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Clinicopathological Characteristics of Cutaneous Melanocytic Lesions for Predicting Biological Behavior: 5 Years Retrospective Study in National Referral Hospital

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ABSTRACT

Background
Cutaneous melanocytic lesions have varieties of subtypes ranging from benign (nevus) to malignant lesions (malignant melanoma). Differentiating benign and malignant melanocytic lesions is challenging, particularly due to overlapping clinicopathological characteristics. This study was conducted to determine clinicopathological characteristics of cutaneous melanocytic lesions and the prevalence ratio of each characteristic for predicting malignant behavior.

Method
Cross-sectional study was conducted with data retrieved from Anatomic Pathology Department of Faculty of Medicine Universitas Indonesia and Dr. Cipto Mangunkusumo Hospital. Data of 145 histopathology-confirmed cutaneous melanocytic lesions cases between 2018 – 2022 were sampled and collected. Bivariate analysis was used to determine the prevalence ratio of each characteristic to predict malignant behavior.

Result
Out of 145 cases, 14.5% were malignant lesions (melanoma) and the rest were benign (nevus). Clinicopathology features and characteristics were correlated with malignant behavior, such as cytological atypia ($p < 0.01$), dermal mitosis (PR=91.5; $p<0.01$), asymmetry (PR=31.8; $p < 0.01$), suprabasal melanocyte (PR=21.4; $p < 0.01$), lower extremity location (PR=6.5; $p < 0.01$), sized >6 mm (PR=5.2; $p < 0.01$), and male gender (PR=3.3; $p < 0.01$).

Conclusion
Clinicopathological characteristics of cutaneous melanocytic lesions such as cytological atypia, dermal mitosis, asymmetry, suprabasal melanocyte, lower extremity location, sized >6 mm, dermal lymphocytic infiltrate, and male gender were predictive to predict malignant lesions.

Keywords: clinicopathological characteristics, cutaneous melanocytic lesions, melanoma, nevus, skin cancer

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INTRODUCTION

The cutaneous melanocytic lesions encompass wide array of diagnoses, ranging from benign (nevus) to malignant lesion (melanoma). Melanoma caused 57,043 deaths worldwide and 699 in Indonesia per year.[1] Skin cancer is less common in people of color, but often diagnosed at a more advanced stage and has a worse prognosis. One of risk factor in skin cancer induction is ultraviolet (UV) radiation. Melanin is one of most important in skin protection. Skin melanin can be an UV absorbent and also antioxidant or radical protection. Individual with colored skin compared to those with white skin has lower incidence for skin cancer.[2] The gold standard of diagnosis of cutaneous melanocytic lesions relies on H&E histopathological examination, with clinical correlations. However, they still provide a complex challenge for pathologists due to overlapping clinicopathological features.[3]

Nevus and melanoma have a complex relationship. Some melanomas develop from nevus, and the rest has no known precursor lesion. One of the clinical clues used to differentiate malignant from benign lesion is ABCD (Asymmetry, Border irregularity, Color variegation, Diameter > 6 mm, Evolution).[4] However, with the advance of medical service, increasing number of "small" melanoma (diameter ≤ 6 mm) are detected.[5] Patient's gender should be considered, since the proportion of malignant lesion among cutaneous melanocytic lesions is higher in male patients. Based on Liu et al which found that 70% of their patients were female. Another interesting finding is 30,6% of male patients had malignant lesion while only 9,2% on female patients. Ramadhini et al in their research had 29,6% malignant melanocytic lesion on male patients.[6,7] The location of the lesion should also be considered, but the site predilection varied across all races and ethnicities. In Asian people, the acral is the most common site for cutaneous melanoma. Acral melanoma has worse prognosis than nonacral melanoma due to its late presentation, diagnosis, and high aggressivity. This melanoma is different subgroup of subcutaneous melanoma and mostly find in palmoplantar and subungual.[8]

Histopathologically, malignant melanoma typically shows cytological atypia, with pleomorphic, large nuclei, with prominent nucleoli. Typical malignant lesion also shows asymmetrical architecture, suprabasal melanocytes, dermal mitoses, and dense dermal lymphocytic infiltrate. However, these histopathological characteristics can also be found in benign lesions. Cytological atypia can be found in dysplastic and Spitz nevus. Suprabasal melanocyte can be found in Spitz nevus, Reed nevus, acral nevus, and irritated nevus. Dermal mitoses can be found in children, after external irritation, in developing lesions, or in proliferative nodules of congenital naevi. Both asymmetry and dermal lymphocytic infiltrates can be found in benign lesion to some extent.[9]

Given the overlapping histopathological features of malignant and benign melanocytic skin lesions, further study is required to identify the histopathological characteristics associated with biological characteristics. Retrospective studies on the clinicopathological profile of melanocytic skin lesions have not been extensively conducted in Indonesia. This retrospective study aims to investigate the association between clinicopathological characteristics, including age, gender, lesion location, tumor size, asymmetry, cytologic atypia, suprabasal melanocytes, dermal mitoses, and dermal lymphocytic infiltrates, with the malignancy of melanocytic skin lesions.

METHODS

Study Design

This was a cross sectional study, which use data from the archive of Anatomic Pathology Department, Faculty of Medicine Universitas Indonesia (FMUI) / Dr. Cipto Mangunkusumo Hospital (CMH) and electronic health record (EHR) of CMH which is the national referral hospital in Indonesia. This study was carried out according to principles outlined in the Declaration of Helsinki. The study protocol was approved by the Ethical Committee, Faculty of Medicine, Universitas Indonesia, by the registration number KET-733/UN2.F1/ETIK/PPM.00.02/2022 and protocol number 23-05-0829. All cutaneous melanocytic lesions referred to our hospital from January 2018 to December 2022 were included. Inclusion criterion was all skin specimens which were diagnosed with cutaneous melanocytic lesion through histopathological examination in CMH. The exclusion criterion was cases with incomplete clinicopathologic data and unavailable histopathology specimen in our archive.

Research Procedures

Clinical data collected were age, gender, tumor location, and tumor size. Asymmetry, cytological atypia, suprabasal

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melanocyte, dermal mitosis, and dermal lymphocytic infiltrate were assessed on H&E staining. Cutaneous melanocytic lesions were diagnosed and classified according to WHO Classification of Skin Tumors (Elder et al., 2018). The lesions were considered benign if the morphologic code is /0 and malignant if /3.

Statistical Analysis

Statistical analysis was done using IBM SPSS® Statistics 25.0. Bivariate analysis was done using unpaired T-test or Mann Whitney U test for numeric variable (age); Chi-square or Fisher's exact test for categorical variables. The results are considered statistically significant when the p-value is less than 0.05 with a 95% confidence interval.

RESULTS

Clinicopathological Features of the Patients

There were 145 patients, median age of whom was 29 years old (range: 0–82 years old) in which was tend to be higher in malignant group compared to benign group (Figure 1). About 15% of the cases (21 patients) were diagnosed as malignant lesion (melanoma), while the rest were benign lesions (124 patients). The number of female patients in this study amounts to 75% of the population (109 patients). The tumor presented in lower extremity in 14.5% cases. More than half of the tumor (53.8%) have size larger than 6 mm. Asymmetry was found in 38.6% cases, cytological atypia in 15.9%, suprabasal melanocyte in 16.5%, and dermal mitosis in 17.9%. Dermal lymphocytic infiltrate was present in almost half of the cases (45.5%). The complete clinicopathologic characteristics of the samples were described in Table 1.

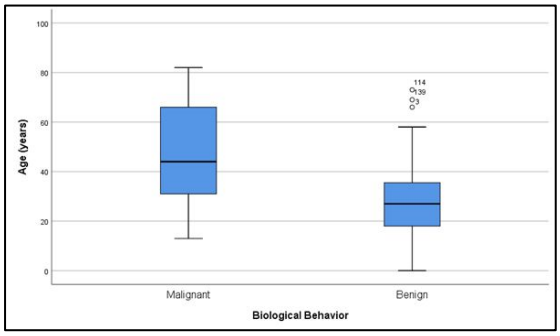

Figure 1. The median age of malignant and benign cutaneous melanocytic lesions.

Table 1. Clinicopathological features of the patient.

Parameter	N (%)	Median (Min-Max)
Age (years old)		29 (0-82)
Gender		
Male	36 (25)	
Female	109 (75)	
Tumor location		
Lower extremity	21 (14.5)	
Others	124 (85.5)	
Tumor size		
>6 mm	78 (53.8)	
≤6 mm	67 (46.2)	
Asymmetry		
Present	56 (38.6)	
Absent	89 (61.4)	
Cytological atypia		
Present	23 (15.9)	
Absent	122 (84.1)	
Suprabasal melanocyte		
Present	24 (16.5)	
Absent	121 (83.5)	
Dermal mitosis		
Present	26 (17.9)	
Absent	119 (82.1)	
Dermal lymphocytic infiltrate		
Present	66 (45.5)	
Absent	79 (54.5)	

Clinicopathological Features Based on Biological Behavior

Table 2 showed the clinicopathologic characteristics of the samples based on biological behavior (malignant vs benign) and their prevalence ratio. Malignant lesions were found in older patients than benign lesions (44 years vs 27 years old). The most common benign lesion is intradermal melanocytic nevus (Figure 2), while the most common malignant lesion is nodular malignant melanoma (Figure 3).

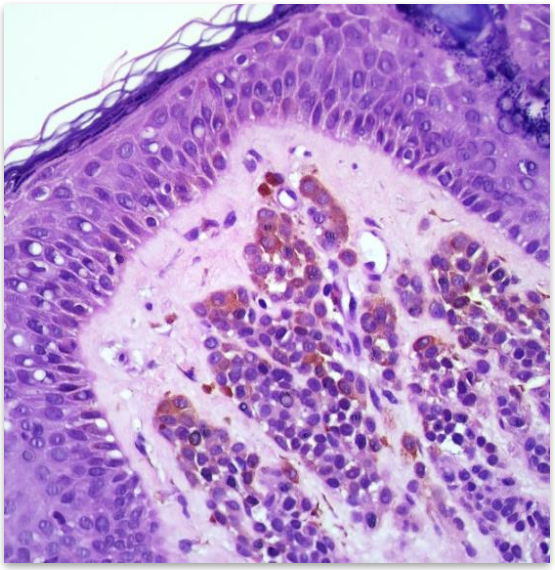

Figure 2. Benign melanocytic lesion (intradermal melanocytic nevus) (HE 400 times).

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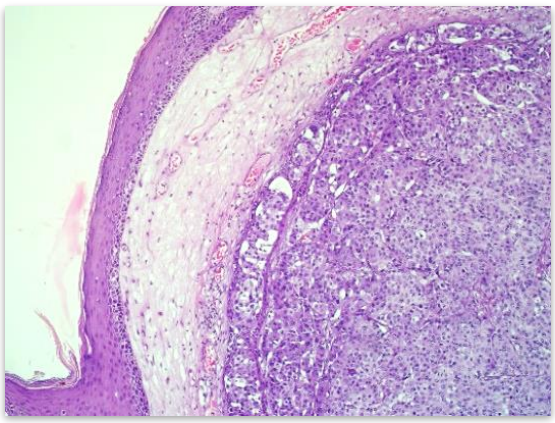

Figure 3. Nodular malignant melanoma. (HE 100 times)

To determine the prevalence ratio for malignancy, we did bivariate analysis. In bivariate analysis, all characteristics are statistically significant for predicting malignancy. Dermal mitosis had the highest prevalence ratio, it increased the probability of malignancy by 91.54 (95% CI 12.86–651.84), asymmetry 31.79 (95% CI 4.39–230.30), suprabasal melanocyte 21.43 (95% CI 7.90–58.09), lower extremity location 6.50 (95% CI 3.16–13.35), tumor size > 6 mm 5.15 (95% CI 1.59–16.74), dermal lymphocytic infiltrate 5.09 (95% CI 1.80–14.38), and male gender 3.33 (95% CI 1.54–7.19). All malignant lesions showed cytological atypia, so the prevalence ratio for cytological atypia could not be calculated.

Table 2. Clinicopathologic Characteristics of the Sample Based on Biological Behavior.

Parameter	Biological Behavior (Median (Min-Max) or n(%))		p-value	Prevalence Ratio (CI 95%)
	Malignant	Benign		
Age (years old)	44 (13-82)	27 (0-73)	0.000[m]	
Gender				
Male	11 (30.5)	25 (69.5)	0.002[cs]	3.331 (1.544-7.186)
Female	10 (9.2)	99 (90.8)		
Tumor location				
Lower extremity	11 (52.4)	10 (47.6)	0.000[cs]	6.495 (3.159-13.354)
Others	10 (8)	114 (92)		
Tumor size				
>6 mm	18 (23.1)	60 (76.9)	0.002[cs]	5.154 (1.587-16.736)
≤6 mm	3 (4.5)	64 (95.5)		
Asymmetry				
Present	20 (35.7)	36 (64.3)	0.000[cs]	31.786 (4.387-230.296)
Absent	1 (1.1)	88 (98.9)		
Cytological atypia				
Present	21 (91.3)	2 (8.7)	0.000[fe]	N/A
Absent	0 (0)	122 (100)		
Suprabasal melanocyte				
Present	17 (70.8)	7 (29.2)	0.000[fe]	21.427 (7.904-58.085)
Absent	4 (3.2)	117 (96.8)		
Dermal mitosis				
Present	20 (76.9)	6 (23.1)	0.000[fe]	91.538 (12.855-651.836)
Absent	1 (0.8)	118 (99.2)		
Dermal lymphocytic infiltrate				
Present	17 (25.8)	49 (74.2)	0.000[cs]	5.087 (1.800-14.378)
Absent	4 (5)	75 (95)		

M = Mann-Whitney test; CS: Chi-square; FE: Fisher's exact; CI: Confidence Interval

DISCUSSION

The diagnosis of cutaneous melanocytic lesions has long been a challenge for both dermatologists and pathologists. Nevus and melanoma have complex relationships, with overlapping clinicopathological features.[10]

Atypical nevi and an increased incidence of melanocytic nevi have been identified clinically as risk factors for melanoma development. Nevi increases a person's risk of developing melanoma by around seven times when they have more than 100 nevi on their individual. In contrast to the absence of atypical nevi, the presence of many atypical nevi was associated with a six-fold increased risk for the formation of melanoma. It was believed that nevi may serve as precursor lesions in the development of melanoma due to the dose-dependent connection observed between nevus numbers and melanoma. The majority of nevi will stay stable and not develop into melanoma, also the chance of a single nevus progressing to melanoma is extremely low (less than 0.0005% annual risk).[10]

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Benign melanocytic lesions usually already have one mutation in the MAPK pathway (Mitogen-Activated Protein Kinase), for example, the BRAF p.V600E mutation in acquired naevi. This indicates that benign melanocytic lesion can be a precursor to malignant melanoma, as it is composed of proliferating melanocytes that have one of the several mutations required for the tumorigenesis process of malignant melanoma.[3,9] If another mutation occurs in the melanocytic lesion, such as a mutation in the telomerase reverse transcriptase (TERT) gene, then the benign lesion can develop into a malignant one. The TERT gene plays a role in the expression of the telomerase enzyme, which functions to synthesize new DNA telomeres. This gives the tumor cells the ability to divide continuously.[11,12]

Melanoma can develop without specific precursor lesion or from nevus, with overlapping genomic abnormalities. WHO 2018 classification of melanoma stated 9 different subtypes according to their evolutionary pathways. Pathway I (superficial spreading melanoma/low-CSD melanoma) develops from common nevi, pathway IV (Spitz melanoma) from Spitz nevi, pathway VII melanomas arising in congenital nevi, and pathway VIII melanomas arising in blue nevi. The precursor lesions for pathway II (lentigo maligna melanoma/high-CSD melanoma), pathway III (desmoplastic melanoma), pathway V (acral melanoma), pathway VI (mucosal melanoma), and pathway IX (uveal melanoma) have not yet been identified. Nodular melanoma may occur in most of the pathways.[4]

Pathway I melanoma develops from precursor lesions called nevi with BRAF V600E or NRAS Q61R/L mutations. Pathway IV melanoma develops from Spitz nevi with HRAS mutations or translocations with kinase gene fusion. Pathway VII melanoma develops from congenital nevi with NRAS mutations, and stage VIII develops from blue nevi with GNAQ or GNA11 mutations. The precursor lesions for melanoma in other stages are not clearly known and are suspected to develop de novo.[3,4,9,13]

Despite the advances of immunohistochemistry and genomic analysis, the diagnosis for cutaneous melanocytic lesions still relies on histopathology, with clinical correlations. Immunohistochemistry can aid in differentiating melanocytic differentiation from others. For identifying malignant from benign lesions, some IHC are still being studied, such as PRAME (Preferentially expressed Antigen in Melanoma).[14] PRAME, also known as CT130, MAPE, and OIP-4, is a cancer/testis antigen (CTA) that is primarily expressed in melanoma. It belongs to the CTA gene family and codes for a membrane-bound protein that is recognized by T lymphocytes. PRAME is typically absent or has low expression in normal tissues and also the PRAME gene is hypermethylated in normal tissues while hypomethylated in malignancy.[15]

Our study collected all skin histopathology specimens diagnosed as cutaneous melanocytic lesions for 5 consecutive years. A total of 145 cases were included, consisting of 21 malignant cases (14.5%) and 124 benign cases (85.5%). The most common subtype among the malignant cases was nodular melanoma (38%), and among the benign cases was common acquired dermal nevi (62%). Another study of 3,745 patients also found that common acquired dermal nevi is the most prevalent lesion.[7]

Melanoma is a tumor of high mutational burden and become more prevalent in older patients. The mutation accumulated throughout life increased melanoma incidence with increasing age.[16] The median age for melanoma in this study was 44 years old, statistically older than the median age for nevi (27 years old). The established risk factor for some melanoma subtype is sun exposure, which can cause point mutation (cytosine transition to thymidine). The accumulation of this point mutation is called cumulative sun damage/CSD.[13] Paulson et al found that the incidence of malignant melanoma decreases in adolescents and young adults, while it increases in older age groups, especially above 40 years old.[17] Ramadhini et al also found that the majority (80%) of malignant melanoma cases were found in patients above 40 years old, while the incidence of nevi was higher in those below 40 years old (69%).[6] In that study, the average age of benign melanocytic lesions patients was 27 years, with 25.58% being below 20 years old, 60.08% being between 20-39 years old, 12.84% being between 40-59 years old, and 1.5% being 60 years old and above.

Cutaneous melanocytic lesions were found more often in women in this study. Interestingly, the proportion of malignant lesion in men was far higher than women. Liu et al found that 70% of their patients were female. A notable finding is that among male patients, 30.6% of them had malignant lesions, while among females, it was only 9.2%.[7] These findings may be attributed to hormonal differences. Melanoma is a highly immunogenic

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tumor, where host immune responses play an important role in eliminating tumor cells. Estrogen has been known for enhancing immunity, antibody, and inflammatory responses, while testosterone suppress nonspecific immune response.[18] Women also were found to have a higher skin health awareness, which was associated with 50% decline in melanoma mortality.[19]

More than half of lesions are found in head and neck (64%). Head and neck are sun-exposed areas, a risk factor for nevi development. For malignant lesions, more than half was found in lower extremity, mostly in acral (85%). Many acral melanomas are of the acral lentiginous type. Melanoma sites for POC (people of color) is different from whites. Study found that the sole of the foot is the most common site for melanoma. The etiology of acral melanoma is still under study but UV radiation seems to have no significant role, and there is possibility that this lesion may be induced by trauma.[2]

The ABCDE rules (asymmetry, border irregularity, color variegation, diameter > 6 mm, and evolution) are useful for early identification of melanoma.[5] This study found 3 cases (4.5%) of melanoma have diameter ≤6 mm. It was found that lesions >6 mm have a 5.15 times higher risk of being malignant compared to lesions ≤6 mm. This should raise awareness of the possibility of "small melanoma". However, the statistical analysis result concludes that we can still use the classic 6 mm size cut-off to predict malignancy, with comprehensive clinicopathological correlation.

Histopathologically, asymmetry was assessed by drawing imaginary line in vertical axis at the center of lesion. Most malignant lesion will have asymmetrical architecture. The pitfall of this assessment is the fact that histopathology specimen shows 2-dimensional picture of a 3-dimensional specimen.[9] Although some benign lesions showed asymmetry (29%), but the difference is still statistically significant with malignant lesions.

Cytological atypia is the hallmark histopathological feature of melanoma. The tumor cells of melanoma showed high degree of pleomorphism, with variable size and shape, and prominent nucleoli. This study found that all melanoma showed cytological atypia. However, not all specimens with cytological atypia are malignant. Two cases of nevi showed cytological atypia (dysplastic nevus and Spitz nevus). Other benign lesions also can showed cytological atypia, such as Reed nevus, cellular blue nevus, deep penetrating nevus, acral nevus, and recurrent nevus.[20]

Morphologically, dysplastic nevi have characteristics between acquired melanocytic nevi and melanoma, with radial growth. Dysplastic nevi exhibit features such as junctional shoulder/shoulder phenomenon (extension of junctional nevus component beyond the dermal boundary), bridging/anastomosis of nevus nests between adjacent rete ridges, and the presence of lymphohistiocytic inflammatory cells. Nevus cells show cytological atypia, including enlarged, pleomorphic nuclei, and prominent nucleoli with varying degrees. Distinguishing dysplastic nevi from early/in situ melanoma is not easy. However, in general, melanoma usually exhibits asymmetrical lesions, indistinct borders, lack of melanocyte maturation, and a high mitotic rate.[3,13,20]

Spitz melanocytic tumors consist of large epithelioid and/or spindle-shaped cells. Spitz nevi refer to lesions without atypical features and have a low risk of becoming malignant. Typically, Spitz nevi are smaller than 5 mm in diameter, symmetrical, and have well-defined borders.[32] Clinically, Spitz melanoma usually has a larger size (>5 mm), asymmetrical shape, indistinct borders, and ulceration may occur. Histopathologically, Spitz melanoma shows high-grade cytological atypia with a mitotic index of >6 mitoses per square millimeter of dermis, and necrosis and dense lymphocyte infiltrates may be present.[3,13]

In melanocytic proliferation, mitosis can be found in lesions in the epidermis or dermis. The presence of mitosis in the dermal part of the lesion is important to observe, both in terms of quantity and form (typical or atypical). In this study, mitosis was found in 26 cases (18%), where 20 cases were malignant lesions and 6 cases were benign lesions. In all benign lesions, the mitosis observed was typical. On the other hand, in malignant lesions, the average number of mitosis found was 9 mitosis/10 HPF (high-power fields). The proportion of mitosis findings in malignant and benign cases differs significantly, where lesions with dermal mitosis are 91.5 times more likely to be malignant than benign. When evaluating melanocytic mitosis, it is important to pay attention to the location, as mitosis can also be found in keratinocytes, endothelial cells, and inflammatory cells.[9,21]

Suprabasal melanocyte and dermal lymphocytic infiltrates are another clues for malignancy in melanocytic lesion, although it can be found in benign lesions.[9] Usually,

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melanocytes are found within the basal layer of epidermis. Lesions with suprabasal melanocytes was 21 times more likely to be malignant, and lesions with dermal lymphocytic infiltrates was 5 times more likely to be malignant. However, these should be correlated with various other clinicopathological findings when diagnosing melanocytic skin lesions.

Melanocytes can normally be found in the basal layer of the epidermis or sometimes in the suprabasal layer (granular, spinosum, or corneum). In malignant melanoma however, melanocytes in the suprabasal layer is a common finding. Suprabasal melanocytes can also sometimes be found in Spitz nevus, Reed nevus, acral nevus, nevi affected by trauma, or in skin with chronic sun damage. Suprabasal melanocytes can sometimes be found in benign melanocytic skin lesions.[9]

Lymphocytic infiltrates finding illustrate human's immune response. In malignant melanocytic lesions, dense lymphocytic infiltrates are commonly found along the base of the tumor, forming continuous strip-like clusters in the dermis.[22,23] Lymphocytes in the dermis can be found in both malignant and benign lesions, but it is denser in malignant lesions. Malignant melanoma is one of the most immunogenic neoplasms, as it has the ability to stimulate complex immune reactions.[9,22] In this study, dense dermal lymphocytes were found in 81% of malignant cases and 39.5% of benign cases. In some case, benign melanocytic lesions can also express melanoma-associated antigens.

In general, the human immune system actively eliminates proliferating melanocytes to prevent tumor growth, so individuals with immunodeficiency have a higher incidence of nevi.[24] Although the proportion of benign lesions with dense dermal lymphocytes is relatively large in this study, it differs significantly from malignant lesions. This indicates that this characteristic finding can still be used to increase our suspicion of malignancy.

The caveat for this study was the limited sample size, particularly in malignant lesions. Therefore, more studies should be conducted.

CONCLUSION

The age of malignant cutaneous melanocytic lesions was older than benign lesions. Male gender, lower extremitu location, tumor size >6 mm, asymetry, cytological atypia, suprabasal melanocyte, dermal mitosis and dermal lymphocytic infiltrate correlated with malignant behavior.

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