Research Article,

Association of Clinicopathologic Features with the Depth of Invasion in Acral Melanoma

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Abstract:

Thickness is the major prognostic indicator for patients with melanoma. The deeper of the invasion, the higher the incidence of metastasis and the lower the survival rate. To reduce mortality, knowledge of the characteristics associated with melanoma depth is needed.

Retrospective cross-sectional study was conducted to 40 cases of acral melanoma, in the Anatomical Pathology Department of Faculty of Medicine, Universitas Padjadjaran /Hasan Sadikin Hospital. To examine association between depth of invasion and clinicopathological features data were analyzed used non-parametric Mann Whitney test. P value $p \leq 0.05$ was considered significant.

Result: Tumor infiltrating lymphocyte have associations with depth of invasion on acral melanoma with significant result (p=0.003).

Conclusion: TILs was associated with the invasion depth of acral melanoma and may play important roles during the invasion process of acral melanoma.

Keywords: Depth of invasion, Acral Melanoma, Tumor Infiltrating Lymphocyte

Introduction:

Melanoma maligna (MM) is a malignancy originating from the skin's melanocyte system. This tumor is the most aggressive of all skin malignancies. Small tumors can be experienced invasion and metastasis with poor prognosis.[1] the incidence of MM is approximately 4% of the entire skin malignant tumor; however it is causes 75-90% of deaths from this disease. The incidence of MM continues to increase in the population white skin especially in people with sun exposure. Incidents of new cases in Europe 10-25 per 100,000 population, at United States 20-30 per 100,000 population and the highest incidence is found in Australia as much as 50-60 per 100,000 population.[2],[3] In the Asian and African race the most type of MM is Acral Melanoma (AM) which has more aggressive nature and worse prognosis than other types because it has a pattern of tumor growth in the radial growth phase and vertical growth phase, namely the pattern of tumor cell growth laterally (epidermis) and vertical invasion to the dermis.[4]

Many prognostic factors for melanoma are known

(Rigel et al, 1991) and numerous prognostic models have been developed in an attempt to predict which patients ultimately will develop advanced disease. The prognostic models include such variables as patient age, location of the melanoma, gender, ulceration, tumor thickness, level of invasion, and other histologic features to better predict outcome. Tumor thickness is the most important prognostic indicator. Lesions with thickness < 0.75 mm metastases are rare. Lesions with thickness > 5 mm have a poor prognosis.[5] in this study, acral melanoma cases diagnosed in 5 years were investigated retrospectively. The objective of this study was to describe the epidemiological and clinicopathologic characteristics of acral melanoma to identify the clinicopathologic variables associated with the depth of invasion.

Material and methods:

The research material is paraffin blocks of patients who have undergone excisional and surgical biopsy and has been diagnosed histopathological as MM located on the acral period between 1 January

2014 and 31 December 2019. Ethical clearance was approved from Health Research Ethics Committee of Faculty of Medicine Universitas Padjadjaran with a waiver of informed consent (LB.02.01 / X.6.5 / 18/2020).

Acral Melanoma was defined define as a melanoma located on the non-hair bearing skin of the palms and soles or under the nails, which has histopathology pictures of both acral melanoma and such subtypes as superficial spreading melanoma and nodular melanoma. Clinicopathological parameters included in the analysis were: age, sex, ulceration, and degree of lymphocytic infiltration. Tumor Infiltrating Lymphocytes (TILs) were defined as lymphocytes infiltrating and disrupting tumor nests and/or in direct contact with tumor cells in H&E staining. The invasion depth was measured using dotSlide software from the epidermal surface to the deepest part of the invasion in the dermis.

Results:
Patient's characteristics.
In this study, total samples numbered 44 but only 40 were eligible.

Table 1 shows that the mean age of acral MM patients was 63 years old. Both male and female showed comparable results of 62,5% and 37,5%, and the mean of depth of invasion was 8.155mm. There is no sample that has Clark Level I and Clark Level (II-V) and TILS divide into two groups as shown below.

Table 1. Research subject characteristics

Variable	N=40
Age (years)	
Mean±SD	63.38±13.503
Sex	
Male	25(62.5%)
Female	15(37.5%)
Depth of Invasion (mm)	
Mean±SD	8,155±4,707
TIL	
Absent	27 (67.5%)
Brisk	7(17.5%)
Non Brisk	6(15%)
Ulceration	
Positive	38(95%)
Negative	2(5%)

Association of depth of invasion on acral melanoma with patients characteristic.
The association between depth of invasion on acral melanoma and patient's characteristic was analyzed. TIL have associations with depth of invasion on acral melanoma with significant result (p=0.003). No significant correlation was seen between depth of invasion and other characteristic patient, such as patient age, sex and ulceration. (p>0.05, table 2)

Table 2. Association of Clinicopathological Characteristics and Depth of Invasion on Acral Melanoma

Variable	Depth of Invasion Mean±SD (mm)	P value
Age		
63.38±13.503	8.155±4.707	0.783
Sex		
Male	8.292±4.251	0.639
Female	7.927±5.536	
Ulceration		
Yes	7.111±2.536	0.926
No	9.707±7.433	
TIL		
Absent	9.622±4.837	0.003
Positive		
Brisk	4.861±2.817	
Non Brisk	5.397±2.385	

Discussion:
Despite the advances in global healthcare, malignant tumors remain a major threat to human health. Melanoma is the most aggressive skin cancer with unpredictable behavior. Thus, accurate prognostic prediction is paramount for the selection of appropriate therapies and management

of melanoma patients.[1] Tumor infiltrating lymphocytes (TILs) are a local histopathological reflection of the host's immune response against cancer cells. Currently, TILs have gained increasing attention in the treatment and prognosis prediction of melanoma. Many studies have indicated that TILs are a favorable prognostic factor for melanoma patients, and the presence of TILs might lead to a better prognosis.[6]

TIL are a polymorphic group that is composed mainly by effector T lymphocytes, regulatory T lymphocytes, natural killer (NK) cells, dendritic cells and macrophages. The distribution, the density, the profile and the activation state of the cells which constitute TIL can be variable and modulate the clinical outcome.[3] According to Clark *et al* TIL infiltrate can be classified as: absent, non-brisk or brisk and this quantification is still accepted by most authors.[7] TIL are considered *absent* when leukocytes are absent or if they are present, they do not infiltrate the tumor. Non-brisk TIL represents the infiltrate distributed only focally and not along the entire base of the invasive component. Brisk TIL is defined by lymphocytes that infiltrate diffusely the entire invasive component or infiltrating across the entire base of vertical growth phase.[8] According to Table 2, the depth of invasion in acral MM associates with TILs mostly in non brisk type have deeper invasion (mean: 5.397) compared with non brisk (mean: 4.861). This finding was consistent with a hypothesis proposed in 1978 that concluded from a retrospective study including 669 melanoma patients that a dense lymphocytic infiltrate in primary tumors improved their survival rates.[9] this is also supported by the findings in subsequent studies of melanoma and fit with studies in other tumors.[1] According to Brauer *et al.*,thick melanomas increase the risk of early metastasis (between six months to three years of the initial tumor), compared to late metastases, that occur after eight years of the primary tumor.[10] In this study, the results showed (table2) that the deeper the invasion the negative TIL results were obtained.

TILs appear to indicate that your immune system has recognized the melanoma cells as abnormal and is trying to move into the melanoma to attack it. Some studies suggest that the presence of increasing number of TILs may be associated with a better prognosis. A recent report suggested the prognostic importance of TILs in high-grade breast cancers. Kurozumi et al. recently investigated the relationship between TILs and prognosis in 294 cases and reported that high stromal TILs expression was a good prognostic marker in ER-negative cancers.[11]

TILs are implicated in not only effector T cells but also in functionally exhausted T cells, tolerogenic or T regulatory (Treg) cells, dendritic cells (DCs), natural killer (NK) cells, myeloid-derived suppressor cells (MDSCs), macrophages, and other immune cell types.[11,12] As the main antitumor effector cells, CD8+ T lymphocytes comprise the majority of TILs and have been linked to a better prognosis in several types of cancer.[13] Clemente et al. in a study of 285 patients obtained a 5-year survival of 77% in patients with infiltration present, compared to 37% in those with absent infiltrate, in this study both tumor thickness and TILs being considered independent prognostic indicators.[14] Thomas and colleagues found, in a study on 3330 primary invasive melanomas, that absent TILs were associated with a higher AJCC tumor stage, in comparison with nonbrisk and brisk infiltrate, which correlated with a lower tumor stage.[15,16]

Conclusion:

In our study was found there is a significant association between TILs and the depth of invasion of acral melanoma, where the deeper of invasion, the TIL results become negative, so TILs can be considered as prognostic factors in acral melanoma.

Acknowledgments:

Conflict of Interest:

The authors declare that there are no conflict of interests in this study

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