



Acral Lentiginous Melanoma

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Abstract

Acral Lentiginous Melanoma (ALM) was first defined by Reed as pigmented lesions occurring on the extremities. Although ALM is a relatively rare form of melanoma and accounts for approximately 4% to 6% of all melanoma cases in white patients, it represents the most common expression of melanoma patterns in people with darker skins and Asians. The patients with ALM are prone to have a poor prognosis which may be mainly caused by delayed diagnosis and a particular aggressiveness of ALM. Although the etiology of ALM is poorly understood, it has been reported that melanocytic nevi and trauma are the risk factors associated with ALM and the growing trend occurrence of the melanomas may be related to outdoor workplace. Moreover, exposure to the sun and agricultural chemicals were also the risk factors of ALM, and the more opportunities to expose to the direct sunlight, the larger numbers of nevus would be developed, particularly in kids. ALM, which is darkly pigmented, blue-black macules or nodules with irregular borders, often arises in the least pigmented areas on the volar surface of the hands, feet, fingers, toes and subungual sites. The diagnosis of ALM should be considered fully a dynamic view of melanoma growth and the clinicians should be familiar with the comprehensive knowledge of the tumor location. Wide local excision to achieve negative margins has been recognized as the conventional treatment for all kinds of ALM. Novel treatments such as chemo immunotherapy, biologic therapy and targeted agents are being applied in patients with advanced ALM and they have acquired some promising preliminary results. Earlier diagnosis of ALM is imperative so as physicians should maintain a high index of suspicion and carry out comprehensive physical examinations for all vulnerable populations.

Keywords: Acral lentiginous melanoma; Extremity; Pathogenesis; Diagnosis; Novel treatment

Introduction

Melanoma is one of the most malignant tumors which is hazarding the people's health and life in the world [1,2]. Numerous reports of melanomas in the western countries are available, and these form part of general reports [3-8]. It has been proved that the number of new cases of cutaneous melanoma was 22.3 per one hundred thousand person/year based on 2010-2014 cases in US population and it is estimated that there will be 87,110 new cases of cutaneous melanoma and an estimated 9,730 people will die of this disease in 2017 [9]. In Europe, about 26,100 males and 33,300 females were confirmed with malignant melanoma in 2000 [10-12]. Spain, as well as several Nordic countries, the mobility of cutaneous malignant melanoma has a tendency to grow [3,10,12].

However, clinical studies demonstrate that Asian melanoma patients present more advanced disease and worse prognosis than the white and light skin patients [13-17]. Moreover, reports dealing with the incidence of melanomas in darker-skinned populations [18-25] show that the darker-skinned populations with lower incidence of melanoma even when living in the same locality [1]. In conclusion, all dates demonstrate that melanoma can occur in different races and nationalities.

There are four histologic patterns of human malignant melanoma: Superficial Spreading Melanoma (SSM), Nodular Melanoma (NM), Lentigo Maligna Melanoma (LMM) and ALM. SSM, NM and LMM were postulated by Clark et al. [26].

SSM is the most frequent type of cutaneous malignant melanoma, which often occurs on the backs of middle-aged males and lower extremity of females and evolves from a precursor lesion [8,26-29]. NM accounts for about 15% to 20% of melanoma cases [26,30]. It has been reported that NM includes three distinct variants which are characterized by smooth, uniform nodular and blue-black plaque with an irregular outline and an ulcerated lesion, respectively [26]. It is generally recognized that the only difference between NM and SSM is the speed of dermal invasion [31]. LMM, commonly covering greater of human skin region than any subtypes of the melanomas, is accounting for about 4% to 15% of melanoma patterns and often misdiagnosed as SSM [26]. ALM

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Table 1: Melanoma subtypes according to the WHO classification.

Melanoma subtypes	ICD-O-3 codes
Malignant melanoma- 4 major subtypes	
Superficial spreading melanoma	M8743/3
Nodular melanoma	M8721/3
Lentigo maligna melanoma	M8742/3
Acral lentiginous melanoma	M8744/3
Others	
Desmoplastic melanoma	M8745/3
Melanoma arising from a blue nevus	M8780/3
Melanoma arising in a giant congenital nevus	M8761/3
Melanoma in childhood	M8720/3
Maevoid melanoma	M8720/3
Melanoma, NOS	M8720/3

ICD-O-3: International classification of diseases for oncology. 3rd edition; NOS: not otherwise specified; reprint from World Health Organization classification of tumours. International Agency for Research in Cancer.

was first defined by Reed as pigmented lesions occurring frequently on the extremities [32]. Although ALM accounts for approximately 4% to 6% of all melanoma cases in white patients, it represents the most common expression of melanoma patterns in blacks and Asians [8,33-36]. The patients with ALM are prone to have a poor prognosis which may be mainly caused by delayed diagnosis and a particular aggressiveness of ALM [7,37-40]. SSM-ALM was proposed by Sondergaard, demonstrating that there may exist a possible transition between SSM and ALM [41]. Numerous researchers reviewed ALM as a clinicopathologic subtype of melanomas, but they did not discover any markedly different in patients between ALM and other patterns of melanoma in acral regions [41-45]. Diagnostic and prognostic criteria of ALM is existence controversy [45], therefore the objective of this study is to retrospectively analysis the ALM which may contribute to clearly understand the characteristics of ALM and provide a reference for the diagnosis and treatment of ALM. Melanoma subtypes is seen in (Table 1).

Aetiology/Pathogenesis

The occurrence and development of ALM are related to melanocytic nevi, trauma, environmental factors, chemical stimulation, and smoking and genetic factors etc. ALM has been designated as malignant melanoma of acral areas, which represents the unique histopathological subtype of melanomas [46-48]. Green *et al.* found that burned skins are approximately 2 to 3 times higher risk of ALM than normal skins by investigating a case-control study of two-hundred and five melanoma patients [49]. The growing numbers of nevi on fingers, toes, soles and on some specific areas where friction occurs have a high correlation with ALM and people with some nevi are about 3 times greater risk than those without nevi and dysplastic nevi [49-54]. Moreover, exposure to the sunlight and agricultural chemicals may be risk factors in the aggressiveness of ALM [48,49,55]. Some studies demonstrated that trauma, such as severely penetrative injuries in acral regions, is a possible risk factor associated with ALM, in addition, pre-existing skin cancer and malignant tumor history were also significantly associated with ALM [48,49,56]. Nagore *et al.* proved that tobacco smoking play important role in melanoma occurrence, especially in the patients who are over 60 years old [57].

Numerous genetic factors may highly influence on melanoma

development [58-64]. Dys regulation of Mitogen-Activated Protein Kinase (MAPK) pathway, a signaling cascade, has been related to melanomas, including BRAF, EGFR, KIT, RAS, MEK and ERK mutations [65-71]. Although BRAF and NRAS mutations has been reported in approximately 80% of all sporadic melanoma patients, the incidence rate of BRAF, NRAS and wild-type KIT mutations in ALMs is 17%, 15% and 15% to 40%, respectively [17,72-74]. Paolino found that lower serological levels of vitamin D in ALMs with clothes covered sites was often accompanied with low percentage of BRAF mutation [75,76]. It has been observed that anomalies in chromosome 1 and 9 occur in familial melanoma patients [77,78]. It should be added that TERT promoter mutation is uncommon but play a vital role in the melanoma pathogenesis [79-81].

Clinical features

ALM, which is darkly pigmented, blue-black macules or nodules with irregular borders, often arises in the least pigmented areas on the volar surface of the hands, feet, fingers, toes and subungual sites [29,82,83]. ALM can appear more frequently at sites of the plantar surface of the feet which is a concealed area of the body and may be difficult to appreciate [84,85]. In addition, melanomas often demonstrates distinct clinical features, which may increase the difficulty of clinical diagnosis [20,29,86]. Subungual melanomas, an uncommon variant of melanoma which arises in the nail bed, is often misdiagnosed as subungual hemorrhages because of the quite similar early symptoms [33,87-89].

It is generally accepted that ALM is often initially misdiagnoses to other conditions including non-healing traumatic wounds, chronic paronychia, diabetic ulcers, warts, fungal infections, pyogenic granulomas, or subungual hematoma, in addition, when fully evolved a large, ulcerated, bleeding and exophytic nodules containing regions of ALM, it may indicate a worse prognosis for the patients [33,82,87,88]. These melanoma lesions are highly diffuse infiltrating and metastasis before effective treatment can be initiated, because of the fact that it is difficult to make correct diagnosis in time [84].

Therefore, early recognition accompanied with skin screen examination is vitally imperative, including volar, nail plate, toes and fingers [33,48,90]. On the one hand, physicians should possess the expertise and skills to recognize the lesion and must be familiar with the characteristics of this subtype of melanomas [33,48]. On the other hand, it is equally important for the patients to improve awareness of melanoma and seek for the professional advice which may decrease the diagnosis uncertainty [48]. Both physicians and patients should use the mnemonic *ABCDE* rule to detect the suspicious lesions [91-93]. However, compared with adult melanoma, pediatric melanoma demonstrates different clinical presentations [94-97]. New consensus clinical diagnostic criteria for pediatric melanoma have been developed [94,98] as in (Table 2).

Histology feature

The histological features of melanoma (including ALM) include glabrous skin, invasion depth and pattern, lack of melanocyte maturation, weak positivity of epithelial markers, pagetoid cells, pigmented lesion, etc. Reed proposed the fourth histologic form of melanoma, the ALM, which often occurs on mucous membranes and glabrous skin of acral areas, furthermore, glabrous skin characterized by skin surface normally hairless located in volar, plantar, and subungual areas [29,32,44,99]. He also defined diagnosis of ALM on the ground of its histological features, indicating a diffuse

Table 2: Comparison of “ABCDE” characteristic of adult and pediatric melanoma.

	Hallmarks of adult melanoma	Alternative characteristic of pediatric melanoma
A	Asymmetry	Amelanotic
B	Border irregularity	Bump/bleeding
C	Color variation	Colorless/uniform color
D	Diameter	De novo/any diameter
E	Evolution	Evolution: size, shape, color

A: Asymmetric shape of the spoy/mole, one half the moles does not match the other;
 B: Border of the spot is irregular, ragged, notched or blurred;
 C: Color of the spot is variegated and includes shades of brown/black or sometimes could include patches of pink, red, white or blue;
 D: Diameter of the spot is >6 mm;
 E: Evolving nature of the spot in terms of size, shape or color.

proliferation of atypical melanocytes along the basilar epidermis which is distributed in a lentiginous shape with distinctive acanthosis and elongation of the rete ridges [32].

Sondergaard and Olsen pointed out that ALM should be considered a subtype of SSM as they found a histological transition between the SSM and the ALM, demonstrating that SSM was closely related to ALM [44,100]. Some researchers define the ALM as lesions on acral areas, others emphasize that the conception of ALM should contain mucous membrane melanomas based on close biology relationship between ALM and melanomas of mucous membranes [29,42,44,101,103].

It is reported that clinical pathologic analysis of ALM should include Clark level, Breslow thickness (Table 3), growth phase (radial or vertical), vascular and lymphatic invasion, regression, mitotic rate, pigmentation, presence of microscopic satellites, peri tumoral and intra tumoral inflammation, predominant cell type, sub turnor blood vessels and presence of intradermal nevus [44,104]. Slingluff *et al.* suggested that Clark’s level IV or greater, Breslow depth greater than 1.5 mm, ulceration, and stage of disease should be regarded as poor prognostic signs of acral melanomas [44]. The characteristics, identifying distinct variants of malignant melanomas, comparing with the features of ALM, is showed in (Table 4) [29].

In a study of malignant melanoma, Mihm and Lopansri found that most ALMs have a SSM-like histological conditions of numerous pagetoid cells which possess the distinctive feature of irregularly shaped nests composed of plump spindle cells of pleomorphic melanocytes [46].

Typical histology feature of ALM is believed to be more conspicuous, with increasing Breslow’s thickness, junctional nests of

tumour cells develop, pagetoid spread and up-migration nests to the cornified layer (Table 3) [45,84,105].

When a pigmented lesion of the skin is suspected of being ALM, especially subungual lesions, it is imperative to obtain an adequate biopsy specimen as soon as possible [33,84]. In a study of CMM patients, it has been observed that most acral melanoma demonstrated the radial and vertical growth phases [106]. Microscopic findings in that study show that the lesions are often dark-brown to black surrounding irregular borders and uncommonly elevate in the former phase and the intra epidermal component, including large, atypical melanocytes with nuclei and nucleoli [106]. While in the latter phase, the nodules are often accompanied with ulceration and the vertical growth component contained either spindle-shaped cells or epithelioid cells [106]. The presence of epithelioid and spindle-type melanoma cells, which can be evaluated by Hematoxylin-eosin staining technique, indicate the degree of lymphocyte infiltrate and the melanin content in melanoma cells [107].

Diagnosis and differential diagnosis

It has been showed that primary melanoma is often diagnosed by microscopy due to the appearance of junctional activity, while secondary tumors are characterized by completely located beneath the epidermis [108,109]. Mihm and Lopansri emphasized the importance role of evaluation of clinical and histology characteristics of melanoma in diagnosis. They concluded a list of criterion for assisting diagnosis of malignant melanoma, in addition, Hutcheson recently summarized the pitfalls of ALM diagnosis [40,85].

The diagnosis of ALM should be considered fully a dynamic view of melanoma growth, besides, the clinicians should be familiar with the comprehensive knowledge of the tumor location [45]. Prior to make a biopsy, the regional lymph nodes should be examined by physical palpation which may be helpful in differential the diagnosis of lymphadenopathy [84,110]. Moreover, a detailed neurologic examination and laboratory studies, including a complete blood count, and chest radiographs are also necessary to be ordered as melanomas often metastasize via the lymphogenic system and the hematogenic system [84,111,112]. Although ALM is easily misdiagnosed as acral lentiginous nevi, immunohistochemistry can be useful in distinguishing between ALM and acral nevus by using epithelial makers (epithelial membrane antigen and cytokeratins AE1/3 and CAM5.2) and melanocytic markers (S-100, Melan-A, HMB-45) [83,104,113]. When the microscopy method is ineffective in diagnosing the ALM or suspicious cases exist, biopsy should be performed [114]. The ABCDE criterion (Table2) and newly evaluation are both useful in diagnosing malignant melanoma.

Table 3: The histologic characteristic of melanoma and ALM, the microscopic features of ALM comparison.

	Histology features criteria characterize the variants of	The features of ALM	The microscopic features of ALM
1	Preliminary growth at the dermal-epidermal interface (radial growth)	A lentiginous radial growth component	Asymmetric and poorly circumscribed
2	Expansile growth in the papillary dermis or infiltrative growth in the reticular dermis	Vertical growth in which level 4 invasion is relatively common	Primarily lentiginous growth of single melanocytes at the dermo epidermal junction over a nested or pagetoid
3	Cytology (spindle or epithelioid cells)	Spindle cell features preponderantly in the vertical component	Cytologic atypia
4	Response of the epidermis to an abnormal clone of melanocytes	Psoriasiform epidermal hyperplasia in the radial component (a feature that clearly distinguishes the lesion	Dermal component that is spindle cell with desmoplastic stroma
5	Host immune response (lymphoid infiltrates and patterns of regression prominent desmoplasia in the vertical component	A good host immune response with focal areas of regression	Deep dermal mitoses
6		Prominent desmoplasia in the vertical component	Lack of maturation

Table 4: Clark and Breslow classification of malignant melanoma.

Clark's levels of melanoma invasion		Breslow's classification	
level	Tissue invaded	Group	Lesion thickness
I	Epidermis only	I	<0.85 mm
II	Into papillary dermis	II	0.85 mm - 1.69 mm
III	Junction of papillary and reticular dermis	III	1.70 mm - 3.64 mm
IV	Into reticular dermis	IV	>3.64 mm
V	Into subcutaneous tissue		

For staging purposes, the American Joint Committee on Cancer (AJCC) has revised a classification system for melanomas in 2018 which is used to designate the T (tumor) N (node) M (metastasis) classification and a consistency of diagnosis for clinicians.

ALM patients should be closely observed and followed up for two years, including 4 times in the first year and twice in the following year as the melanoma recurrence often arise within 18 months after first diagnosis of melanomas [115,116]. A novel automatic algorithm has been proved to differentiate the “furrow” and “ridge” forms of pigmentation and video macro scope are also very effective instruments for the diagnosis of ALM [117,118].

Treatment

Wide local excision to achieve negative margins has been recognized as the conventional treatment for all kinds of ALM [33,84,119]. The results of a prospective study of WHO reveal that there is no striking difference in local recurrence rates between lesions of melanomas excised with 1 cm and 5 cm margins [120,121]. However, numerous national guidelines, which only include very few ALMs, have been published the excision margin according to Breslow thickness of the melanoma [122-125]. It must be pointed out that 1 cm excision margin widths should be used for melanomas in children younger than 14, regardless of thicknesses and primary sites [94,96,126].

Lymphatic mapping and Sentinel Lymph Node Biopsy (SLNB) is an effective technique to identify and dissect suspicious nodes in the operation, and in some cases, it is necessary for patients to be examined by inguinal or axillary nodes palpation [84,127,128]. ALM patients performed wide local excision of the primary lesions, especially for the invasive subungual melanomas, often need minor amputation at the nearest uninvolved joint, in an attempt to preserve a residual function [128,129]. However, when the lesion is particularly extensive, a ray amputation is recommended, including the entire digit or the distal metatarsal or metacarpal head [42,106,130].

As amputations of the fingers or toes, especially in the thumb and the great toe, often lead to increased risk of functional disabilities, conservative or functional surgical management is an effective method to preserves function [131,132]. However, conservative surgery and warrant amputation should no longer be recommended in advanced stages of subungual melanoma involving bone and joint spaces [131].

The primary melanomas of volar digital surfaces are often treated with amputation, which may result in soft tissue defect after tumor excision. Full-thickness skin grafting is a reasonable option for repairing palmar tissue defects caused by thin melanomas resection [133]. When the soft tissue defects locate on the weight-bearing potions of the foot, myocutaneous flap can be recommended as a

procedure for reconstruction [29,134].

In several cases of minimally invasive or in situ subungual ALM, when the tumor and whole-nail apparatus was excised, the resultant defect on the dorsal side of the distal phalanx should be reconstruction with a full-thickness skin graft taken from the internal aspect of an arm [128,129,131]. Although the opportunity of and indications for operation still controversial, many researchers widely accept that the functional aspect of surgical treatment is more important on fingertips as compare with on the tips of toes [129,135,136].

ALM on the dorsal surface of the thumb can be often treated by conservative “surgical degloving” which may preserve a partial motor function of thumb, followed by a plastic reconstruction with a radial ante brachial flap (Chinese flap) [137]. For the treatment of melanoma of the thumb, radical margin excision and bone amputation are often recommended. Thumb defects will seriously affect the normal functions of the hand, including the holding and grasping functions [138]. Numerous methods have been reported to reconstruct the function of hand and can get the fine results on the different amputation level of thumb (IP joint or MP joint) [139-143]. For the amputation near MP joint in melanoma of thumb, thumb reconstruction should be treated by pollicization of index phalanx, a free neurovascular wrap-around flap from the great toe or free to transfer [138-141]. For the amputation near IP joint of the thumb, reconstructive method should be included free trimmed toe transfer, a reversed radial forearm flap or a volar advancement flap [138,142-144]. Many other methods for reconstruction of defects in the hand have also been reported, such as cross finger flap which may be the preferred option for repairing sizeable nail bed defects [33,145,146].

Mohs micrographic surgery, a non-amputative local excision which may avoid excising excessive margins of normal skin and reduce risk of local recurrence caused by residual inadequate margins, should be considered for malignant melanomas on palms, nail apparatus, soles, ankles, particularly for amelanotic melanomas and subungual melanomas blocked by nail plates [7,147,150]. This technique, including the entire recognition of the surgical margins with the mapping of residual neoplasia, is suitable for removing melanomas of nail unit as it could preserve much more normal tissue as compare with conventional surgery [40,151].

Although some studies show that the ALM patients receive a long term rehabilitation therapy and slowly restore the ability to perform as many activities as possible, such as thumb opposition and grip strength, it should be made clear that active and passive motion of involved phalanx should be initiated as soon as possible after operation of tumors and reconstruction of the hand [33,137]. Furthermore, with the kind assistance of an experienced hand therapist, the patients would obtain the best function outcome [152]. Management of skin melanomas requires oncological and reconstructive surgical criterions to optimize the safety of treatment and the quality of life, and this requires exceeding collaboration among the team, including an oncology surgeon, a hand surgeon, an oncologist, and a certified hand therapist, rather than the responsibility of only one clinician [33,129].

Isolated Limb Perfusion (ILP), a treatment method for the patients with advanced melanoma by delivering high-dose chemotherapeutic agents, including melphalan (L-phenylalanine mustard), carboxamide, actinomycin-D, cisplatin, thiopeta, interleukin-2 (IL-2) with lymphokine-activated killer cells, without systemic side effects [84,153,154]. In the event of unresectable in-transit metastasis

melanoma affecting an extremity should be treated by ILP combined with melphalan and tumor necrosis factor alpha (TNF-alpha) with a complete remission in 59% of 130 patients [155,156]. Additionally, a more simplified and minimally invasive method named isolated limb infusion (ILI) has been used to treat in transit metastatic melanoma by regional therapy without an invasive surgical procedure.

Adjuvant therapy is also important for treating advanced melanomas and preventing recurrence, including chemotherapy, either with a single agent (DTIC) or poly chemotherapy, biologic therapy with recombinant Interferon (IFN)- α and/or interleukin (IL)-2, and radiation [157-159]. Although radionuclide therapy has hardly been used for metastatic melanoma so far, it may hold potential for this disease as it combines the advantage of either external beam radiotherapy or brachytherapy, often associated with few side-effects or long-term effects [160].

The murine [131] I-anti-p97 and anti-gp240 fragments can be used in radio-immunotherapy for curing malignant melanoma, besides that, nuclear medicine is considered to be potentially significant therapeutic [160-162]. Selective excision (wide or circumscribed excision) should be considered in regional metastatic melanoma. But for distant metastasis melanoma, curative therapy is generally unrealistic and the treatment of choice should base on site of metastasis, clinical features, "biological" age, and the patient's wishes [155]. The cytokines (chemo immunotherapy) or the combination of cytostatics (poly chemotherapy) can be recommended in palliative care in metastasis melanoma cases and may reduce tumor-related symptoms [155]. It has been showed that BRAF and NRAS mutations are present in about eighty percent of all sporadic melanomas and the NRAS Q61R or Q61K and BRAF V600E mutations are regarded as the most common [72]. NRAS and KIT mutations were most frequently detected in acral melanomas in one study and TERT gene alteration was detected in approximately 30% of ALM [71,163].

It has been proved that activation of the Mitogen-Activated Protein Kinases (MAPK) pathway, also known as the Ras/Raf/MEK/ERK pathway, contributes to melanoma immune evasion and development [164].

Recent breakthroughs in the treatment of advanced melanoma are based on scientific development views of oncogenic signaling and the immuno biology of this cancer.

Multiple of targeted therapies, designed against specific mutant proteins in selected pathways, are increasingly crucial in the treatment of melanoma [165,166]. Vemurafenib, a BRAF inhibitor drug targeting BRAF V600E (GTG/GAG) mutations, was approved by the Food and Drug Administration (FDA) to treat patients with metastatic melanoma and contributed to increase in life expectancy [167]. In addition, there has been numerous drugs targeting other proteins in the pathway, including imatinib (targeting KIT), tipifarnib (targeting RAS), sorafenib (targeting BRAF), dabrafenib (targeting BRAF) [167-171]. Many MEK inhibitors targeting MEK1/MEK2 are currently in clinical trials for the treatment of melanoma, such as CI-1041, PD035901, AZD6244, trametinib, MEK162 [172-176]. Numerous therapies, such as anti-CTLA4 antibodies (ipilimumab) and anti-PD1 antibodies (nivolumab and pembrolizumab), are finding their way into the treatment of patients with advanced ALM and recently obtaining significant outcomes, there is thus hope for progress in the treatment of metastatic melanoma [155,177-183]. However, signal inhibitor treatments are becoming evident that they are associated with complications and side effects in recent clinical trials. Our recent

study (in the review) evaluated the specific therapeutic efficacy of recombinant immunotoxin *in vivo* and *in vitro*, which are targeting the Melano Cortin 1 receptor (MC1R) of the cells. The specific cytotoxicity of recombinant immunotoxin to A375 and B16-F10 was over 93% by cell viability assay; however, it had no cytotoxicity to the human LO2 cells. The anti-tumor activity of immunotoxin was evaluated in mice with induced melanoma through intra-tumor administration. The results showed that 100% melanoma growths were inhibited, and 57% of the tumors were disappeared completely. Histopathology results showed it can effectively inhibit intrahepatic metastasis. In conclusion, recombinant immunotoxin in our study may support a possible new approach for the treatment of melanoma.

Prognosis

The unfavorable prognosis of ALM may partially be explained by the greater tumor thickness of this melanoma subtype compared with SSM and LMM, especially when delayed diagnosis of ALM or at more advanced stage [8,45,184]. Two micro staging methods, Clark's levels and Breslow's thickness, are generally used to predict prognosis of malignant melanoma [110]. It has been observed that shortened survival time is closely correlated to growing Clark's level, and the 5-year survival rate of patients with stage III or IV ALM was about 26% [184]. The Breslow thickness, male gender and clinical amelanosis are also statistically associated with a poorer prognosis evaluating by a Cox regression model [128].

Even though ALM is a rare subtype of melanoma with specific epidemiological characteristics, it is important that physicians should be alert to the possibility of danger in all vulnerable populations and carry out comprehensive physical examinations on palms, soles, and nail beds of patients [8]. Earlier diagnosis of ALM is also imperative; moreover, the prognosis will become worse once ALM metastases reach the visceral organs, with a median survival of 6 months or less [84,110,185].

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