

Original article

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Received on: 10/02/2020

Approved on: 29/05/2020

Study conducted at the Clinical Hospital of the Universidade Federal de Goiás, Goiânia (GO), Brazil.

Financial support: None.

Conflict of interest: None.



Acral melanoma - Clinical and epidemiological study

Melanoma acral - Estudo clínico e epidemiológico

DOI: <http://www.dx.doi.org/10.5935/scd1984-8773.20201222526>

ABSTRACT

Introduction: The characteristics of acral melanoma (MA) diagnosed in Brazil are poorly studied.

Objectives: To evaluate the MA characteristics of patients diagnosed at the Dermatology Service in a referral hospital and to verify whether the possible differences between them would be important in determining the diagnosis, treatment, and prognosis. Methods: The series was divided into localized and advanced disease. The patients were compared according to sex, color, age, thickness and level of invasion of the primary lesion, staging, and time from the tumor perception and doctor attendance.

Results: Data analysis showed an increased frequency of MA in non-white patients, with a higher age range, but without significant differences. There were also no significant differences regarding sex and staging, as well as regarding the time from the tumor perception and doctor attendance.

Conclusions: MA occurs mainly in patients who are normally not aware of skin cancer (non-whites) and belong to a higher age group. This form of cancer is unknown to the general public; and in the medical population, the acral region, especially the feet, is overlooked on physical examination.

Keywords: Melanoma; Prognosis; Survival Analysis

RESUMO

Introdução: As características do melanoma acral (MA) diagnosticado no Brasil são pouco estudadas.

Objetivos: Avaliar as características do MA dos pacientes diagnosticados no Serviço de Dermatologia em um hospital de referência e verificar se as possíveis diferenças entre eles teriam importância na determinação do diagnóstico, tratamento e prognóstico.

Métodos: A casuística foi subdividida em doença localizada e doença avançada. Os pacientes foram comparados quanto ao sexo, cor, idade, espessura e nível de invasão da lesão primária, estadiamento, tempo decorrido entre a percepção do tumor e o atendimento pelo médico.

Resultados: A análise dos dados mostrou frequência aumentada do MA em pacientes não brancos, com faixa etária mais elevada, porém sem diferenças significativas. Não ocorreram diferenças significativas também quanto ao sexo e estadiamento, bem como com relação ao tempo decorrido entre perceber a neoplasia e procurar o médico.

Conclusões: O MA ocorre, principalmente, em pacientes que normalmente não são alertados para câncer da pele (não brancos) e pertencem a uma faixa etária mais elevada. Essa forma de câncer é desconhecida do público em geral; e na população médica a região acral, especialmente pés, é esquecida no exame físico.

Palavras-chave: Análise de Sobrevida; Detecção Precoce de Câncer; Melanoma

INTRODUCTION

In the last decades, the incidence of cutaneous melanoma has increased worldwide. It is considered the fifth most common cancer in the United States. There has been a constant annual increase in melanoma, since 1950, of 6% in incidence and 2% in mortality.¹ In Brazil, according to the National Cancer Institute (INCA) statistics for the 2018-2019 biennium, approximately 2,920 new cases in men and 3,340 new cases in women are expected each year. This incidence is relatively low, but with high lethality rates.²

An anatomical-clinical classification subdivides cutaneous melanoma into four types: superficial spreading, nodular, lentigo maligna, and acral lentiginous.¹ Acral melanoma (AM) affects palmoplantar regions, digital extremities, mucosal and submucosal regions. It is more frequent in non-whites (35% to 60%). It has no preference for sex and, in general, occurs in the seventh decade of life. In the digital extremities, it may present as brownish subungual tumor lesion, striated melanonychia, longitudinal fragmentation of the nail plate, in addition to chronic and persistent paronychia.⁵

Current knowledge about melanoma risk factors, epidemiology, and prevention, in general, is based on studies in whites and the most common melanoma subtypes. Thus, there are not many studies explicitly aimed at the study of acral melanoma, which is more common in the black, Asian and elderly populations. Also, based on the literature's descriptions, AM is the subtype with the worst prognosis and where the affected patients present the lowest survival rates. So, there is a need for new studies that highlight the clinical and epidemiological aspects of AM.³

For patients with acral melanoma, the recommendation is similar to that of melanoma in other locations: to perform a biopsy, almost always excisional, followed by complete excision of the lesion with margins according to the Breslow thickness assessment. The goals of resection are to cure and prevent local recurrence. Insufficient margins are related to a higher rate of recurrence and lower survival. In this sense, acral melanoma is a major surgical challenge, since the closure of the primary wound is more difficult in this location and in extensive cases. Sometimes it needs reconstruction. Amputation should not be performed if possible. Functional surgeries are currently suggested. It is recommended to avoid the mutilations of the past.⁸ Second intention healing is recommended to facilitate follow-up, aiming to early detect the recurrence. This is because hyperchromia is observed in melanodermic patients undergoing reconstruction using a flap or graft.

There are different distributions of genetic changes in the main genes among the melanoma subtypes. They are classified according to anatomical location and sun exposure. This indicates strong involvement of different molecular pathways in tumorigenesis. In particular, an increased prevalence of activation of cKIT mutations, mainly accompanied by gene overexpression and/or amplification and, to a lesser extent, BRAF and NRAS mutations, has been described in a specific subset of mucous and acral melanomas.⁴

Therefore, this study's objective is to evaluate the clinical and epidemiological characteristics of acral melanoma in patients treated at a Dermatology reference unit and compare

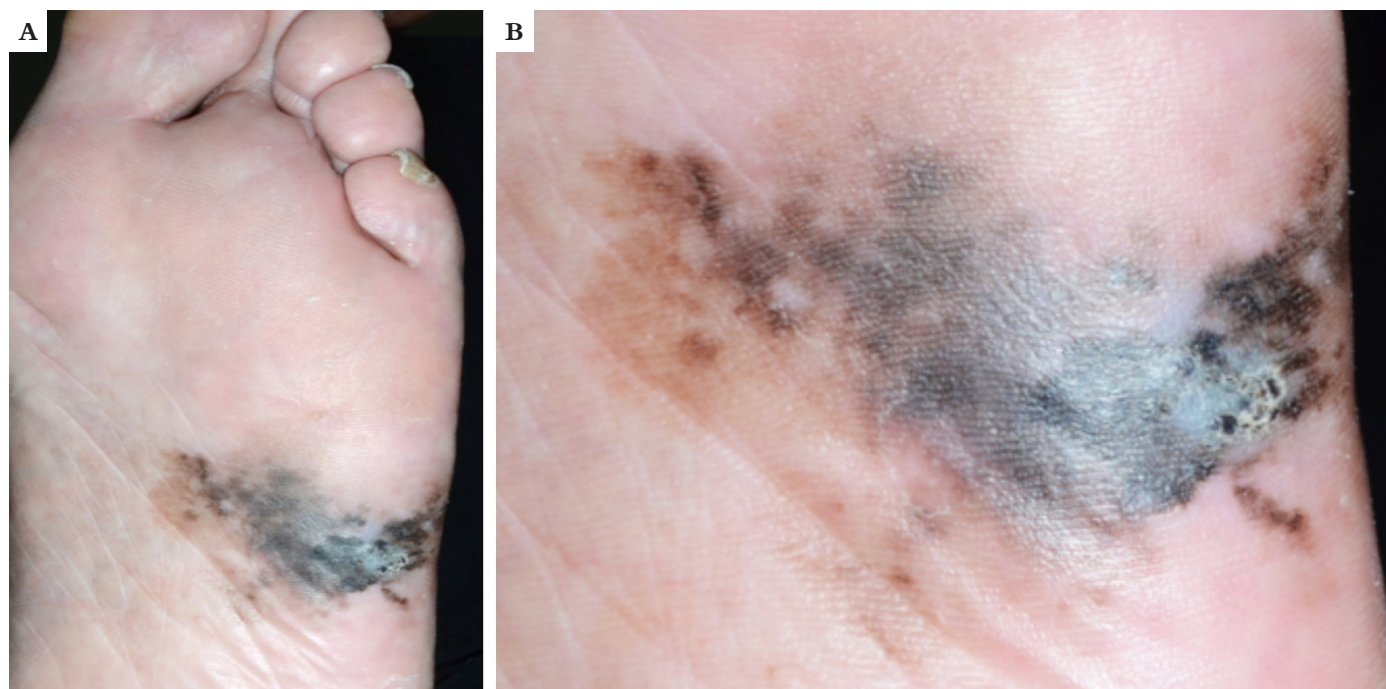


FIGURE 1: Acral lentiginous melanoma **A)** Blackened macula with the characteristics of: Asymmetry, Irregular margins, Varied colors, Large diameter and Progressive radial growth; **B)** Detail of the macula of imprecise limits - Illustrative iconography: from the photographic archive of the Department of Dermatology of UNESP - Botucatu

the results with those already described in the national and international literature.

METHODS

This is a retrospective, cross-sectional, and descriptive study conducted at the Reference Service in Dermatology. Ten cases of acral melanoma were recorded in this Service from January 1990 to October 2019.

The present project was sent to the Research Ethics Committee, and the data collection started after its approval. All ethical-legal precepts are following the rules of the 196/96 resolution of the National Health Council.

The study included patients previously diagnosed with melanoma in palmoplantar locations, digital extremities, mucosal and submucosal regions. They were diagnosed and followed up at the Dermatology Clinic, regardless of age, sex, Breslow index, or instituted therapy. This study excluded patients who did not agree to participate or who did not sign the Free and Informed Consent Form (ICF), or who did not present anatomopathological material available for study at the Pathological Anatomy Service.

All patients were assessed for the variables sex, color, age, tumor location, histological subtype, Clark level, Breslow thickness, growth phase, presence of perineural and perivascular invasion, metastasis, and treatment outcome. We also assessed the time elapsed between the patient noticing the lesion and attending the medical consultation.

Regarding age, the mean and median were used, in addition to separating patients by age group (<40 years and >40 years); regarding color, they were classified as white and non-white. Breslow index was divided into two groups: <1 mm and >1 mm. We then categorized the patients into two groups: localized disease and advanced disease, according to clinical and pathological staging TNM 9th edition AJCC-2019. The "localized disease" group comprised patients in stage IIC; and the "advanced disease" group included those with disease above stage III.

The statistical evaluation was performed using the chi-square test and the Mann-Whitney U test, establishing a significance level of 5% ($\alpha=0.05$). We calculated 95% confidence intervals (95% CI) for the estimates used.

RESULTS

The distribution of cases regarding gender showed three men (30%) and seven women (70%). There was no statistical difference when comparing the two groups ($p=0.500$). Regarding color, the group presented four cases of white patients (40%) and six cases of non-white patients (60%).

As for age, the data showed an average of 53.2 years and a standard deviation of 14.7 years. Concerning location, 80% of the patients had lesions on their feet and 20% on their hands; no mucosal lesions were identified. As for the subtype, 40% were acral lentiginous type, 30% extensive superficial, and 30% was not described in the anatomopathological study.

The determination of the average thickness of the Breslow index of primary lesions was possible in seven cases: 30% with Breslow <1mm, 50% with Breslow higher than or equal to 1mm, and 20% were not described in the medical record.

The mean thickness was 3.89mm, and the standard deviation was 5.45. In the localized disease group, the mean was 1.02mm, with a standard deviation of 0.64. In the advanced disease group, the mean Breslow index was 11.05, with a standard deviation of 5.73. There was no significant difference between the two groups (Mann-Whitney U test, $p = 0.053$).

Regarding the proposed staging, in case series and methods, no statistical differences were found between the groups of localized disease and advanced disease, especially the location in the feet, acral lentiginous subtype, Clark level, radial growth phase, death/loss to follow-up, and duration of evolution >5 years as markers of worse prognosis. Female gender was also not considered a risk factor, using the chi-square test.

DISCUSSION

The literature already describes a higher frequency of AM in black patients and patients aged between 60 and 70 years. There is no difference described between the sexes, in agreement with the data obtained here.

The sample of the present study was small, therefore, possibly, the difficulty in calculating statistical significance. Also, the review of medical records is not always enlightening: data such as race, education, difficulty in accessing the health system are essential in the diagnosis (late vs. early) and interfere in the prognosis of these patients, but they are not always well described. The data included a long collection period (20 years). There was a difficulty in standardizing the anatomopathological report's description because of the difference in describing the data collection at the beginning compared to the end of the period. This difference impairs the power of correlating data such as ulceration, number of mitoses, perivascular and perineural invasion with the disease outcome.

In this sense, a prospective study, with a defined and duly completed questionnaire, in addition to standardizing the description of pathological findings, could be more successful in determining risk and prognostic factors. On the other hand, medium- and long-term follow-up could verify whether there will be evolutionary differences concerning metastases and survival among patients in the advanced versus localized disease group. In case it is not possible, another work would have to be considered to differentiate the biological behavior of the various types of growth, mainly when analyzing molecular and genetic factors and mutations.

For example, from a pathogenic point of view, BRAF mutations are the most common oncogenic changes in melanoma. Mucous and acral melanomas often have a wild-type BRAF, but they may have mutations in the cKIT gene. Recent evidence suggests that mucosal melanomas with cKIT activation may respond to KIT inhibitors available for use, such as imatinib, sunitinib, dasatinib, and nilotinib.

And that possibility could change the prognosis and survival in patients with advanced disease. The role of these changes in the genesis of melanoma still needs to be better defined.⁴

Regarding the age and location of the lesions, older patients could have greater difficulty in self-examination. For this reason, they could be diagnosed later and contribute to a possible worse outcome.

Campaigns for skin cancer prevention emphasize low phototype as a risk factor and recommend photoprotection as the main measure. The AM affects, as demonstrated in the literature, preferably non-white patients, with primary lesions located mainly in the plantar region, areas without any influence of solar radiation. Also, risk factors for MA are currently unknown.

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CONCLUSIONS

This study allows us to extract the following observations regarding acral melanoma (AM) patients diagnosed at the Dermatology Service:

- There are no statistically significant differences between genders; there is a predominance of elderly patients (>40 years old), non-whites, and plantar location; a higher Breslow index is generally related to late diagnosis and worse outcome;
- Public campaigns for the prevention and diagnosis of skin cancer should emphasize the possibility that this form of cancer is not linked to sun exposure, skin color, and preferential age;
- For the AM, there is no form of prevention. Its risk factors are still unknown; therefore, we must prioritize early diagnosis;
- Immunogenic studies could help correlate tumor behavior, aggressiveness, recurrence possibility, and response to treatment to increase disease-free survival in these patients. ●

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