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Clinical report

Acral melanoma in Cambodia: challenges associated with a rare and aggressive disease encountered in a developing country setting

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Background: Melanoma is a highly malignant skin cancer. Acral lentiginous melanoma (ALM) is most common among Asians. The prevalence of ALM among melanoma cases in Cambodian is not known.
Objective: To describe the prevalence of ALM among cases of melanoma and the stage of disease at presentation to the health facilities and health providers.
Method: Electronic clinical records were obtained from Children's Surgical Centre (CSC) database between January 2002 and April 2014. Types and stages melanoma at presentation were documented.
Result: A total of 10 out of 26 melanoma patients had ALM. Their average age at diagnosis was 65.3 years. Most primary lesions were located on the plantar or lateral surfaces of the foot. Most histopathological descriptions were consistent with ALM. Seventy percent had lymph node metastases.
Conclusion: A high proportion of ALM was found associated with trauma as a potential risk factor. Most frequency presented at a late stage of disease. Providers must be made aware of the disease and render appropriate management early for good outcome.

Keywords: Acral melanoma, Cambodia, metastasis, stages at presentation

Melanoma is a highly malignant skin tumor and is well-known as dangerous to life in countries of fair-skinned and sun-loving people. It affects 19.0 people per 100,000 population in the USA [1] and 51.8 per 100,000 per year in Australia [2]. In Asia, it is a considerably rare disease where incidence usually remains below 1 in 100,000 with slight variation in different ethnicities: for example 0.7/100,000 for Japanese [3]; 0.5/100,000 for Chinese Singaporeans, and 0.2/100,000 for Indian Singaporeans [4]. Data on melanoma in the Asian population at large is limited, and reports from less developed Asian nations such as Cambodia are particularly scarce.

An acral melanoma—from the Greek word "Akron", referring to the extremities—arises in the hand or foot, subungual skin, the sole of the foot, or the palm of the hand. Lentigo, the Latin word for freckle, refers to a small brown spot on the skin. Acral lentiginous melanoma (ALM) has been found to be the most prevalent type of melanoma in Asian people, found in approximately in 50% of all melanoma cases, compared with 2%–3% in people of Western European origin [5]. It is an aggressive subtype of melanoma: in the USA, 5-year survival has been reported to be 80.3% for ALM, by contrast with 91.3% for all cutaneous melanomas [6]. Asians living in the USA, compared with non-Hispanic whites, have lower 5-year survival of 70.2%, largely because of late presentation [7, 8].

Unlike most melanoma, ALM does not arise secondary to UV exposure. Other studies report trauma and KIT gene mutation as potential causative factors [9-11]. Given the diversity of Asia, and especially the wide disparity in socioeconomic conditions, it is reasonable to expect variations in presentation and management of this disease among Asian nations. Here we report a case series of 10 patients with ALM presenting to the Children's Surgical Centre (CSC), a nonprofit hospital in Phnom Penh, Cambodia. This study describes presentations and prognoses, and discusses the challenges of management in this developing setting.

Methods

This retrospective study was approved by our Ethics and Institutional Review Committee and Board

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in 2013. Patients had gave written or verbal informed consent before surgery for publication of data including photographs. A large proportion of our patients are illiterate and their consent had to be verbal. Verbal consent was formally documented, witnessed, and archived on patient records in accordance with the principles and guidelines of the Declaration of Helsinki. An initial population of patients was selected from the electronic clinical records at the CSC by searching for relevant keywords (melanoma; acral; and various misspellings), which gave a total of 26 candidate patients from January 2002 to April 2014. We applied secondary inclusion criteria to patients' electronic and hard-copy records, to identify cases of melanoma that were either histopathologically confirmed, or those patients who did not have a biopsy at the CSC, but for whom there was a high degree of clinical suspicion for melanoma—that is, recurrence of pigmented lesion excised elsewhere with a patient-reported diagnosis of melanoma. Nine patients were excluded because of lack of access to hard-copy records, including pathology records, effectively limiting the search from April 2007 to April 2014. A total of 10 patients met inclusion criteria for analysis.

Retrospective analysis was applied by detailed review of the charts for these 10 patients, considering patient demographics, primary wound characteristics, including site and size, known duration of lesion before presentation, presenting symptoms, history of trauma, stage at presentation, and management. Where data is not complete, it is noted in the results. To determine the patient prognosis, follow up contact was attempted by phone for all patients and was successful for 6 patients.

Results

Patient characteristics

The 10 patients who met inclusion criteria presented between December 2009 and April 2014. Their average age at diagnosis of melanoma at our center was 65.3 years (range 40–75 years), and the median age was 68.5 years. Of the 10 patients, 7 were men and 3 were women.

Primary lesion characteristics

Primary lesions were located on the plantar or lateral surfaces of the foot in 9 patients and of unknown site for 1 patient who presented with a lymph node metastasis. As a result, this patient was excluded from further analysis of primary lesions. The median duration of the lesions before diagnosis was 2 years (range 1–29 years). Presenting symptoms of primary lesions included changes in size (8 patients), ulceration (7 patients), pain (3 patients), bleeding (2 patients), and itch (1 patient). In 2 cases, patients reported a previous burn or wound at the primary lesion site. Although all 9 primary lesions were located on acral locations, one lesion was identified on histopathology as a nodular melanoma. The other specimens did not have a subtype of melanoma identified on report. On review, the histopathological descriptions were consistent with acral lentiginous melanoma.

Stage of patients

At the time of presentation, 3 patients had undergone previous excision of the primary lesion with poor local control of disease leading to local recurrence of disease. Seven patients had palpable inguinal lymphadenopathy or biopsy proven lymph node (LN) metastasis (5 patients). Two patients had no palpable lymphadenopathy and LN examination was not documented in one patient.

Accurate staging of lesions was precluded because of limited pathology reports and clinical work up. Breslow depth was not reported for any patient, lymph node examination was not undertaken in 1 patient, and staging for further metastases was absent in 7 patients. We estimated the likely stage for all patients, in accordance with the AJCC staging system [12] based upon histopathological reports, including qualitative description of dermis invasion and lymph node biopsy results, clinical information, including ulceration of primary lesions, presence of palpable lymph node, and chest x-ray results as 3 patients with stage II, 5 patients with stage III, and 2 patients with stage IV.

Treatment

Most patients were managed surgically, although one with a recurrent primary lesion was referred to another hospital. Of the patients with primary lesions, 8 were treated with an excisional biopsy, of varying width of resection margin (0.5–2 cm); of these, there were no re-excisions based upon histopathology. One patient received an incisional biopsy followed by wide excision of the primary lesion. Lymph node biopsy was undertaken for 5 patients. Inguinal node dissection was performed on two patients. Chemotherapy was not available as a treatment option because of economic and regional availability factors.

Follow up

Follow up plans were not strictly followed by most patients. Contact by phone was made with 6 of the 9 patients to obtain follow up data on survival and local disease recurrence. One patient was still at the ward at the time of study, and therefore was excluded in the follow up data analysis. The average duration of follow up was 12.5 months (range 2–29 months). Of the 5 patients for whom data was available, 6-month survival was found for 3 patients. At the follow up, 1 patient had persistent local disease, 2 patients were reported dead, and 3 had no local or systemic disease.

Case reports

We present three case studies to illustrate management challenges.

Case 1

A 72-year-old man presented with a chronic pigmented lesion (**Figure 1)** on the lateral border of the right foot of 1 year duration, reporting cauliflower-like growth over the previous 7 months and inguinal lymphadenopathy for one month. Chest x-ray and liver ultrasound were clear. An excisional biopsy of the lesion on the foot was performed with 0.5 cm margin. Pathology reported invasive melanoma with negative margins. PB did not return for planned inguinal lymphadenectomy and further follow up, and was later reported by telephone as having passed away 3 months following his initial presentation.

Case 2

A 68-year-old man, presented with ulceration of the right plantar heel that first appeared in 1985. The patient reported that the small black lesion did not change in size until four months before presentation **(Figure 2)**, at which time the mass started to grow quickly and became very painful. Lymph nodes were not palpable in the groin or popliteal regions. X-ray imaging of the chest showed no obvious metastases. Excisional biopsy was performed with a 1.5 cm margin, and a plantar-rotation flap was used to cover the wound. Pathology confirmed melanoma with clear margins. After the wound healed, there was no evidence of tumor recurrence at the primary site or in the lymph nodes.

Case 3

A 69-year-old man, presented with a heel mass that had been present for one year. The mass had grown quickly in the previous 6 months, was painful, and occasionally bled. On physical examination, a 5 cm × 4 cm black fungating mass was present on his heel (**Figure 3**). A left inguinal lymph node was visibly enlarged. A chest x-ray image showed no metastases. Excisional biopsy was performed, and the wound was skin grafted. Histopathology confirmed invasive melanoma with clear margins.

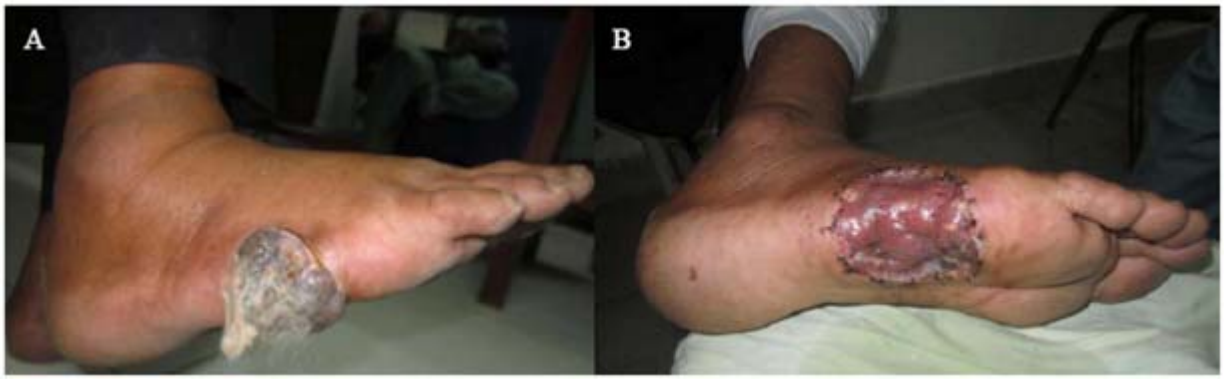

Figure 1 **A:** Patient 1 presents with a primary melanoma, present for one year, **B:** Partial split thickness skin graft two weeks following excisional biopsy (photographs with permission).

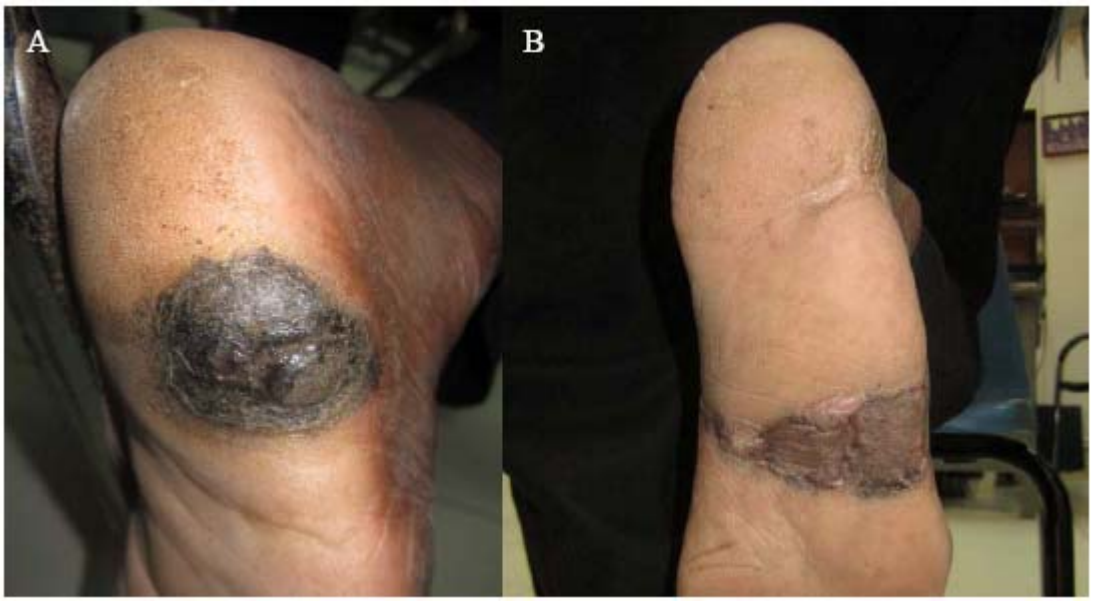

Figure 2 **A:** A painful lesion that increased in size for the last 4 months prior to presentation, **B:** At 8 months follow-up after the flap operation (with permission).

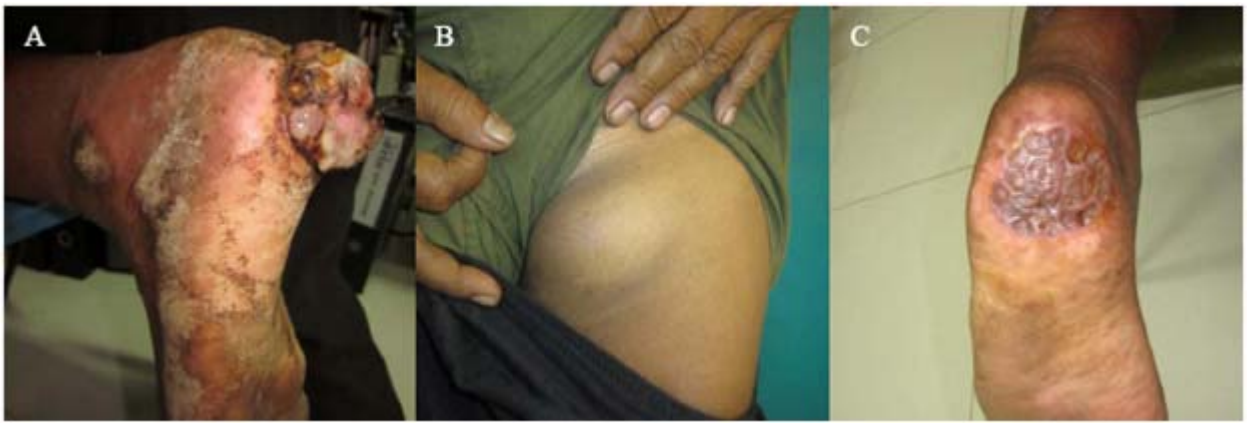

Figure 3 **A:** A 5 cm × 4 cm mass of 1 year duration, **B:** Lymph node in left inguinal region, **C:** At 3 months follow-up (photographs with permission).

Discussion

The patient demographic and wound characteristic findings of this study are largely consistent with the existing literature on melanoma in Asia. The mean age in other studies is slightly lower than our 65.3 years (from 55.9 [13] to 61 years [14]). The proportion of ALM of all melanoma in other studies ranges from 41.8% [15] to 85.9% [9], therefore the reported 8/10 "likely ALM" reported here is within the reported range of the region. The palms and plantar foot are also the most common sites of ALM reported in Asia, although typical percentages range from 44% [16] to 69% [13], rather than 100% of ALM diagnosed at CSC. Known duration of lesion prior to presentation in other studies of ALM ranges from 13.5 months [17], to 27 months [16], where this case series had a 18.3 months average.

Given that ALM occurs in sites without significant UV exposure, theories on the etiology of ALM are developing. Trauma is one potential etiological factor proposed in the literature. Other articles note correlation of KIT gene mutation [11]. We report a positive history of previous trauma at the site of the melanoma in 2 of 9 patients, consistent with other case series [9].

Studies on melanoma from Asia are typically from more developed countries, where health literacy, empowerment and access is higher than in Cambodia. Late presentation to health care is suggested in this series by the median length of known duration of lesion prior to diagnosis of 2 years, the high prevalence of ulceration as a presenting symptom (recognized as a poor prognostic factor), and the significant proportion of patients with proven inguinal metastasis or at least lymphadenopathy. Indeed, we note that most Asian melanoma case series report approximately only 10%–12% patients at stage III or IV at diagnosis [13, 16], compared to 7/10 in this series. Similarly, with incomplete follow up, our survival data is not conclusive. Nevertheless, assuming a best-case scenario for all other patients, we have at best an 8/10 patient 6-month survival in this series, compared with an overall 80.3% 5-year survival rate of ALM in a study from the USA. We note, however, 5-year survival rates from studies in Asian countries are typically 41%–49% [9, 14, 15]. This is likely to be a direct result of the late presentation and late stage of the patients in this series.

Special challenges arising from the developing country setting are illustrated by two case studies. A delay in diagnosis is apparent for both cases; clinically, the masses that had developed are quite substantial. This may reflect a lack of awareness among the Cambodian people about the potential seriousness of such presentations, and/or a generally high threshold for seeking, especially Western, medical care.

The treatment in Case 1 was limited to primary resection of the melanoma with a 0.5 cm margin. After pathological confirmation of the disease, there was no wider resection, and no surgical management of the inguinal lymphadenopathy. Given his death was only 3 months after presentation, it is likely that more aggressive treatment may have been too late to alter his prognosis, but appropriateness of 'optimal' treatment should be considered. In Case 2, the presence of the large inguinal lymph node and weight loss suggests similarly advanced disease at presentation, for which prognosis would be poor even with further treatment. The lack of an inguinal node dissection subsequent to pathological diagnosis of melanoma metastasis and scarcity of availability of chemotherapy suggest a widespread lack of options in this country to treat advanced cases of melanoma.

There are many reasons why sequential surgical therapy, that is, biopsy followed by definitive treatment, may not be practical in this setting. These include the extra resources required for multiple surgeries, high attrition rates of patients between visits and lack of awareness of optimal surgical management by surgeons encountering a rare disease. Given that cosmetic concerns are less likely in Cambodian society, opting for a simple standard margin of excision of at least 1 cm for suspected melanoma with concurrent lymph node biopsy may be a reasonable treatment strategy.

This study must be considered in light of its limitations. As a retrospective study, the data is limited to clinical records. The relatively simple nature of these records at the CSC, including the histopathology reports where few quantitative measures of the lesions were provided, limits the depth of analysis. It is quite possible that more cases of melanoma presented during the study interval were either not recognized by clinicians, or not described in sufficient detail to meet the inclusion criteria for this study. This, along with the surgical nature of the unit, may account for the lack of stage I lesions in this series.

Conclusions

This case series of patients is largely concordant with similar studies of melanoma in Asia, with a high proportion of ALM in older patients, and with trauma as a potential etiological factor. However, this case series also suggests that patients with melanoma in Cambodia frequently present at a late stage of disease, with consequently poor prognosis. This is likely because of a combination of factors, including lack of recognition of the disease by patients alongside cultural and financial barriers to access health care. Ensuring Cambodian doctors are aware of the typical presentation of melanoma, and appropriate management of the disease in various stages in the Cambodian population will improve outcomes for patients with melanoma in Cambodia.

No authors have any conflict of interest to report.

References

1. U.S. Cancer Statistics Working Group. United States cancer statistics: 1999–2010 incidence and mortality web-based report. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute. [online] 2013 [cited 2014 Jul 01]. Available from: *http://www.cdc.gov/uscs*
2. Australian Institute of Health and Welfare (AIHW).

Australian Cancer Incidence and Mortality (ACIM) books: Melanoma of the Skin. [online] 2014 [cited 2014 Jul 01]. Available from: *http://www.aihw.gov.au/acim-books*

3. Ishihara K, Saida T, Otsuka F, Yamazaki N. Prognosis and statistical investigation committee of the Japanese Skin Cancer Society. Statistical profiles of malignant melanoma and other skin cancers in Japan: 2007 update. Int J Clin Oncol. 2008; 13:33-41.
4. Sng J, Koh D, Siong WS, Choo TB. Skin cancer trends among Asians living in Singapore from 1968 to 2006. J Am Acad Dermatol. 2009; 61:426-32.
5. Chang JWC. Acral Melanoma: a unique disease in Asia. JAMA Dermatology. 2013; 149:1272-3. [editorial]
6. Bradford PT, Goldstein AM, McMaster ML, Tucker MA. Acral lentiginous melanoma: incidence and survival patterns in the United States, 1986-2005. Arch Dermatol. 2009; 145:427-34.
7. Cormier JN, Xing Y, Ding M, Lee JE, Mansfield PF, Gershenwald JE, et al. Ethnic differences among patients with cutaneous melanoma. Arch Intern Med. 2006; 166:1907-14.
8. Zell JA, Cinar P, Mobasher M, Ziogas A, Meyskens FL, Anton-Culver H. Survival for patients with invasive cutaneous melanoma among ethnic groups: the effects of socio-economic status and treatment. J Clin Oncol. 2008; 26:66-75.
9. Jung HJ, Kweon S-S, Lee J-B, Lee S-C, Yun SJ. A clinicopathological analysis of 177 acral melanomas in Koreans: relevance of spreading pattern and physical stress. JAMA Dermatol. 2013; 149:1281-8.
10. Choi YD, Chun SM, Jin SA, Lee JB, Yun SJ. Amelanotic acral melanomas. Clinicopathological, *BRAF* mutation, and *KIT* aberration analyses, J Am Acad Dermatol. 2013; 69:700-7.
11. Torres-Cabala CA, Wang W-L, Trent J, Yang D, Chen S, Galbincea J, et al. Correlation between KIT expression and *KIT* mutation in melanoma: a study of 173 cases with emphasis on the acral-lentiginous/mucosal type. Modern Pathology. 2009; 22:1446-56.
12. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009; 27:6199-206.
13. Roh MR, Kim J, Chung KY. Treatment and outcomes of melanoma in acral location in Korean patients. Yonsei Med J. 2010; 51:562-8.
14. Chang JW, Yeh KY, Wang CH, Yang TS, Chiang HF, Wei FC, et al. Malignant melanoma in Taiwan: a prognostic study of 181 cases. Melanoma Res. 2004; 14:537-41.
15. Chi Z, Li S, Sheng X, Si L, Cui C, Han M, Guo J. Clinical presentation, histology, and prognoses of malignant melanoma in ethnic Chinese: A study of 522 consecutive cases. BMC Cancer. 2011; 11:85. doi: 10.1186/1471-2407-11-85.
16. Lee HY, Chav WY, Tang MBY, Chio MTW, Tan SH. Melanoma: differences between Asian and Caucasian Patients. Ann Acad Med Singapore. 2012; 41:17-20.
17. Bristow IR, Acland K. Acral lentiginous melanoma of the foot and ankle: A case series and review of the literature. J Foot Ankle Res. 2008; 1:11.