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Research Article

Patterns of Invasive Tumour Border in Cutaneous Melanoma are Associated with Prognostic Indicators

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Abstract

The pattern of histological invasion observed in certain malignancies such as colorectal carcinoma and breast carcinoma has been shown to be associated with prognosis. To date the prognostic significance of the histological pattern of invasion has not been described in malignant melanoma. We evaluated the histologic invasive border pattern in a series of 76 malignant melanomas to determine its relationship with other clinical and prognostic pathologic variables. Lymphovascular invasion, perineural invasion and precursor naevus were observed more commonly in melanomas with an infiltrative compared to a pushing border (9.0% vs 4.6%; 15.0% vs 9.3%; and 21.0% vs 14.0%, respectively). Ulceration was seen almost twice as commonly in the pushing compared to the infiltrative variant (30.2% vs. 15.0%), and regression was also more commonly observed in melanomas with a pushing versus an infiltrative border (16.3% vs 9.0%). No difference was seen with gender, age, tumour location, size, subtype, pigmentation, Breslow thickness, lymphocytic infiltrate or mitoses. We suggest that tumour border pattern be included in pathology synoptic reporting of malignant melanomas to facilitate further research and potential clinical application.

Keywords: Malignant Melanoma; Melanoma Tumour Border; Lymphovascular Invasion; Perineural Invasion; Ulceration; Regression

Introduction

Cutaneous melanoma is the most rapidly increasing cancer in white populations [1]. The histology report remains vital for staging of the melanoma and guiding further investigations and treatment. The pattern of histological invasion observed in certain malignancies such as colorectal carcinoma has been shown to be associated with prognosis [2]. In aggressive colorectal carcinoma, an extensive dissection of host tissue is seen with loss of a clear tumor–host interface. This pattern, termed "infiltrative tumor border configuration" has been consistently associated with poor survival outcome and early disease recurrence. [3]. Consequently, assessment of the tumor border configuration as an additional prognostic factor is recommended by the AJCC/UICC to aid the TNM-classification in colorectal carcinoma. By contrast a pushing border in breast cancer is associated with a triple negative phenotype and a worse prognosis [4]. To date the prognostic significance of the histological pattern of invasion has not been described in malignant melanoma.

We evaluated the histologic invasive border pattern in a series of malignant melanomas to determine its relationship with other clinical and prognostic pathologic variables. We reviewed 76 cases diagnosed as primary cutaneous invasive melanoma from 2015 to 2020. Clinical data and pathologic tumour checklist parameters were obtained from patient records including patient gender, age, tumour location, size and subtype, pigmentation, Breslow thickness, ulceration, vascular/perineural invasion, lymphocytic infiltrate, mitoses, regression, and presence of precursor naevus. Slides

were reviewed with an infiltrative border defined as an irregular border with single cells or small clusters of 2-4 cells, and a pushing border as a solid tumour front or a front with nodules and/or large, medium, and/or small nests of 5 or more cells. An infiltrative border was observed in 33 cases and a pushing border in 43. Lymphovascular invasion, perineural invasion and precursor naevus were observed more commonly in melanomas with an infiltrative border. Ulceration and regression were more commonly observed in melanomas with a pushing border. No difference was seen with other clinical or pathologic variables.

Material and Methods

Seventy-five cases diagnosed as primary cutaneous invasive melanoma from 2015 to 2020 were retrieved from the Sligo University Hospital pathology tissue archives for clinical audit. Clinical data and pathologic tumour checklist parameters were obtained from anonymized histopathology reports. These included gender, age, tumour location, size and subtype, pigmentation, Breslow thickness, ulceration, vascular/perineural invasion, lymphocytic infiltrate, mitoses, regression, and presence of precursor naevus. Hematoxylin and eosin-stained sections and immunohistochemistry slides of Melan-A and HMB-45 were available for each case. Slides were reviewed by a consultant histopathologist and non-consultant senior dermatology registrar to determine the invasive border pattern as either infiltrative or pushing. An infiltrative border was defined as a tumour with single cells or small clusters of 2-4 cells. A pushing border was defined as a solid tumour front or a front with nodules and/or large, medium, and/or small nests of 5 or more cells. We evaluated the pattern of melanoma invasion in the context of the other clinical and pathologic variables. Fisher's exact test was used to determine statistical significance.

Results and Discussion

Of the 76 cases examined, an infiltrative border was observed in 33 and a pushing border in 43 melanomas. Although not statistically significant, lymphovascular invasion, perineural invasion and precursor naevus were observed more commonly in melanomas with an infiltrative compared to a pushing border (lymphovascular invasion, 9.0% vs 4.6%, perineural invasion, 15.0% vs 9.3%, and precursor naevus, 21.0% vs 14.0%). Ulceration was seen almost twice as commonly in the pushing compared to the infiltrative variant (30.2% vs. 15.0%), and regression was also more commonly observed in melanomas with a pushing versus an infiltrative border (16.3% vs 9.0%: Table 1). Breslow thickness was similar in both invasive patterns. There was no difference with respect to age, gender, anatomical location, subtype, mitoses or tumour infiltrating lymphocytes between the pushing and infiltrative groups.

Malignant melanoma tumour border	Lymphovascular invasion	Perineural invasion	Precursor naevus	Ulceration	Regression
Infiltrative n = 33	9.0%	15.0%	21.0%	15.0%	9.0%
Pushing n = 43	4.6%	9.3%	14.0%	30.2%	16.3%

Table 1: Prevalence of prognostic pathologic variables in infiltrative and pushing melanoma tumour border.

The pattern of histological invasion observed in certain malignancies such as colorectal carcinoma and breast carcinoma has been shown to be associated with prognosis [2]. In colorectal adenocarcinoma, infiltrative tumour border, or tumour budding, has been associated with poor survival outcome and early disease recurrence [3]. Consequently, assessment of the tumour border as an additional prognostic factor is recommended by the AJCC/UICC to be included in pathology tumour synoptic reports and to aid the TNM-classification. In contrast, a pushing border in breast cancer is associated with a triple negative phenotype and a worse prognosis. [4] To date the prognostic significance of the histological pattern of invasion has not been described in malignant melanoma. We evaluated the histologic invasive border pattern in a series of 75 malignant melanomas to determine its relationship with other clinical and prognostic pathologic parameters.

Clinical border irregularity of pigmented cutaneous lesions is recognised as an important feature for clinicians and patients to identify lesions that could be melanoma [5,6]. Aside from well-established literature on the importance of depth of invasion and vertical growth, [7-10] reports on histologic tumour border in invasive malignant melanomas are surprisingly sparse and inconsistent. While advancing tumour edge was found to be unrelated to growth and metastases in a study of 32 fast-growing malignant melano-

mas, [11] pushing dermal borders were associated with poor prognosis in a series of 57 reviewed cases of malignant melanoma in teenagers. [12] Although there is a paucity of research on histologic tumour border in malignant melanoma, the tumour-stroma connection and extracellular matrix appear crucial to the regulation of neoplastic growth, invasiveness and initial metastases [13,14]. It follows that tumour border histologic characteristics, to the extent they are included in tumour-stroma connection and extracellular matrix interactions, are likely involved.

In our study of 76 malignant melanomas, we found ulceration and regression to be associated with a pushing tumour border (Figure 1). Ulceration is a well-known negative prognostic indicator, [15,16] while the prognostic value of regression is controversial [17]. If, as some authors hypothesize, regression indicates a robust systemic immune response, [17] then the underlying commonality with regression and ulceration may be enhanced tumour inflammatory response. The greater coherence of a pushing tumour border may somehow facilitate or be the result of such inflammation. While some constituents of the tumour inflammatory response have tumour-killing effects, others protect tumour cells and promote growth and metastases [18]. We found precursor naevus more commonly observed in melanomas with an infiltrative border (Figure 2). There are known clinical, prognostic and histologic differences between tumours associated with precursor naevi compared to those without [19]. Melanomas developing in association with pre-existing congenital or acquired nevi tend to occur in younger patients, and are more frequently located on the trunk, with a history of frequent sunburns. They also trend towards better overall survival. Pathologically they are usually of the superficial spreading type and harbor the BRAFV600E mutation. Infiltrative tumour border may be another correlate of precursor naevus-associated malignant melanomas. Finally, and perhaps more intuitively, we found infiltrative tumour border in melanomas more commonly associated with conventionally negative prognostic factors of lymphovascular and perineural invasion [20,21]. This is similar to infiltrative tumour border being associated with a negative prognosis in colorectal adenocarcinoma [2,3].

Figure 1: Pushing tumour border in malignant melanoma, H and E (left) and Melan-A (right) stains.

Figure 2: Infiltrative tumour border in malignant melanoma, H and E (left) and Melan-A (right) stains.

Conclusion

In our study of 76 malignant melanomas, we found ulceration and regression to be associated with a pushing tumour border. These variables may have commonalities with tumour inflammatory response. We also found infiltrative tumour border in melanomas more commonly associated with conventionally negative prognostic factors of lymphovascular and perineural invasion. Additionally, infiltrative tumour border may be another correlate of precursor naevus-associated malignant melanomas. Future work with larger samples and clinical outcome data would be useful. We suggest that tumour border pattern be included in pathology synoptic reporting of malignant melanomas to facilitate further research and potential clinical application.

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