

Research on Recent Advances in Subungual Melanoma

Qiu Zheng¹, Tao Cai^{2*}

¹ Chongqing Medical University, Chongqing, China

² The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Email Address

15902305525@163.com (Tao Cai)

*Correspondence: 15902305525@163.com

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Abstract:

Subungual melanoma is a malignant tumor with low incidence, high degree of malignancy and poor prognosis. In this paper, the epidemiology, etiology, clinical manifestations, histopathological features, diagnosis, treatment and prognosis of subungual melanoma at home and abroad are analyzed and summarized, aiming to further improve the level of diagnosis and treatment of this disease and improve the prognosis of patients.

Keywords:

Subungual Melanoma, Melanoma, Clinical Characteristics, Diagnosis, Treatment, Prognosis

1. Introduction

Subungual melanoma (SUM) is a rare malignant melanoma (MM), which usually originates from the nail matrix or nail bed, and can involve the periungual skin or periosteum. Due to its low incidence and high misdiagnosis rate, it has not attracted enough attention from clinicians. The etiology and pathogenesis of SUM are complex and have not been fully elucidated. SUM can be initially diagnosed by typical clinical manifestations, and pathological examination is the gold standard for diagnosis. Surgery is the first choice and main treatment for SUM. Immunotherapy, targeted therapy and chemotherapy are important adjuvant treatments.

2. Epidemiology

Melanoma has become the fastest growing malignant tumor in recent years, with an annual growth rate of 3-5%. Although its incidence in China is still low, its incidence is increasing rapidly, and the current incidence is 0.9 per 100 000, with about 20000 new cases per year. [1,2] In the United States, melanoma is the fifth most common malignancy in men and the sixth most common malignancy in women. [3] SUM accounts for 0.7-3.5% of MM, which is significantly different between different regions and races. The proportion of MM in Asian region is 10-23%, while that in European and African American is 0.18-2.8% and 25%, respectively. [4,5] According to foreign literature, the onset age of SUM was concentrated between 41 and 67 years

old. Kong Yunyi et al. reported that the median onset age of 65 cases of SUM in China was 51 years old. [6,7]

3. Causes of Disease

Current studies believe that mechanical extrusion, friction, maceration, trauma, dysplastic nevus or personal/family history of melanoma are potential risk factors for the occurrence and development of SUM. [8,9] Ultraviolet (UV) is a risk factor for cutaneous melanoma. In the past, it was generally believed that UV was not related to the pathogenesis of SUM, but in recent years, whole-genome sequencing of melanoma has shown that UV may be one of the pathogenic factors. [10] The malignant transformation of melanocytes into melanoma is a process that requires complex interactions between exogenous and endogenous triggers as well as tumor-intrinsic and immune-related factors. [9] Like other malignant tumors, SUM also has certain gene mutations, and common gene mutations include BRAF mutation, NRAS mutation, KIT mutation, NF1 mutation, etc. [11,12]

4. Clinical Findings

The high-risk population of SUM is middle-aged and elderly people, and most of them occur in the great toe or thumb. As the disease progresses, local infectious inflammatory manifestations may occur, such as redness, swelling, bleeding and exudation, destruction of nail and nail bed, nail exfoliation, ulceration, and pain. Some patients may have dark brown hyperpigmentation or patchy periungual skin (Hutchinson's sign). If ulceration occurs, it may not heal for a long time and granulation tissue proliferation. Some patients may have no pigmented changes, which is easily confused with onychomycosis, warts, pyogenic granuloma and other diseases. Subungual hemorrhage or mass, nail dystrophy, and nail loss can also occur in advanced SUM. Therefore, histopathological biopsy is still needed to confirm the diagnosis. [13,14] In the early stage, SUM is often misdiagnosed as other benign nail diseases due to its non-specific manifestations. Local lymph node or distant metastasis and corresponding clinical manifestations may occur in the later stage.

5. Pathology

The pathological characteristics of SUM are mainly reflected in four aspects: the morphology, distribution, number and inflammatory cell infiltration of melanocytes. Microscopically, the melanocytes were mainly epithelioid cells, [7] with large, dark nuclei, irregular morphology, and significantly enlarged nucleoli. Multinucleated melanocytes were common. In the early stage, the cells were mainly composed of single cell lentigo, nests of different sizes of melanocytes, and Paget-like melanocytes with obvious cellular atypia. In addition, the number of melanocytes at the epidermal-dermal junction is helpful to judge benign and malignant lesions. If the number of melanocytes is less than 30 /mm, it is more likely to be benign lesions, and if the number is more than 40 /mm, it is more likely to be malignant lesions. [14] Infiltration of inflammatory cells in the papillary dermis may indicate malignant lesions, but this may not be the case in the early stage. [15] HMB45, Melan-A, S-100, SOX-10, MRT1, Tyrosinase and MITF are commonly used immunohistochemical markers for the diagnosis of melanoma. [16] S-100 has the highest sensitivity, but its specificity is poor, so it can be used as a screening index. The specificity of Melan-A and HMB45 is high, but the sensitivity is different. Therefore, it is suggested that two or three of the above markers should be used together with S-100 to improve the detection rate of

melanoma. [17] In addition, it has been reported that preferentially expressed antigen in melanoma (PRAME) as an immunohistochemical marker has a sensitivity of 75% and a specificity of 98.8% in the diagnosis of melanoma. [18] In recent years, fluorescence in situ hybridization (FISH) technology has been applied to the diagnosis of melanoma, which has certain advantages in the diagnosis of melanoma. [7,19]

6. Diagnosis

The diagnosis of SUM is mainly based on clinical manifestations and pathology, and further staging can be performed combined with imaging. Pathology is the gold standard for the diagnosis of melanoma, and immunohistochemistry is the main auxiliary method for the differential diagnosis of melanoma. [17] The “ABCDEF” principle is a simple and practical method for clinical diagnosis of SUM. A (Age) : age 20-90 years old, with a high incidence of 50-70 years old; B (Band): subungual brown-black stripe, ≥ 3 mm in width, irregular or blurred boundary; C (Change) : rapid enlargement of subungual streaks in a short period of time or no improvement after adequate treatment of nail dystrophy; D (Digit): incidence of affected fingers/toenails: thumb > great toe > index finger, single finger/toe > multiple fingers/toe, dominant hand > non-dominant hand. E (Extension) : subungual stripe spreading to the medial or lateral nailfold or free edge of the nail plate; F (Family) : family or personal history of melanoma or dysplastic nevus syndrome. [20] Imaging examination is helpful to determine whether the patient has metastasis, preoperative and therapeutic evaluation. Ultrasound of regional lymph nodes (neck, axilla, groin, popliteal fossa, etc.) is generally required, while ultrasound, CT, MRI, whole body bone scan and PET/CT of head, chest, abdomen and pelvis should be determined according to the patient's condition and economic situation. Among them, PET/CT can evaluate the metastatic lesions more comprehensively. Dermoscopy has the advantages of simple and non-invasive, which can further improve the diagnostic rate of SUM. An isolated longitudinal melanonychia tends to be an in situ SUM, whereas a longitudinal melanonychia with Hutchinson's sign or a deck lesion often suggests an aggressive SUM. [21] Sentinel lymph node biopsy (SLNB) is the best method to determine occult lymph node metastasis. [22] Chinese guidelines recommend sentinel lymph node biopsy for patients with tumor breslow thickness > 1mm or unknown breslow thickness but with ulceration. [17] American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) recommend sentinel lymph node biopsy for patients with moderate tumor thickness ($1.0 \text{ mm} < \text{breslow thickness} \leq 4.0 \text{ mm}$). However, sentinel-node biopsy may also be considered in potentially beneficial patients with a breslow thickness of 0.8 to 1.0 mm or a breslow thickness of less than 0.8 mm with ulceration. [23]

7. Treatment and Prognosis

SUM is a subtype of acral melanoma. Due to its insidious onset, special location, and easy to be misdiagnosed or missed diagnosed, it often progresses to the middle and late stages when diagnosed, and thus the prognosis is relatively poor. At present, there is no guideline for the diagnosis and treatment of SUM at home and abroad, and its treatment plan is basically the same as that of cutaneous melanoma. Surgery is still the main and preferred treatment for this disease. Chemotherapy, immunotherapy, targeted therapy and their combination are the main postoperative adjuvant treatments for SUM, which are of great significance for preventing tumor recurrence and

improving the survival rate of patients with advanced melanoma, and are suitable for patients with a high risk of recurrence (stage IIB and above).

7.1. Surgery

The extent of resection is determined according to the Breslow thickness of the primary tumor. The Chinese guidelines recommend: (1) when the thickness is $\leq 1.0\text{mm}$, the margin is 0.5-1 cm; (2) When the thickness is 1.01 ~ 2mm, the margin is 1 ~ 2cm; (3) When the thickness is more than 2mm, the margin is 2cm. Patients whose pathological biopsy failed to report a clear Breslow thickness or whose lesion was huge could be treated as a thickness $> 2\text{mm}$. [17] The surgical methods of SUM are roughly divided into two types: extended local excision and amputation, but the specific choice of operation is still not clear. Although there is a lack of clear indications for extended local excision, it is mostly suitable for patients with low-risk subungular melanoma in situ and with Breslow thickness $< 0.5\text{mm}$ and without periosteum involvement. It has been reported that there is no significant difference in long-term survival rate and recurrence rate between extended local excision and amputation in these patients. [24,25,26,27,28] Since most SUM only involves the distal segment of the finger or toe, and the remaining finger/toe can be retained after extended resection without seriously affecting the local function, amputation is the first choice for these patients. [17] Due to the special location of SUM, when the lesion does not involve the periosteum, it is necessary to take into account the complete resection of the tumor and the maximum preservation of the function of the fingers or toes. Therefore, the choice of local extended resection or amputation should be comprehensively evaluated according to the patient's condition and the intention of function preservation. Whether complete lymph node dissection (CLND) is necessary for patients with positive sentinel lymph node biopsy remains controversial at home and abroad. A global, multicenter MSLT-II study showed that immediate complete lymph node dissection in patients with positive sentinel lymph node biopsy did not improve survival, but it confirmed clinical stage and reduced the rate of regional lymph node recurrence. [29] In China, acral melanoma is predominant, and the average depth of primary tumor invasion is also deep. Therefore, complete lymph node dissection can be performed immediately for patients with positive sentinel lymph node biopsy. Ultrasonography can also be used for follow-up. If regional lymph node metastasis is found, complete lymph node dissection can be performed. [22]

7.2. Chemotherapy

The main ones are some cytotoxic drugs, including temozolomide, dacarbazine, fotemustine, paclitaxel, cisplatin and carboplatin, etc. However, whether it is used alone or in combination, the overall effective rate is only 10%-15%. [17] Paclitaxel combined with carboplatin also has certain efficacy in the treatment of melanoma, especially for those patients who cannot receive immune checkpoint inhibitors, which can be considered as a treatment option. [30]

7.3. Immunotherapy

Interferon α (IFN- α) : mainly includes IFN α -1b and IFN α -2b. IFN α -2b has been used as the first-line drug for the treatment of melanoma in the past guidelines at home and abroad. However, due to its high side effects and unsatisfactory efficacy, the National Comprehensive Cancer Network (NCCN) no longer recommends IFN α -

2b as the first-line drug for melanoma. Domestic studies have shown that for stage IV patients, IFN α -1b may have better efficacy and safety than IFN α -2b. [31]

Immune checkpoint inhibitor (ICI): By binding to specific receptors/ligands expressed by immune cells, it can relieve the self-inhibition of immune cells and restore their anti-tumor effect. Studies have shown that its efficacy is better than BRAF/MEK inhibitors and chemotherapy. [32] PD-1 and CTLA-4 are two well-studied molecular targets located on the surface of T cells at present. pembrolizumab and nivolumab are PD-1 inhibitors, and ipilimumab is CTLA-4 inhibitor. It has been approved by the US Food and Drug Administration (FDA) for patients with unresectable or metastatic melanoma. Pembrolizumab has previously been shown to reduce the risk for postoperative recurrence in patients with stage III melanoma, and the KEYNOTE-716 study extends this group to stage IIB and IIc disease. [33] The study showed that in stage III and IV patients, the median progression-free survival (PFS) was 6.9 months with nivolumab alone and 2.9 months with ipilimumab alone, with significantly better efficacy of nivolumab than ipilimumab. [34] Of note, in a study of PD-1 monoclonal antibody in patients with stage III and IV acral melanoma, patients with SUM had significantly lower ORR and overall survival(OS) than patients with other acral melanomas (primary lesions in the palm or sole). [35] Compared with other subtypes of melanoma, acral melanoma has a lower number of tumor-infiltrating lymphocytes, a lower mutation burden, and a lower expression of PD-L1, which may explain its lower response rate to ICIs.[36] Although SUM is a subtype of acral melanoma, its unique biological and molecular characteristics may account for its low response rate to PD-1 monoclonal antibody, and deeper studies are needed in the future. [11] As a PD-1 inhibitor independently developed in China, toripalimab had a median PFS of 3.6 months and a median OS of 22.2 months in patients with advanced melanoma.[37] With pucotenlimab, the median PFS was 2.9 months and the median OS was 16.6 months. [38]

Other immunotherapy: Interleukin-2 (IL-2) has the ability to stimulate natural killer cells (NK cells) and a variety of T cells, and can be combined with stereotactic body radiation therapy (SBRT) for the treatment of melanoma. Adoptive cell therapy (ACT) is to collect lymphocytes from patients, select, expand and activate them in vitro, and then infuse the treated lymphocytes back to the patients to induce immune anti-tumor responses. T-VEC oncolytic virus is a genetically modified double-stranded herpesvirus that is injected locally into tumor sites to lyse tumor cells at these sites and expose tumor antigens to the human immune system. The oncolytic virus also further activates the immune system to achieve anti-tumor effects. Imiquimod is a topical small molecule immunomodulator that activates Toll-like receptors on antigen-presenting cells to promote the induction of CD4⁺ T cells and the anti-tumor response of CD8⁺ T cells. Currently, imiquimod is mainly used in external genital warts, superficial basal cell carcinoma (BCC) and solar keratosis, but its application in melanoma is still lack of sufficient research. Further studies are needed to evaluate the efficacy and safety of these immunotherapies. [39,40,41,42]

7.4. Targeted therapy

BRAF/MEK inhibitors: Mitogen-activated protein kinase (MAPK) pathway plays an extremely important role in the regulation of cell growth, differentiation, stress and inflammation. Ras/Raf/MEK/ERK pathway, as a classical pathway of MAPK, has been a popular research direction of various antitumor drugs. Because BRAF is an important member of the Raf family of protein kinases, both BRAF inhibitors and

MEK inhibitors are indicated for melanoma patients with BRAF mutations. Most BRAF mutations were V600E, followed by V600K, V600R, K601E, G466E, G469E, G469R and other rare mutations. [12] At present, BRAF inhibitors for melanoma at home and abroad include vemurafenib, dabrafenib, encorafenib, etc. MEK inhibitors include trametinib, Binimetinib, Selumetinib, and others. Vemurafenib, a selective inhibitor of BRAF V600E mutation, had a significantly longer median PFS and OS than dacarbazine in patients with metastatic disease. [43] However, in another study of stage III and IV patients, dabrafenib did not seem to have a significant advantage over dacarbazine in 5-year survival rate, which was 24% and 22%, respectively. [44] One study showed that in patients with stage IIIB or higher BRAF V600E/V600K mutation, the median OS was 23.5 months with conerafenib, 33.6 months with conerafenib plus bimetinib, and 16.9 months with vemurafenib. [45] BRAF mutation accounts for only 10-23% of patients with acral melanoma, compared with 50-60% of patients with cutaneous melanoma. [46,47] Since the majority of melanoma patients in China are acral melanomas, the overall efficacy of BRAF/MEK inhibitors is worse than that of other types of melanoma.

KIT inhibitors: KIT mutations/amplifications account for 11 to 36% of acral melanomas. [48] Imatinib is an effective KIT inhibitor for acral melanoma. Patients with KIT mutation/amplification had an impressive response rate to imatinib, the objective response rate (ORR) and disease control rate (DCR) were 21.8% and 60.3%, respectively. The median PFS and OS were 4.2 months and 13.1 months, respectively. [49] The efficacy of other KIT inhibitors such as nilotinib, ripretinib and dasatinib in melanoma is still being investigated.

CDK4/6 inhibitor: Palbociclib has also been gradually used in melanoma in recent years. Studies have reported that the median PFS and OS of patients with advanced acral melanoma carrying CDK mutations treated with palbociclib were 2.2 months and 9.5 months, respectively, and its efficacy needs further study. [50]

7.5. Combination therapy

Combined immunotherapy: IFN- α can enhance the anti-tumor effect of CD8⁺T cells in the tumor microenvironment and up-regulate the expression of PD-L1. [51] a retrospective analysis of advanced melanoma in China showed that previous use of pegylated IFN α -2b (PEG-IFN α -2b) could enhance the efficacy of pembrolizumab. In another study of stage IV melanoma, the combination of IFN α -1b and PD-1 monoclonal antibody also showed promising efficacy. [52,53] IFN combined with PD-1 monoclonal antibody is expected to become a new combination therapy. CTLA-4 inhibitors and PD-1 inhibitors produce anti-tumor effects through different mechanisms, and their combination has synergistic effects. For example, nivolumab combined with ipilimumab has more obvious advantages than nivolumab or ipilimumab alone, which has been confirmed in relevant clinical studies. [34,54] In addition, studies have shown that nivolumab plus ipilimumab significantly improves clinical outcomes compared with the combination of BRAF+MEK inhibitors, with increasing clinical benefits over time. [55] Preliminary clinical studies have suggested that oncolytic virus combined with ICIs is feasible for the treatment of advanced melanoma. [56]

Targeted combination therapy: Long-term use of BRAF inhibitors alone is prone to resistance, and most patients will still experience further disease progression. [57] More and more studies have shown that the combination of BRAF+MEK inhibitors

has good safety and tolerability, and is also the currently recognized standard combination regimen. [47] COMBI-AD clinical trial provides a targeted treatment mode of dabrafenib + trametinib for stage III patients with BRAF mutation. [58]

Chemotherapy combined with immunotherapy: Temozolomide enhances the anti-tumor activity of pembrolizumab by inhibiting or depleting regulatory T cells in the tumor microenvironment. [51] Relevant studies have shown that the combination of temozolomide or albumin paclitaxel and PD-1 monoclonal antibody is a feasible scheme for the treatment of advanced melanoma. [59,60]

Targeted therapy combined with immunotherapy: Although BRAF inhibitors can increase the expression of PD-1 and its ligand PD-L1 in patients with advanced melanoma, and MEK inhibitors have a protective effect on tumor-infiltrating CD8+T cells, the current study did not find additional clinical benefits of combining PD-1 monoclonal antibody on this basis. [61,62,63,64,65]

Immunotherapy combined with anti-angiogenesis therapy and chemotherapy: At present, immunotherapy alone or combined with targeted therapy has not achieved satisfactory results for acral melanin. [66,67] Recently, with the release of data from a phase II clinical study led by Chinese investigators, the median progression-free period is as high as 18.4 months, making the combination of temozolomide, apatinib and camrelizumab the optimal regimen for the treatment of advanced acra melanoma in China. [68,69]

8. Conclusions

In conclusion, because of the poor prognosis of SUM, early detection and diagnosis are extremely important. Immunotherapy, targeted therapy and chemotherapy are still the most effective treatments for melanoma. However, SUM has a poor response to current immunotherapy and other systemic therapies due to its unique tumor microenvironment and genomic characteristics. Overall, combination therapy is more effective than monotherapy, and more and more studies on combination therapy are underway. With the further understanding of the pathogenesis and genome of SUM, more effective drugs and treatment regimens are likely to emerge, which will improve the survival and quality of life of patients.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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