

Acral Melanoma of the Extremities: A Study of 33 Cases in Sarawakian Patients

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SUMMARY

Background: Acral melanoma involve the non-pigmented palmoplantar and subungual areas and are commonly seen among Asians. Patients commonly display advanced stage of disease at presentation. It may appear unnoticed and mimic benign lesions.

Methods: Data for this retrospective study was retrieved from Histopathology Unit, Sarawak General Hospital, Malaysia archive from 2003 to 2009.

Result: 62.3% cases of malignant melanoma were acral melanoma. The mean age of diagnosis was 64.3±12.1. The involved sites were the heel (39.4%), middle and frontal plantar area (24.2%), toe (24.2%) and web spaces (9.1%). The clinical presentations were; an enlarging mass (60.6%), non-healing ulcer (24.2%) and abnormal pigmented lesion (15.2%). Most cases exhibited Breslow thickness >4.00 mm (87.9%) and Clark's levels V (50%). The majority showed moderate (non brisk) tumour infiltrating lymphocytes (57.6%). Ulceration (84.8%) and lymphovascular involvement were seen (24.2%).

Conclusion: Acral melanoma is the commonest malignant melanoma in this Sarawakian cohort. Most of the cases presented with advanced stage disease.

KEY WORDS:

Acral melanoma, Sarawak, Malaysia

INTRODUCTION

Malignant melanoma (MM) is a malignancy of pigment-producing cells (melanocytes) which are located predominantly in the skin. They are also found in the eyes, ears, gastrointestinal tract, leptomeninges, and oral and genital mucous membranes. Although it contributes to only 4 % of all skin malignancies, Franke et al categorically stated that MM has the highest fatality rate amongst them due to its intrinsic tendency for lymphatic and haematogenous metastasis^{1,2}.

In view of the fatality rate, Franke et al went on to elaborate that the severity of MM has led to a conscious effort on the part of clinicians to diagnose and treat MM as far as possible in its early stages. De Vries et al noted that the Asians generally face a substantially lower risk of MM compared to the Caucasians³. Despite of this fact, within the Asian

population, MM exhibits a unique characteristic whereby it appears to be more often found at non-pigmented areas of skin i.e. on the palm, soles (palmoplantar region) and at the nail bed. Tokura et al defined this distinct variant of MM as acral melanoma (AM), describing it as MM located on non-hair bearing skin of the palms and soles or under the nail bed¹. (Figure 1)

MM located at these sites is not easily picked up and thus is usually only diagnosed when patients present in advanced clinical stage of the disease. This leads, inevitably, to poor disease prognosis, a point touched on by Franke et al². Interestingly, even after adjustment for other prognostic variables, Spatz et al revealed that males diagnosed with MM are far more likely to incur an adverse outcome, i.e. mortality in all stages, a phenomenon in which no biological mechanism could explain so far⁴.

Rosai put forth that AM lesions at these sites often appear unnoticed to patients due to the anatomical location and lack protective effect of pigmentation at the affected areas. AM often clinically mimics benign lesions as the affected areas were covered by thick layers of keratin⁵.

Another interesting difference between AM as compared to other MM variants is the risk factor. Bradford et al determined that the causative role of UV radiation in AM is considered to be negligible, although in general, exposure to ultraviolet radiation (UV) is considered to be the major risk factor for MM⁶. Most of the published studies on MM have been obtained from United States, Europe and Australia whereby the incidence comprised of mostly patients with non AM (NAM). Takata et al were concerned that the postulated pathogenesis of MM may be somewhat biased, having been postulated based on predominantly NAM subtype namely the superficial spreading melanoma. This histological subtype is the commonest variant among Caucasians⁷.

Bradford pointed out that recent genetic studies have revealed unique features of AM when compared to NAM. The main somatic genetic alterations identified in AM so far are the cyclin D1 gene amplification and KIT mutation⁶. The cyclin D1 gene amplification in AM is detected early in the radial phase growth hence it is considered as one of the earliest events in the development of the neoplasm. Bastian et al concluded that AM is a distinct type of MM characterized by focused gene amplification which occur early in its tumorigenesis⁸.

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Bae *et al* reported a case of AM in an in situ phase which took almost 12 years to develop into an invasive phase⁹. This slow-developing premalignant lesion may lead to difficulties in reaching the diagnosis and in the management. This was why Park *et al* stressed that correlation between clinical features, histopathology and dermoscopic appearance is vital for an accurate diagnosis of the disease at this stage. The lesion clinically appeared as hyperpigmented macule at the sole and nail bed. Histologically, it exhibited as basal layer melanocytic hyperplasia with focal atypia and diffuse lentiginous pattern of spread. These early dysplastic changes may provide a window for detection and screening of early stage AM¹⁰.

Takata *et al* in the 2009 Pigment Cell Melanoma Research postulated a concept that all MM, especially AM in particular, may have arisen de novo and not from melanocytic naevus⁷. This concept classifies MM based on anatomical site of presentation and the presence or absence of chronic ultraviolet-induced damage of the surrounding skin. The classification includes MM on chronic sun damage, MM on skin without skin damage, AM and mucosal MM and is in stark contrast to the long-accepted Clark's classification which categorized MM into superficial spreading melanoma, nodular melanoma, lentigo maligna and acral lentiginous melanoma⁷.

The classification is strongly supported by molecular analyses revealing different characteristics among the MM groups. The genetic differences provide valuable information for treatment selection particularly in patients with distant metastasis, a point shared by Takata *et al* who also stressed the limited contribution made on clinical management by the current Clark's classification⁷.

BRAF genes mutations are frequently seen on non-chronically sun-damaged skin which is prevalent among Caucasian. However in AM and mucosal MM, KIT gene mutation and amplification of cyclin D1 are more frequently detected⁷. The definitive identification of AM by virtue of histological features and genetic abnormalities has become more significant with Kashani-Sabet *et al* revealing their findings that indicated promising anti-MM target specific therapies¹¹. As there are established correlations between the prognostic factors of MM and the biological characteristics of the tumour, the detection of prognostic-related histological features would become vital to improve management of the disease process.

In 1970, Breslow described that tumour thickness, cross sectional area and the depth of invasion are the important prognostic factors for MM recurrence and metastasis at 5 years¹². Breslow's index is currently regarded as the quantitative surrogate for multifactorial biological events that promote MM progression and invasion.

Tokura *et al* associated tumour ulceration in any given level of tumour infiltration with poor prognosis and this was agreed to by Balch *et al* who in their paper concluded that patients with ulcerated MM had lower survival rates compared to non-ulcerated MM of similar T (primary tumour in TNM staging) categories^{1,13}. The exact biological significance of ulceration is as yet undetermined. Spartz *et al* put forth two postulations

on ulceration; the first being that ulceration could be a surrogate of the tumour's own intrinsic biological behaviour that favours dissemination or the second being that ulceration directly favours dissemination of neoplastic cells⁴. These postulations are somewhat strengthened by Eggermont *et al* findings in which a better response to interferon was noted in ulcerated MM compared to non-ulcerated MM¹⁴.

All three parameters discussed above namely the thickness of tumor as defined by Breslow, Clark's classification by level of invasion and tumour ulceration are currently incorporated into the pathological classification (pT) of MM¹.

Spartz *et al* claimed that MM proliferation as determined by mitotic rate is a powerful and independent predictor for survival, an idea supported by Kannengiesser *et al* who maintained that genetic abnormalities identified in MM which predict for metastasis and death were mainly associated with DNA replication and repair^{4,15}. Spartz elaborated that aggressive MM required active and effective replication and repair mechanisms to rectify errors induced during replication. Overexpression of these DNA-repair genes is associated with a higher rate of metastasis and death⁴.

With regards to immune defense mechanism against neoplastic proliferation, Spartz's *et al* findings also offer a silver lining in the form of tumour infiltrating lymphocytes (TIL) in MM. TIL are involved in the killing of tumour cells and may induce spontaneous regression. Brisk TIL in vertical growth is one of the prognostic factors for a higher rate of survival and better prognosis⁴.

In routine histopathology practice, immunohistochemistry is the commonly used method to determine the origin of neoplastic cells. S100 and HMB45 immunohistochemistry are well described markers for MM¹⁶.

To our knowledge, there is no incidence study on AM among Malaysian or any other model that has a multi-ethnic composition which on a large scale could be extrapolated to show incidence pattern in various ethnic groups.

The aim of this study is to ascertain the incidence, demographics, clinical presentations and histological parameters in local AM cases that were encountered in the Sarawak General Hospital (SGH) which is the referral centre for the state of Sarawak.

MATERIALS AND METHODS

The data was retrieved from Histopathology Unit, Department of Pathology, Sarawak General Hospital archives from the year 2003 until 2009. This center receives specimens from all government and private hospitals throughout the state of Sarawak as it is the only referral center in the state for histopathological services. The patients' particulars together with the clinical and pathological features of AM cases were recorded. The histopathological diagnosis (Figure 2) of these cases were further reevaluated and confirmed by three accredited histopathologists. The diagnosis was confirmed with immunohistochemistry showing immunoreactivity towards S100 and HMB45 (Figure 3).

Table I: Histological profile of acral melanoma in 33 Sarawakian adult cases

Breslow thickness at diagnosis	0.01 – 1.00 mm: 0 (0%) 1.01 – 2.00 mm: 1/29 (3.0%) 2.01 – 4.00 mm: 7/29 (21.2%) >4.00 mm: 21/29 (87.9%) Mean: 7.8 mm±5.5 (2 to 29)
Clark level	Level V: 15/30 (50%) Level IV: 13/30 (43.3%) Level III: 2/30 (6.7%) Level II and I: 0 (0%)
Mean number of mitosis	24.5±18.7/10 hpf (4 to 85)
Pigment production	33/33 (100%)
Tumour infiltrating lymphocytes (TIL)	Absent: 12/33 (36.4%) Non-brisk: 19/33 (57.6%) Brisk: 2/33 (6.1%)
Tumour ulceration	Present: 28/33 (84.8%) Absent: 5/33 (15.2%)
Lymphovascular involvement at presentation	Present: 8/33 (24.2%) Absent: 25/33 (75.8%)

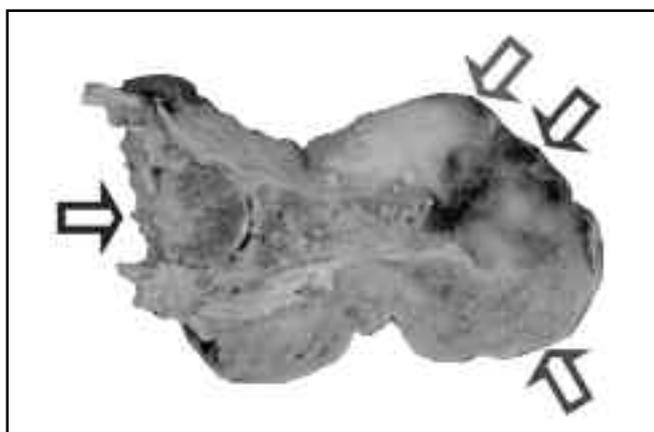


Fig. 1: Gross features of a sample of acral melanoma of the big toe (sagittal cut section). The tumour mass (red arrow) has infiltrated the nail bed into the connective tissue, destroying the underlying distal phalanx bone (green arrow). Areas of ulceration and hemorrhage were noted (blue arrow). The purple arrow indicates the proximal phalanx bone resection margin.

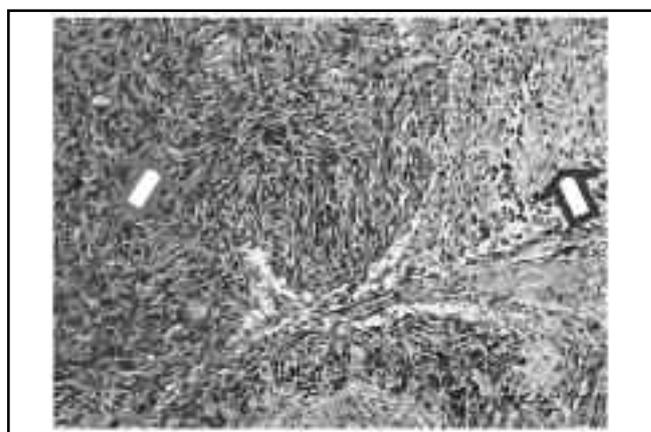


Fig. 2: Malignant melanocytic cells are forming invasive sheets pattern (red arrow) with surrounding haemorrhage and clusters of melanin pigments (blue arrow). The malignant cells were pleomorphic with plump to spindle in shape. (H&E 20X).

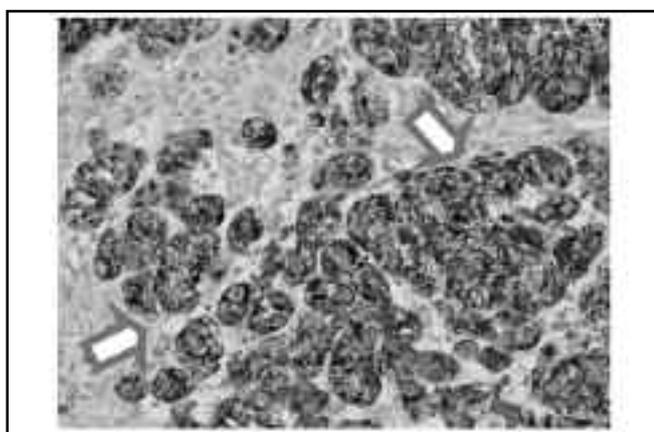


Fig. 3: HMB45 immunoreactivity displayed in acral melanoma cells as pointed by the red arrows (The immunoreactive cells were stained brownish by this method) (HMB45 40X).

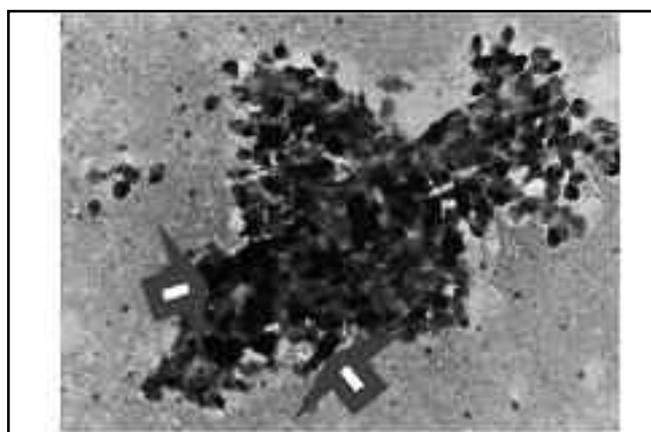


Fig. 4: Fine needle aspiration of metastatic acral melanoma of the big toe with infiltration to the inguinal lymph node. The cells were pleomorphic with plump and spindle-shaped appearances. There were scattered pigmentation noted (blue arrow). The background is composed of degenerated cells and red blood cells.

The established prognostic histological parameters of MM were adopted in the assessment of these AM cases. The parameters include:

- i. Breslow thickness. This is a continuous variable measuring the depth of tumour invasion. It is divided into 4 categories; 0.01 – 1.00 mm, 1.01 – 2.00 mm, 2.01 – 4.00 mm and thicker than 4.00 mm. It is measured from the top of the granular layer to the deepest invasive depth of the tumour¹.
- ii. Clark's level of invasion. Weedon stated that the prognostic significance of Clark's level of invasion was due to its secondary correlation with tumour thickness¹⁷. It was divided into: Clark's level I where the tumour is confined in the epidermis (melanoma in situ), confinement of the tumour in the papillary dermis in level II, filling and expansion of papillary dermis by the tumour in Level III, infiltration into the reticular dermis in Level IV and subcutaneous invasion in level V.
- iii. Number of mitosis. The number of malignant cell mitosis was counted microscopically in ten high-power fields at the invasive edge of the lesion. The detection of mitosis in the dermis is predictive for survival and sentinel lymph node involvement¹⁸.
- iv. The tumour infiltrating lymphocytes (TIL) response was categorized as brisk, non-brisk and absent⁴. A brisk TIL response is defined as continuous band of lymphocytes seen at the base of AM or throughout the tumour and is associated with a higher rate of survival. Patchy presences of lymphocytes without continuous band at the base of the tumour constitute the non brisk response. Absent response is when no inflammatory cell can be seen throughout the tumour or its surrounding area.
- v. Associated tumour ulceration. This parameter was evaluated from macroscopic examination of the lesion and the clinical history at presentation. The ulceration may also be observed during physical examination and confirmed by microscopic examination. Histologically, ulceration was identified when there was evidence of an area with complete loss of the epidermis overlying the tumour and associated with host inflammatory response¹⁸.
- vi. Lymphovascular invasion. The invasion was assessed microscopically as well as macroscopically. Macroscopic evaluation includes inguinal and regional lymph nodes involvement detected during clinical examination on presentation and supported by histological or cytological confirmation (Figure 4). Microscopic examination was used to detect microscopic lymphovascular permeation. The malignant cells were seen infiltrating the lymph node or permeating the lymphovasculture.

The Clark's classification of MM histological subtypes (i.e. superficial spreading, nodular and acral lentiginous melanoma) was not assessed in this study in agreement with Ridgeway *et al* findings that no significant difference in survival rates was noted among the various subtypes when corrected for tumour thickness¹⁹.

RESULTS

A total of 33 (62%) cases of AM compared to 20(38%) cases of NAM were seen in the Sarawak General Hospital from the year 2003 to 2009 There were 23(69.7%) male patients and

10(30.3%) female patients among the AM group with mean age of first diagnosis for AM being 64.3± 12.1years (age range from 40 to 87years). The ethnicity of the cases was as follows: Malays 11 (33.3%), Iban 9 (27.3%), Chinese 5(15.2%) and Bidayuh 3 (9.0%) patients. The ethnicity of 5 other patients could not be determined as it was unrecorded.

20 of the patients (60.6%) presented initially with a progressively enlarging foot masses. 8 of them (24.2%) presented with a chronic non-healing ulcer while 5 of them (15.2%) presented with an abnormally pigmented foot lesion. More foot lesions than hand lesions were noted.

The sites of the AM involvement were the heel for 13 patients (39.4%), the non-heel plantar surface for 8(24.2%) of them, the toe for the other 8(24.2%) and web spaces for 3(9.1%) patients. Only one of the cases involved the thumb (Table 2). The mean for Breslow thickness at diagnosis was 7.8 ±5.5 mm. In 30 of the cases which the Clark's level can be determined, 15 (50%) patients exhibited Clark's level V invasion, 13 (43.3%) exhibited level 4 and 2 (6.7%) level III. None of the patients exhibited Clark's level II and I. All of the AM cases were melanotic lesions (melanin pigment producing lesion). No amelanotic variant identified in these cases.

TIL response were brisk in 2(6.1%), not brisk 19(57.6%) and absent 12 (36.4%) in these AM cases. 28(84.8%) of the cases of AM presented with skin ulceration while 8(24.2%) cases presented with lymph node metastasis. (Table I)

DISCUSSION

The incidence of NAM (cutaneous MM) among Sarawakian was previously reported to be low²⁰. There was only one case (3.3%) out of 400 skin biopsy performed by local dermatologists within two years period proven to be MM. Acral lesion was not entirely included in the study as the disease is commonly managed by orthopedic surgeons. In the neighbouring Singapore, Koh *et al* reported 5.9% of skin malignancy was MM²¹. Generally, there are more cases of AM recorded compared to NAM among Asians population as proven by other similar studies^{3, 22, 23, 24, 25}. This is consistent with our findings that 62.3% of MM was AM while the remaining smaller percentage was NAM including cutaneous melanoma as described earlier.

Roh *et al* reported only 48 cases of AM detected within 5 years period in their study among Korean cohort²⁵. Therefore, in our opinion, the small number of cases represented in our study is adequate to justify its power. A similar study on AM done by Bristow *et al* has an approximately similar sample size (27 cases)²⁶.

The actual role of ethnicity as an independent prognostic factor is currently undetermined²⁷. Despite this, Hudson *et al* identified that Caucasian patients had better prognosis than African-origin patients and patients with mixed ancestral origin²⁷. Our cohort of patients was consisted of Sarawakian adults with a mixture of ethnic groups. Majority of the patients in our study were Malays despite this ethnic being the third largest in the state²⁸. No possible explanation can be offered to address this finding.

The mean age of diagnosis in this study concurred with other similar studies in that AM is common in 60 to 70 age group, similar findings were noted in a study by Bradford et al which found that the mean age AM diagnosis was 62.8 whereas 58.5 for NAM⁶. The wide range of ages in this group during their initial presentation highlights the need of increasing awareness by medical practitioners in picking up this disease since it was found in Rex et al study that patients who were first diagnosed only after the age of 60 were significantly associated with greater risk of adverse outcome^{6, 29}. Metzger reported that there was median delay of 12 months in the diagnosis of palmoplantar lesion and 18 months in subungual melanoma. Franke et al also observed a mean time delay of 4.8 years between the first observation of plantar skin lesion and first consultation with physician and another 7 months taken before surgical intervention was performed².

Within our study, 32 out of the 33 AM patients presented with involvement of the foot and out of them 21 had tumour located in the sole and heel. This was in line with other comparable studies that these were the preferred site for AM^{10, 25, 26, 30}. Bristow et al stated that commonly reported initial symptoms include the change in size of the lesion, bleeding, changes in colour and change of lesion form (become raised or nodular in appearance)²⁶. In our cases, most of the patients presented with an enlarging mass.

Tissue biopsy on suspicious nevi on the plantar foot is vital²⁷. An adequate tissue biopsy certainly helps in initial conformation of AM. Bristow and Acland reported that 33% of the study cohort was clinically misdiagnosed as benign lesions²⁶. The diagnosed lesions include warts, fungal infection, hematoma and benign ulceration. Metzger et al reported cases of AM involving 52% of subungual melanoma and 10% of palmoplantar melanoma were clinically misdiagnosed by physician³¹. 6% of the palmoplantar melanoma was reported to be misinterpreted by pathologists³¹. In our experience, the histological diagnosis of these 33 AM cases which were well complimented by complete clinical history and examination was not problematic.

Upon comparison of the histological patterns between the sample of AM and NAM patients, no distinguishing differences could be made out. The only difference between the two groups was the unique sites of involvement in AM patients which was the subungual and palmoplantar areas commonly not exposed to UV radiation. The presence of melanin pigments and immunoreactivity seen towards S100 and HMB45 antigens proved to be useful in the diagnosis of AM comparable to NAM. No amelanotic melanoma seen in this cohort as this variant is not uncommonly seen in NAM.

In MM staging system, the tumour thickness and ulceration are primarily used in pT category rather than the actual size of tumour¹. Most of our cases presented at advanced stage of invasion. This was exemplified by the advanced thickness seen in Breslow thickness and Clark level of invasion, tumour ulceration, high mitotic count and a significant number of cases with lymphovascular involvement. Majority of our AM cases were at least at stage IIC and while almost one quarter

of these cases were already at stage III and above. All of these findings pointed to a poor prognosis.

Bradford *et al* described that in overall, NAM presented with lesser Breslow thickness compared to AM (6). In their study, 70% of NAM was diagnosed at Breslow thickness 0.01-1.00 category compared to only 41.3% in AM. Breslow thickness greater than 4 mm is associated with greater risk of recurrence²⁹.

Rex *et al* described that the disease-free survival and overall survival of AM is significantly lower than NAM²⁹. They also concluded that the survival difference due to the differences in the already known prognostic factors which probably as a result of diagnosis delay. Therefore, early recognition of the lesion is undoubtedly remained the main factor in improving survival. The time taken for diagnosis in our cohort patient was not assessed. A further study addressing this matter in AM will certainly help in improving the treatment.

Surgical management with either wide excision or amputation is appropriate for the primary lesion and adjuvant immunotherapy is indicated^{27, 32}. A 3 cm margin of excision was reported to be effective in all population groups. For patients with advanced local disease, amputation provides the local control and can be curative²⁷. Advances in adjuvant therapy have reduced the need for amputation²⁷. Local recurrence was reported to be up to 5 times higher in AM due to a tendency to use smaller margins of resection in these cases³³.

De Vries et al noted that even after adjustment for other prognostic factors, males are far more likely to incur an adverse outcome, i.e. mortality in all stages [34]. This study had a predominance of males compared to females but as yet remains unresolved in terms of the effect of gender on mortality. Bradford et al noted that AM had 5 and 10 years survival rate of 80.3% and 67.5% respectively [6]. These figures are worse if compared to NAM which has 91.3% and 87.5% survival of the same duration. Again, the increased in tumour thickness and the advanced stage at diagnosis were contributed most probably by delay in diagnosis [6].

CONCLUSION

AM is more common than other histological type of MM in Sarawak, Malaysia. It typically presents late with aggressive histological features and advanced level of invasion. Our findings are comparable to other Asian population studies. Hence, early clinical diagnosis is essential to improve patient's survival. This may involve both patients and practitioners education. Histological examination should always be performed in non-healing acral lesions. Further study assessing the time taken for diagnosis is vital to improve the management of this lesion.

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