 40 years after the first occurrence was documented [12].

Kikuchi et al. [13] have endeavored to connect the dots pertaining to the link between thermal injuries and cutaneous carcinoma. They proposed that the repeated minor injury and the changed microenvironment brought on by the burn could serve as catalysts for the development of cancer [13]. Moreover, they believed that the locally disrupted immune environment could contribute to the pre-tumorigenic milieu.

Although the complete constellation of genetic and somatic drivers of acral melanoma remains obscure, several studies have been conducted to characterize its molecular makeup.

Genetically, there are two distinct types of acral melanoma based on the presence of BRAFV600E mutations [14]. The vast majority of acral melanomas lack said mutations and are characterized by multiple protean oncogenic drivers, which include many gene rearrangements and amplifications [14]. Conversely, BRAFV600E mutants share many similarities with melanomas that arise from nonchronically sun-damaged skin [14]. Their kinship lies in the low DNA copy number changes and their risk factors (Caucasian descent and evolution from precursor lesions) [14].

Genes including CCND1, GAB2, PAK1, TERT, YAP1, MDM2, CDK4, NOTCH2, KIT, and EP300 are frequently overexpressed in acral melanoma [5]. The proportion of TWT mutations is higher in acral melanoma than in cutaneous melanoma [5]. Furthermore, a recent study found that TERT promoter mutations are more frequent in melanomas arising on dorsal acral sites and other acral locations compared to volar locations [15].

Farshidfar et al. [16] found that the amplification of cytoband 22q11.21 is positively correlated with shorter survival in patients with acral melanoma. In fact, it appears that 22q11.21 amplifications are associated with regional metastases and higher numbers of positive lymph nodes. Moreover, they observed that the acral melanomas with focal 22q11.21 amplifications expressed higher titers of genes related to tumorigenesis. Compellingly, they hypothesized that the gene LZTR1, which is found within 22q11.21, could act as a tumor promoter. This phenomenon could be harnessed to identify novel targets for therapeutic intervention. Notably, despite their cohort being composed of patients of Caucasian and East Asian descent, tumor survival was not influenced by ancestry.

The tumor microenvironment of acral melanoma is characterized by a higher density of M2 macrophages compared to the one of superficial spreading melanoma [5]. Moreover, chronic sun-damaged melanoma appears to have higher levels of PD-L1 compared to acral melanoma [5,17], which is also characterized by lower levels of tumor-infiltrating lymphocytes, and a larger neutrophil–lymphocyte ratio [17].

Weiss et al. [18] discovered that acral melanocytes have distinct positional identity programs that make them more likely to develop acral melanoma than their counterparts in other parts of the body. They discovered, using transgenic zebrafish animal models, that CRKL amplifications, in conjunction with the ”pro-acral melanoma” transcriptional state provided by the HOX13 genes, favor the progression of acral melanoma at glabrous sites of the extremities [18]. This means that, when compared to other anatomical sites, volar surfaces are genetically predisposed to develop a specific subtype of melanoma.

The early detection of acral melanoma is pivotal for the effective management of this malignancy [19,20]. Histologically, acral melanoma manifests as a proliferation of individual melanocytes that eventually group together to form nests [21]. Melanocyte nesting, melanocytic distribution regularity, and melanocyte spread into the top layers of the epidermis are the three key architectural elements that need to be assessed in suspicious melanocytic lesions [21]. Notably, cellular atypia frequently has a greater impact on the

diagnosis of early acral melanoma than architectural attributes [21]. The nuclear and cytoplasmic characteristics should be taken into account while analyzing the melanocytic morphology [21]. Moreover, early acral melanoma cells commonly include vertically oriented nuclei [21]. Even though atypia can occasionally be challenging to detect, it is particularly useful in the diagnosis of early ungual acral melanoma [21]. Abnormalities in nuclear size, shape, and color should be evaluated carefully [21]. Numerous studies have shown that atypical melanocytes that are confluent with one another are more likely to be malignant [21].

Dermoscopy has proved to be a useful complementary tool in the definitive diagnosis of pigmented lesions in different areas of the body, including those with challenging anatomy [22,23]. Altamura et al. [24] performed a retrospective study in which they analyzed the dermoscopic features of acral melanoma and found that it presents unique patterns due to the unique anatomy of glabrous areas. The presence of parallel ridge patterns (which are the epiluminescence correlates of melanocytes in the crista profunda intermedia), irregular diffuse pigmentation, and multicomponent patterns are peculiar characteristics of acral melanoma [25]. Invasive acral melanomas generally present irregular blotches, polychromia, atypical vascular patterns, and blue-white veils [26]. Moreover, blue, white, and red appear to be the most common colors that are identified via dermoscopy in these types of melanocytic lesions. The collected data from patients suggest that the volar surfaces of the hands and feet do not display major differences concerning their dermoscopic features [25].

A multicenter study by Mun et al. [26] attempted to correlate Breslow thickness with the dermoscopic findings of acral melanoma. Interestingly, they found that red, blue, and white were more prevalent in lesions with a Breslow thickness > 2 mm. The same applied in atypical vascular patterns (OR 34.589, 95% CI 6.458–305.852) and blue-white veils (OR 9.605, 95% CI 1.971–72.062) [26].

Among the new non-invasive imaging modalities that are being evaluated to study melanocytic lesions, there are reflectance confocal microscopy and optical coherence tomography, a near-infrared light microscopy-based technique [27,28]. Melanoma lesions display architectural disarray, pagetoid spread, dermal and junctional nests, and atypical melanocytes [29].

The main course of treatment for acral melanoma is wide local excision [30]. Depending on where it is, the proposed excision depth is either to the fascia or deep adipose [30]. Woo et al. [31] studied the clinical outcome of a medial plantar artery perforator flap for plantar defect reconstruction after wide excision in 25 patients with foot acral melanoma. Their results support the effectiveness of this reconstruction modality in patients with plantar acral melanoma. Notably, due to their proximity to the phalanx, nail melanomas can be challenging to remove compared to other acral melanomas [30]. The prior gold standard of care entailed the amputation of a digit, notwithstanding the fact that conservative non-amputation treatment for nail acral melanoma is a secure and effective option which is supported by recent international evidence [30].

Although surgery is the gold standard for the treatment of acral lentiginous melanoma, other therapeutic options that are still being investigated are available when the surgical removal of the lesion is not feasible [32,33]. A recent systematic review showed that targeted therapies and immunotherapy are viable alternatives [34].

Before the introduction of immune checkpoint inhibitors and mutation-driven therapy, dacarbazine had been the cornerstone of chemotherapy for advanced-stage melanoma; nonetheless, it had never clearly demonstrated a survival advantage [17,30].

The landscape of immunotherapy tools that have been developed to treat melanoma includes oncolytic viruses, various targeted drugs, and combination therapies. Notably, patients with acral melanoma seem to have worse outcomes when treated with immune check inhibitors compared with patients with cutaneous melanoma. Furthermore, immune checkpoint inhibitors may affect acral melanoma in different ways depending on where it is located [17].

The standard of care for BRAF mutants is the use of vemurafenib-targeted therapy, although its usage is restricted because only one fifth of acral melanomas have this mutation [35]. Three BRAF inhibitors that are often used include vemurafenib, dabrafenib, and encorafenib [17].

Patients with BRAF-mutant melanoma have successfully received treatment using a combination of BRAF and MEK inhibitors [17].Trametinib, cobimetinib, and bindetinib are the major MEK inhibitors that are now utilized to treat melanoma [17].

NRAS mutations are not the target of any effective medication [17]. It is noteworthy that, because NRAS mutations lie upstream of BRAF, the resulting tumor may be vulnerable to BRAF inhibitors [30]. Wang et al. [36] performed a retrospective cohort study investigating the clinical outcomes of 44 Chinese patients with NRAS-mutant melanoma (including acral melanoma) and found that the use of anti-PD-1 drug-based combination therapy might improve clinical outcomes for these patients.

The prevalence of the CDK4/CCND1 mutation and amplification in AM raises the possibility that CDK4/6 inhibitors may be effective as a therapy [17].

KIT mutations are common in acral melanoma compared to cutaneous melanoma, yet effective treatments to target this molecule are still under investigation [35]. At the moment, popular KIT inhibitors include nilotinib, sunitinib, and dasatinib [17].

T lymphocyte induction is encouraged by imiquimod, a Toll-like receptor 7 agonist [17]. Imiquimod and interferon, both immune stimulators, may help boost the number of tumor-infiltrating lymphocytes in acral melanoma, allowing immune checkpoint inhibitors to perform better [30]. By boosting antitumor immunity, anti-angiogenic medications can enhance a patient's response to immune checkpoint inhibitors [17]. There may be a cumulative antitumor effect when chemotherapy and anti-angiogenics are used together [17].

A single-cell analysis of primary and metastatic acral melanoma by Li et al. [37] revealed fewer effector CD8+ T cells and NK cells, as well as the absence of γδ T cells, in contrast to cutaneous melanoma. Also recognized in this research as immunological checkpoints that can be targeted in acral melanoma are VISTA (V-domain immunoglobin suppressor of T cell activation) and TIGIT (T cell immunoreceptor with immunoglobulin and ITIM domain) [17,37]. VISTA is a molecule that is structurally homologous to PD-L1 and is extensively produced in a variety of cells of the immune system [37]. Melanoma cells and antigen-presenting cells both express two molecules called CD155 and CD112, and TIGIT binds to these molecules to limit T and NK cell activity [37].

ADORA2 (adenosine A2A receptor) is another intriguing molecule that might become the focus of novel therapeutic strategies for acral melanoma [17]. Early findings suggest that ADORA2 antagonists can be used in conjunction with anti-PD-1 drugs with promising results in patients who did not respond to anti-PD-1/PD-L1 treatment [17].

A technique known as adoptive cell therapy involves removing tumor-infiltrating lymphocytes from the resected neoplasm, growing those cells using interleukin-2 therapy, and then reinfusing the expanded cells back into patients. [17] Adoptive cell therapy has currently shown some success in advanced cutaneous melanoma patients; however, there are currently insufficient large studies to demonstrate its usefulness in the management of advanced acral melanoma [17].

The use of oncolytic viruses in immunotherapy to kill cancer cells has been extended to melanoma. The available clinical and experimental evidence has established the effectiveness of the oncolytic virus talimogene laherparepvec in treating patients with acral melanoma [17]. The use of talimogene laherparepvec is associated with improvements in tumor-selective T lymphocyte replication [17].

4. Conclusions

Acral lentiginous melanoma is a rare melanocytic malignancy that usually has a bad outcome. Acral melanoma's poor response to targeted therapy and other systemic treatments is caused by its distinct genetics and tumor-immune milieu characteristics. To solve the puzzle of molecular drivers and their relationship with thermal burn injury, more

extensive studies are required. We shared our experience to emphasize the importance of prompt diagnosis and treatment.

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