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Research Article

Prediction of Melanoma Behavior with Ubiquitous Features

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ABSTRACT

Melanoma is a devastating form of skin cancer and is the 5th most common cause of cancer deaths in the United States. Melanoma is responsible for the majority of skin cancer related death in the United States as well. Melanoma behaves in an unpredictable manner and can invade, metastasize, and recur without detection. Observable features such as pagetoid melanocytosis, highest epidermal strata occupied by pagetoid melanocytes, largest melanocytic nest present (LNS), smallest melanocytic nest present (SNS), and the LNS:SNS ratio may aid in predicting a melanocytic malignancy's behavior by providing clues regarding whether a lesion has a propensity to invade, and possibly even how deep the lesion may invade. This single institutional study follows 36 patients and examines 37 formalin-fixed paraffin-embedded tissue specimens mounted on glass slides and stained with Hematoxylin and Eosin. The study investigates numerous factors that may provide clues to the diagnostician and clinician regarding a specific malignant melanocytic lesion's behavior.

Keywords: Melanoma; Pagetoid scatter; Pagetoid melanocytosis; Melanocytic nest; Melanocytic nest size; Invasive Melanoma; Melanocyte behavior

INTRODUCTION

Melanoma is a devastating form of skin cancer which manifests as a malignant melanocytic proliferation that clinically presents as irregular papules, patches, or plaques on the skin. Melanoma is responsible for the vast majority of skin cancer-related deaths in the United States. The incidence of malignant melanoma is rapidly increasing worldwide, and this increase is occurring at a faster rate than that of any other cancer except lung cancer in women [1]. The average age at diagnosis is 57 years, and up to 75% of patients are younger than 70 years of age. Melanoma is more common in Caucasian patients than in African- American and Asian patients [2]. Melanoma is notorious for affecting young and middle-aged people, unlike other solid tumors which mainly affect older adults. It is commonly found in patients younger than 55 and it accounts for the third highest number of lives lost across all cancers. In 2012, 232,000 new cases of melanoma and 55,000 deaths were registered worldwide, ranking 15th among most common cancers worldwide [3]. Known risk factors of melanoma include genetic abnormalities such as xeroderma pigmentosum, familial atypical multiple moles and melanoma syndrome, BRCA2 mutation, and congenital melanocytic nevi [4]. Atypical mole syndromes formerly termed B-K mole syndrome, dysplastic nevus syndrome, and familial atypical multiple mole melanoma, increase the ten year risk of melanoma by 10.7% vs. 0.62% of controls. There is a parallel relationship between melanoma incidence risk and the number of family members affected, and there was nearly a 100% risk of disease if two or more relatives had dysplastic nevi and melanoma [2].

Environmental factors like chronic or intermittent exposure to significant ultraviolent (UV) radiation, especially before the age of 35, significantly increases the risk of melanoma [5]. UV-A sunlight has been implicated as a cause of melanoma (e.g., tanning salon-related UV radiation), but most skin damage is actually caused by UV-B rays. Chronic immunosuppression is another exposure related risk factor for melanoma development in that if a patient is immunosuppressed because of an existing neoplastic condition or is being treated for an existing neoplasm with chemotherapeutics, the risk for melanoma increases fourfold. For example, approximately 5% of patients with a personal history of melanoma will be diagnosed with a second melanoma [1].

The populations that are at increased risk for melanoma are those with inherited phenotypic traits associated with fair skin, light hair, red hair, freckles, and light eye color. A positive family history of melanoma can be a strong risk factor for the evolution of this disease. With an increased number of first-degree relatives with melanoma, the risk of developing the disease increases. Patients with one first-degree relative with melanoma are 1.7 times more likely to be diagnosed with melanoma, whereas those patients with two first-degree relatives are at a nine-fold increase in risk. In addition, as patients with a positive family history grow older,

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the cumulative risk of developing melanoma also increases. Lower socioeconomic status (SES) has been linked to more advanced disease at the time of detection. One survey of newly diagnosed patients found that low-SES individuals have decreased melanoma risk perception and knowledge of the disease [2].

Melanocytes are neural crest derived cells that are found in the stratum basale of the epidermis, hair follicles, mucosal surfaces, meninges, and in the choroidal layer of the eye. In response to UV radiation, skin keratinocytes produce melanocyte- stimulating hormone (MSH) that binds the melanocortin receptor 1 (MC1R) on melanocytes that then produce and release melanin. Melanin is absorbed by keratinocytes to operate as a shield from further UV radiation and preventing further DNA alteration [6]. On chronically or intermittently sun exposed skin surfaces such as the head, neck, and dorsal aspects of the upper extremities, the mutation burden becomes dangerously high and oncogenic drivers such as B-Raf protooncogene (BRAF), neurofibromin 1 (NF1), and NRAS become activated. This will lead to uncontrolled replication of the mutated melanocytes and eventually melanoma [7]. There are also certain benign melanocyticlesions which are considered precursors of melanoma such as the common acquired nevus, dysplastic nevus, congenital nevus, and cellular blue nevus.

Numerous variants of melanoma exist, but some of the most common variants seen in practice include superficial spreading melanoma in situ (50%-75% of cases), nodular melanoma (15%-53% of cases), lentigo maligna (5%-15% of cases), and acral lentiginous melanoma (5%-10% of cases). Superficial spreading melanoma (SSM) is more commonly seen on the trunk in males and the legs in females. Nodular Melanoma (NM) can affect patients at any age, has only a vertical growth component, and can appear as a blue-black nodular, polypoid, or pedunculated lesion with possible ulceration. Lentigo Maligna (LM) most commonly occurs in the elderly, and mostly appears on the face and upper extremities. Unique features which can be seen in LM are multinucleated melanocytes with prominent dendritic processes ("starburst giant cell"). Acral Lentiginous Melanoma (ALM) is a variant of melanoma that is seen underneath fingernails, can be often seen in elderly males, and is commonly seen in African American and Asian patients.

To prevent the progression of nevi to melanoma, clinicians and dermatologists regularly evaluate existing nevi on their patients'. Skin and look for the worrisome features of melanoma. These include asymmetry, irregular borders, color variations (especially red, white, and blue tones in a brown or black lesion), a diameter greater than 6 mm, and an elevated surface. These gross clinical features are the ABCDE's of melanoma. They can help guide clinicians towards the necessity of performing a full-thickness excisional biopsy on the suggestive lesion for pathologist evaluation. Indicators of poor disease prognosis are male gender and an anatomic site of the trunk or face. Both locations portend to a worse prognosis than extremity lesions [2].

Currently, many morphological features are reported according to the College of American Pathology (CAP) cancer summaries including mitotic rate, microsatellitosis, regression, lymphovascular invasion, perineural invasion, and tumor infiltrating lymphocytes. Although only two have proven to correlate with prognosis and overall survival, the Breslow depth and ulceration status [8]. Pagetoid scatter of melanocytes is defined as the abnormal movement of melanocytes vertically and horizontally through the epidermal strata, rather than remaining in the basal layer where they normally reside. This histologic feature is mentioned in the literature but has not been linked to melanoma behavior or prognosis. Vesna et al. says pagetoid melanocytosis in melanoma has been interpreted as due to an active infiltrative process, in a fashion similar to mammary or extramammary Paget's disease [9]. Pagetoid spread of melanocytes, when it represents malignancy, is probably an active infiltrative process even in melanoma in situ, but a passive 'passenger' mechanism via the maturing keratinocytic flow is also plausible [10].

Melanocytes form clusters of cells designated as "nests" which are normally seen at the base of rete ridges in benign nevi. These are junctional nests. Haridas et al. says cell proliferation and cell migration are two potential mechanisms that could conceivably drive melanoma nest formation [11,12]. In cases of melanoma, nests can be situated in abnormal locations which may include anywhere within the epidermis and/or dermis. Keratinocyte necrosis is a common feature seen in most cases of melanoma that appear as keratinocytes with hyperchromatic nuclei often with an artifactual intracellular retraction. The quantities of pagetoid melanocytes present within the "hotspot", nest size, nest size ratio, and keratinocyte necrosis have not been found to be associated with melanoma behavior in the literature. During the process of performing this investigation, it has been revealed that pagetoid scatter of melanocytes, and nest size can indeed be related to a melanocytic malignancy's behavior.

MATERIALS AND METHOD

This single institutional retrospective and introspective study involves 37 specimens diagnosed as melanoma and follows 36 patients. Four major variants of melanoma were included in the study, SSM, NM, LM, and ALM. After institutional review board approval, the hospital pathology database, PowerPath©, was searched for cases of in situ and invasive melanoma diagnosed between 2010 and 2018 to look for cases that were suitable and appropriate to be included in the study. Keywords and phrases such as melanoma, and invasive-melanoma were used to search for cases. The study's patient demographics include patients with a current age ranging from 37 to 98 years of age. Our study includes 20 females and 16 males. Many features were meticulously examined for each case, including, tumor site and size, major patient diagnoses, melanoma variant, growth phase, highest epidermal strata occupied by pagetoid melanocytes, number of pagetoid melanocytes in the "hotspot" on one High Powered Field (HPF), Smallest Nest Size (SNS), Largest Nest Size (LNS), ulceration, invasion, and margin status, and depth of invasion. Additional features examined include, Tumor Regression (TR), Lymphovascular Invasion (LVI), Perineural Invasion (PNI), Microsatellitosis, Tumor-Infiltrating Lymphocytes (TIL), Mitotic Rate (MR), lymph node status and size, extra-nodal extension, pathologic stage, metastasis, recurrence, immune-histochemical stains, and mutation status.

The tumor site utilized was the site provided by the clinician in the pathology requisition form. The tumor size was the largest dimension provided in or extrapolated from the gross examination report section of the pathology report. Patient clinical history and follow-up data (if available) was recorded from the central hospital EMR system. This included demographic details such as age, gender, race, adverse events (recurrence, metastasis, or death from disease), last follow-up date, lactate dehydrogenase (LDH) levels, marital status, and major patient diagnoses, all of which was recorded from our Horizon WP Physician Portal© and athena Collector© EMR systems. The variant of melanoma, growth phase,

ulceration status, invasion status, depth, margin status, TR, LVI, PNI, micro-satellitosis, TIL, MR, lymph node and extra-nodal extension status, pathologic stage, stains, and mutation status were recorded from the pathology report from the time of diagnosis which were reconfirmed by the primary investigator when possible. The number of pagetoid melanocytes in the "hotspot" on one HPF was meticulously examined, counted, and recounted by the primary investigator.

A "hotspot" in this study is an area within the center of the malignant melanocytic proliferation that had the most pagetoid melanocytes present. The "hotspot" utilized to perform the quantitation of pagetoid melanocytes is uniquely located in each case. The epidermal "hotspot" was where the quantity of pagetoid melanocytes appears to be greatest, regardless of what epidermal strata are occupied by pagetoid melanocytes. Strict inclusion criteria were defined and implemented for melanocytes in abnormal locations to be counted as "Pagetoid Melanocytes" (PM). A PM is defined as an apparent melanocyte that was situated above the stratum basale and occupied any higher epidermal strata. Cells included in the count of pagetoid melanocytes had to be larger than most keratinocytes, irregular, pleomorphic, present between keratinocytes, have a large nucleus, abundant cytoplasm (clear, eosinophilic, or pigmented), and have intracytoplasmic or intra-nuclear vacuoles. In addition, the cells should not have desmosomes connecting the cell to adjacent cells, and not be a necrotic keratinocyte, which can appear similar to a pagetoid melanocyte.

A "necrotic keratinocyte" is defined as a keratinocyte that has an irregular, hyperchromatic nucleus, with artifactual intracellular clefting, involution, and vacuolization in a cell that is connected to adjacent cells by desmosomes and matures as it occupies higher epidermal strata. Cell counts are performed with a standard manual metal counter. The smallest and largest nests chosen are the smallest and largest apparent nests histologically identified on the same slice of the tumor on which the other two counts are performed (Table1).

Table 1: Melanoma variants in study.

Superficial spreading	Nodular melanoma	Lentigo maligna	Spindle cell	Acral lentiginous
19	4	4	1	1

The SNS and LNS are also uniquely located in every case and may differ between sections. The measurements were performed while utilizing an ocular micrometer from Nikon© on 100x magnification and measuring the apparent largest or smallest nest parallel to the center of the long axis of the nest. The nests that were included in the study were predominantly junctional/intraepidermal nests unless the case did not permit this measurement due to a lack of epidermal nests, in which case, dermal nests were utilized for the measurement. A ratio of the largest nest size to smallest nest size present in a case was developed and calculated by dividing the size in micrometers of the largest nest found in a particular case to the smallest nest identified in the same case and slice. The highest epidermal strata occupied by pagetoid melanocytes are also identified on the same slice. The epidermal strata utilized for these observations were the stratum spinosum, granulosum, lucidum (when appropriate), and corneum (Tables 2 and 3).

Specimens utilized in the study were formalin-fixed paraffin-embedded tissues that were mounted on glass slides and stained with Hematoxylin and Eosin. Microscopic examination was performed with an Olympus CX21 compound microscope at 40, 100, and 400 times magnification. Data documentation and statistical analyses were performed with the Microsoft Excel© application.

DISCUSSION

Melanoma is a devastating disease and the most devastating form of skin cancer, with high rates of recurrence and metastasis to local lymph nodes and distant sites. We performed this study to investigate features and factors that might not be examined at the present during a melanoma diagnostic evaluation, and to shed light upon their utility. The study was retrospectively and introspectively performed by examining each patient's tissue specimens and thoroughly examining their medical records for relevant information. The study followed 36 patients and examined 37 specimens. Patients range in age at first diagnosis from 34 to 97 years of age with the greatest percentages of patients in their 5th (8/36), 6th (8/36), and 7th (8/36) decade of life. There were 16 male patients and 20 female patients included in this investigation. The anatomical sites affected by melanoma included the head, neck, chest, abdomen, back, and bilateral upper and lower extremities with majority of the cases located on a patient's head (9/36), back (8/36), and right upper extremity (6/36). The majority (35/36) of the patients present in the study were documented in our EMR as Caucasian, the remaining patient was reported as other (Table 4).

The variants of melanoma that were studied in our investigation included, superficial spreading, nodular, lentigo maligna, spindle cell, and acral lentiginous. Attending pathologists classified the largest percentage of cases (12/36) as the superficial spreading variant at the time of diagnosis and case sign-out. There were 26 cases of invasive melanoma and 10 cases of melanoma in situ included in the study. The two highest epidermal strata that were occupied by pagetoid melanocytes were the stratum corneum (24/36) and the stratum granulosum (10/36) (Tables 5 and 6).

One of the hypotheses of this investigation was the idea that with pagetoid melanocytes occupying higher epidermal strata, there will be less of a propensity to invade through the dermo- epidermal junction into the papillary dermis and beyond.

Table 2: Invasive vs In situ cases.

Invasive melanoma	In situ melanoma
26	10

Table 3: Anatomical sites of lesions.

Head	Neck	Chest	Abdomen	Back	Right upper extremity	Left upper extremity	Right lower extremity	Left lower extremity
9	1	2	3	8	6	1	3	3

Table 4: Gender distribution of study.

Male	Female
16	20

Table 5: Highest epidermal strata occupied by pagetoid melanocytes.

Stratum spinosum	Stratum granulosum	Stratum lucidum	Stratum corneum
2	10	0	24

Table 6: Miscellaneous features present.

Features	Nos
Ulceration	9
Tumor regression	1
Lymphovascular invasion	1
Perineural invasion	0
Microsatellitosis	0
Tumor Infiltrating Lymphocytes, Brisk	7
Tumor Infiltrating Lymphocytes, Non-Brisk	19
Metastasis status	4
Recurrence status	8
Stains performed	SOX-10: 7; S-100: 2; MART-1: 2; HMB-45: 1
Associated nevi	14
Sentinel lymph nodes taken	6 Cases
Lymph nodes positive	2 Positive Cases
BRAF mutation analysis performed	3
BRAF positive	1
Radial growth phase	16
Vertical growth phase	20

Through the course of this investigation, our data validated this hypothesis. 7/10 cases of melanoma in situ had pagetoid melanocytes in the stratum corneum (which is the highest epidermal stratum), and 3/10 cases of melanoma in situ had pagetoid melanocytes as high as the stratum granulosum (which is the second highest stratum of skin present in non-acral skin). All 10 of the melanoma in situ cases had pagetoid melanocytes occupying higher epidermal strata.

There were two cases where the highest epidermal strata occupied by pagetoid melanocytes was the stratum spinosum (this is the penultimate epidermal stratum), and both cases involved an invasive form of melanoma. The lesions studied in this investigation ranged in size from 0.3 cm-3.2 cm with the largest percentage of lesions (14/36) measuring less than 1 cm. Invasive lesions ranged in depth of invasion from 0.2 mm-7.38 mm, and the largest percentage of lesions (12/26) measured less than 0.5 mm in Breslow depth (Tables 7 and 8).

Melanocytic nests ranged in size from 0.2 μm to 13000 μm. The largest percentage of cases in the category of "smallest nest size" (30/37) are less than 0.5 μm in greatest dimension. The largest percentage of cases in the category "largest nest size" (13/37) are less than 5 μm in greatest dimension. A ratio of largest nest size to smallest nest size was hypothesized and calculated. The LNS:SNS ratios ranged from 1 to 1007 and the largest percentage (13/37) of cases had an LNS:SNS ratio of less than 20. Pagetoid melanocytosis is a feature that has been described in the literature but in the PubMed© search conducted by the primary investigator, using keywords pagetoid, scatter, behavior, depth, invasion, etc., a correlation between pagetoid scatter, lesion behavior, or depth of invasion was not identified (Tables 9 and 10). A negative correlation was found between the number of pagetoid melanocytes in a case and the depth of tumor invasion with a coefficient of -0.16, which was calculated by Excel©.

Table 7: Tumor size (cm).

Range	Nos
Less than 0.5	9
Less than 1.0	14
Less than 2.0	9
Greater than 2.0	4

Table 8: Depth of invasion (mm).

Range	Nos
0	9
Less than 0.5	12
Less than 1.0	6
Less than 2.0	3
Greater than 2.0	6

Table 9: Patient age distribution at first diagnosis (decade of life).

4th	5th	6th	7th	8th	9th	10th
1	8	8	8	7	3	1

Table 10: Smallest nest size (micrometers).

Less than 0.5	Less than 1.0	Less than 2.0	Greater than 2.0
30	4	2	1

The interpretation for this value is, with a higher number of pagetoid melanocytes that are present in higher epidermal strata, either no invasion or a decreased depth of invasion can be observed (Figure 1). Demonstrates decreased depth of invasion or no invasion present in cases with greater numbers of pagetoid melanocytes. The relationship between the two variables appear to be inverse and has a linear downslope (Tables 11 and 12). The cases with the highest numbers of pagetoid melanocytes had little or no invasion. This phenomenon is hypothesized to occur because with most of themelanocytes that had the propensity for pagetoid scatter being occupied by invading the upper epidermis, very few PMs may invade the dermis. There was a positive correlation between the number of pagetoid melanocytes and the LNS:SNS ratio found with a coefficient of 0.011 (Figure 2).

This value is interpreted as, with increased numbers of pagetoid melanocytes, there is a propensity for larger nest formation. This finding was supported with a negative correlation between the number of pagetoid melanocytes and the smallest nest size present with a coefficient of -0.07. This negative correlation was interpreted as, with an increased quantity of pagetoid melanocytes, the likelihood of having smaller nest sizes present within the same case is decreased. A positive correlation was found between the LNS:SNS ratio and depth of invasion with the coefficient calculated as 0.8. This was interpreted as, with larger nests present in a case, there is a higher probability of invasive disease and possibly deeper invasion. This calculation was supported with the finding that 7/7 cases present in the study that had a depth of invasion greater than 1 mm had an LNS:SNS ratio of greater than or equal to 10. There is also a negative correlation between tumor size and the number of pagetoid melanocytes with a coefficient of -0.03. This value was interpreted as, in a large tumor, there may be a lower quantity of pagetoid melanocytes. This phenomenon was hypothesized as, in cases involving larger lesions, the majority of the malignant melanocytes with pagetoid propensity had found their way into the dermis instead of wandering into the upper epidermis. This finding was further reconciled by the finding that a majority of cases (10/12) present in the study that measured greater or equal to 1 cm were invasive, while 2/12 cases that had a lesion greater than or equal to 1 cm were in situ. Table 13 provides details regarding the presence of numerous features that are currently included in the CAP protocol and are regarded as features that are crucial to evaluate in every case of melanoma (Figure 3).

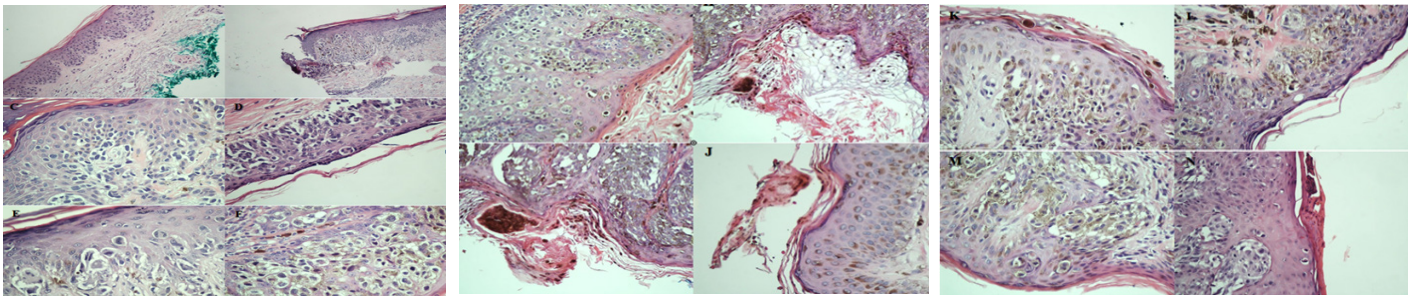

Figure 1: The 14 photomicrographs above are examples of the features that were utilized to include cells in the PM count, including large size, irregularity, pleomorphism, presence between keratinocytes, large nucleus, abundant cytoplasm (clear, eosinophilic, or pigmented), intracytoplasmic or intra-nuclear vacuoles, and no desmosomes connecting the cell to adjacent cells. (A-D) Intermediate (10x) and High (20x and 40x) power photomicrographs of "buckshot scatter" and nested patterns of pagetoid melanocytes dispersed throughout the epithelium and occupying the stratum basale, stratum spinosum, and stratum granulosum. There are PMs invading the papillary and reticular dermis in images B and C. There is moderate vacuolation of the dermal-epidermal junction in image (D-E) High (40x) power photomicrograph of pagetoid melanocytes in a "buckshot scatter" pattern with vacuolation around individual cells and clusters of cells. There is also evidence of melanocyte necrosis with nuclear pyknosis and cytoplasmic degeneration. The malignant cells are not extending beyond the stratum spinosum and appear to be pushing into the reticular dermis. (F) High (40x) power photomicrograph of clusters of PMs in a nested pattern and single melanocytes occupying the entire epidermis up to and including the stratum corneum. PMs are percolating vertically through the epidermis in a single file between nested PMs. Many PMs are producing and retaining melanin within their cytoplasm. (G-J) High (20x and 40x) power photomicrographs of malignant pagetoid melanocytes in a "buckshot scatter" pattern occupying all levels of the epidermis including the stratum corneum. Images H and I show pagetoid melanocytes in a nested pattern with melanin pigment production and retention that are occupying the stratum corneum. Image I shows large nests of malignant melanocytes at the dermal-epidermal junction and in abnormal locations within the epidermis. (K-N) High (20x and 40x) power photomicrographs of malignant pagetoid melanocytes occupying all layers of the epidermis including the stratum corneum in images K and N. The PMs are invading into the dermis in images K and L.

Table 11: Largest nest size (micrometers).

Less than 1.0	Less than 2.0	Less than 5	Greater than 5
5	11	13	8

Table 12: LNS:SNS ratio distribution.

Less than 5	Less than 10	Less than 20	Greater than 20
11	10	13	3

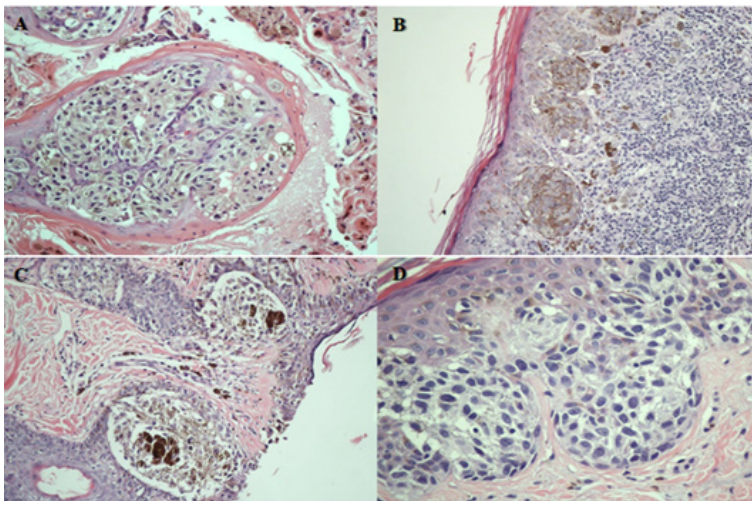

Figure 2: The above four photomicrographs are examples of malignant melanocytic nests which were measured. (A-D) High (20x and 40x) power photomicrographs of medium to large malignant melanocytic nests occupying the dermal-epidermal junction and abnormal locations within the epidermis. Image A shows clusters of smaller nests separated by a thin septae producing one large confluent nest. Image B shows nests of various sizes occupying different points in the epidermis along the dermal- epidermal junction. There is massive dermal lymphocytic infiltration in an effort to combat the invading malignant melanocytes in the dermis that are expressing and retaining melanin pigment. Image C shows prominent vacuolation around nests with melanocytes within nests producing and retaining melanin pigment. One nest in image C is so large that it occupies most of the length of the epidermis.

Table 13: Pagetoid melanocyte distribution.

Less than 10	Less than 20	Less than 50	Greater than 50
1	10	20	3

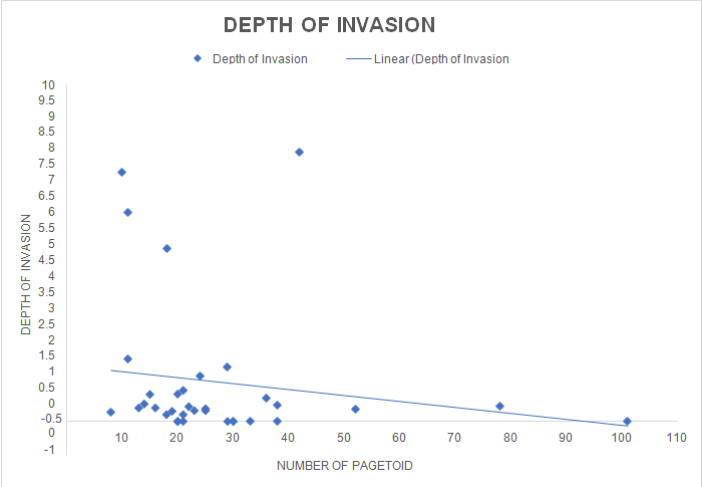

Figure 3: Graph demonstrating a linear relationship between Depth of Invasion (mm) to number of PM.

CONCLUSION

Through the course of performing this study several findings have been elucidated. The most significant finding of our study is that when a majority of the mutated pagetoid melanocytes in a lesion are occupied by invading higher epidermal strata, there can be a correlation with either no invasion or decreased depth of invasion. This correlation was supported with the study finding where 8 of the 10 cases of melanoma in situ included had greater than or equal to 20 pagetoid melanocytes present in the case's unique "hotspot". The finding is further supported by the fact that 6 out of 8 cases with a Breslow depth greater than or equal to 1 mm have less than 20 pagetoid melanocytes present in the "hotspot". Another significant finding revealed in this study is that when pagetoid melanocytes climb higher into the epidermis there is a possibility that the lesion may remain in situ or may not invade deeply into the dermis. This revelation was supported by the fact that all 10 cases of melanoma in situ have melanocytes occupying

the highest epidermal strata.

More rampant pagetoid melanocytosis also led to the presence of larger melanocytic nests, which is especially important for cases involving invasive melanoma. This finding is supported by a negative correlation between pagetoid melanocytes and smaller nest sizes.

Lesions which were larger in size had fewer pagetoid melanocytes, and in larger lesions, there were either no PMs or there were decreased quantities of pagetoid melanocytes present as compared to cases with smaller lesions. The quantity of necrotic keratinocytes in a case had no apparent correlation with disease behavior.

These findings may provide clues to forecast how a lesion might behave through the inspection of the features described. Histologic features such as numerical quantity of pagetoid melanocytes, highest epidermal strata occupied by pagetoid melanocytes, the size of the largest and smallest nest present in a case, and the LNS:SNS ratio may assist in predicting the probability and likelihood of invasion and possibly the depth of invasion.

CONFLICT OF INTEREST

The author declares that they have no conflict of interest and has received no funding for this study.

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