Background: The incidence of nodular melanoma (NM) has been consistently described as at least 10-15% of total melanomas for over 15 years despite advances in diagnostic algorithms and medical technology. NMs are strongly correlated with faster rates of growth and poorer prognosis and thus provide clinicians with a challenge for early recognition.

Objective: To evaluate diagnostic clues of consecutive histopathologically proven NMs in one general practice with particular emphasis on dermatoscopic characteristics and compare this to the published literature.

Method: A retrospective observational study was performed of five consecutive histologically proven NM, from a total of 212 consecutive melanomas from a general practice in Brisbane, Queensland, Australia. Dermatoscopic images, both polarized and non-polarized, which appears to be a unique resource, and dermatopathologic slides were available for all lesions.

Results: All of the NMs in this series were pigmented although one was hypomelanotic. Two of them were symmetrical. The most highly sensitive clues to NM were gray or blue structures and polarizing-specific white lines.

Limitations: Due to the small number of NMs in this report no statistical significance can be attributed to the observational findings.

Conclusion: This small series supports what is already known: that a significant proportion of NMs may be dermatoscopically symmetrical but that known clues to melanoma are frequently present. Nodular lesions, pigmented or non-pigmented, should be excised to exclude NM if there is any clue to malignancy, regardless of symmetry, unless a confident specific benign diagnosis can be made.
Introduction

Nodular melanoma (NM), defined as a melanoma with any junctional component extending no more than three rete ridges beyond the invasive component, is the second largest melanoma subtype, comprising 10-15% of melanomas in Caucasians [1]. NMs have been shown to have a faster growth rate (GR) (median GR 0.49 mm/month) than lentigo maligna melanomas (median GR 0.13 mm/month) and superficial spreading melanomas (SSM) (median GR 0.12 mm/month) [2]. The GR of malignant melanomas (MM) has also been shown to be an independent prognostic indicator for the prediction of relapse after one year of follow up [3]. Studies have been performed in an attempt to determine diagnostic features, both clinical and dermoscopic, which facilitate earlier diagnosis of NM, when Breslow thickness is less and prognosis therefore more favorable [4]. A general practice, with a special interest in skin cancer medicine and dermoscopic photo-documentation of all treated lesions, provides a unique perspective on the evaluation of this condition.

Methods

A retrospective analysis was performed with respect to all NMs diagnosed between January 1, 2008, and June 30, 2013, in a general practice in Brisbane, Queensland, Australia. All lesions treated were prospectively recorded on the Skin Cancer Audit Research Database (SCARD) for both tracking and research purposes [5]. During the time interval of this study, five NMs were diagnosed from a total of 212 melanomas, 163 (76.8%) in-situ and 49 (23.2%) invasive. The percentage of melanomas which were nodular was therefore 2.4% of total melanomas and 10.2% of invasive melanomas. From January 1, 2008, to June 30, 2013, the ‘Number Needed to Treat’ (NNT) with respect to all melanomas diagnosed in this practice, calculated from the prospectively declared intention to confirm or exclude melanoma, was 5.36 [6].

Photo-documentation was routinely performed on all lesions submitted for histopathology, including clinical, macro and dermoscopic images. Dermatopathologic copy-slides were also collected, catalogued and where appropriate, photographed. Dermatoscopic images were taken of all cases with a DermLite Fluid non-polarizing dermatoscope (3Gen, LLC) coupled to a Canon 50D digital camera (Canon USA, Inc.) and after October 2010, also with either a DermLite II HR polarized or DermLite DL3 (polarized and non-polarized) dermatoscope (3Gen, LLC) coupled to an Olympus E-450 digital camera (Olympus Corporation). Both non-polarized and polarized dermatoscopic images were available for each of the five NM.

Cases

The five cases of histologically diagnosed NM are presented in Tables 1 and 2 with relevant clinical, dermoscopic and dermatopathologic information. In estimation of melanoma growth rate (GR) we used the ratio MM thickness/duration of the MM visible growth as defined in a previously described assessment tool [3]. Clinical images are displayed in Figure 1, close-up images in Figure 2 and dermoscopic and dermatopathologic images of each lesion are displayed in Figures 3 to 7.

| Case | Sex | Age | Skin Type | Previous Melanoma | Self Discovered | Diameter (mm) | Breslow (mm) | Mitotic rate (mm/square) | Ulceration | Growth rate (mm/month) |
|------|-----|-----|-----------|-------------------|----------------|--------------|--------------|--------------------------|------------|----------------------|
| 1    | M   | 42  | 3         | no                | yes            | 4            | 1.35         | 5                        | yes        | 1.30                 |
| 2    | M   | 75  | 3         | no                | yes            | 11           | 5.00         | 9                        | yes        | 3.30                 |
| 3    | M   | 85  | 1         | no                | yes            | 10           | 3.80         | 4                        | yes        | 5.10                 |
| 4    | M   | 58  | 1         | yes               | yes            | 4            | 0.82         | 1                        | yes        | 1.09                 |
| 5    | F   | 62  | 2         | no                | no             | 3            | 0.90         | 1                        | no         | N/K                  |

*Growth rate (GR) is calculated according to a previously published calculation tool as melanoma thickness divided by the duration of visible melanoma growth. The GR was Case 5 was not known as the patient had no knowledge of the lesion. [Copyright ©2014 Rosendahl et al.]
Discussion

The incidence of NMs in this study was 10.2% (n=5/49) of invasive melanomas comparing to 10-15% in published large studies [4].
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the doctor without the patient having any prior awareness of it (Case 5). This compares to the non-nodular melanomas in the same practice where only 9.6% (n= 20/207) were discovered by the patient (of the remainder 14 were discovered by another doctor, 5 by another person and the remainder by the treating practitioner). We believe that this highlights the importance of patient education and awareness in the recognition of abnormal changes in skin lesions but it also illustrates the value of a clinician proceeding to examine the total skin surface when presented with any lesion of concern.

The clinical ABCD method is the most widely known algorithmic method for the clinical diagnosis of melanoma and has been promoted both to healthcare professionals and patients [10]. One of the criteria for melanomas to be detected using this method is that they have a minimum diameter of 6 mm. It has been agreed among many authors that a significant proportion of NMs do not fulfil the ABCD criteria including the criterion of a minimum lesion size of 6mm [8,11]. In one series of eleven thin NMs (Breslow thickness 2 mm or less), 63.6% (n=7/11) had a diameter of less than 6 mm [4]. Similarly, in our series 60% (n=3/5) had a diameter less than 6mm and furthermore, each of these also had a Breslow thickness less than 2 mm.

One study of 1789 patients with melanoma found that NM was most frequently found in older men and most commonly on the lower limbs or head and neck [7]. In addition, it was shown to be more strongly correlated with actinic keratosis rather than high nevi counts [7]. This suggests that NMs have an association with sun-damaged skin. In our series 80% (n= 4/5) were male and 75% (n=3/4) of these males were over 50. With respect to body site, 60% (n=3/5) were on the leg (on sun-damaged skin) and 40% (n=2/5) were on the torso (on non-sun-damaged skin).

In a study involving 92 SSMs and 33 NMs, a higher proportion of NM was discovered by the patient (60.6%) compared to SSM (48.9%) [8], and in a study of 22 patients with NM, 61% were first detected by the patient and another 17% detected by another family member and the patient [9]. In our series 60% (n= 3/5) were reported by the patient and another was known of by the patient, but this information was not volunteered until after the lesion was discovered (Case 4). In one case where the lesion was only 3 mm in diameter and on the posterior torso, it was discovered by

Figure 3. Case 1: (A) Non-polarized dermatoscopic image; (B) Polarized dermatoscopic image; (C, D and E) Dermatopathology images. White lines seen in both dermatoscopy images (perpendicularly orientated in the polarized image) arguably correlate with vertical bands of collagen seen in the dermatopathologic overview (C). A mitotic Figure is seen centrally in (E). [Copyright: ©2014 Rosendahl et al.]

Figure 4. Case 2: (A) Non-polarized dermatoscopic image; (B) Polarized dermatoscopic image; (C, D and E) Dermatopathology images. The polarizing-specific perpendicular white lines are concentrated peripherally (B) and arguably correlate with vertical bands of collagen seen peripherally in the dermatopathologic images (C and D). [Copyright: ©2014 Rosendahl et al.]
10% of the lesion had 78.2% sensitivity for melanoma [14]. The clue of ‘blue-black color’ was present in 60% (n=3/5) of the NMs in our series.

The clues to malignancy of gray or blue structures and polarizing specific white lines (defined as perpendicularly orientated white lines visible only on polarized dermatoscopy) displayed the highest sensitivity for NM in our small consecutive series; each of them (n=5/5) had either one or the other clue and 60% (n=3/5) had both.

With respect to dermatoscopic examination there were some similarities between the melanomas in our series (see Table 2) and those in larger published studies.

It has been shown that in NM many of the classic dermatoscopic features of SSM are lacking, however, irregularity of color is usually present in those that do contain pigment [12]. All of the melanomas in our series contained melanin pigment, although in one (Case 3) 75% of the lesion was non-pigmented and this would categorize it as an amelanotic/hypomelanotic melanoma (AHM) [13].

In our series symmetry was present in 40% (n=2/5; Cases 2 and 5) and if the accompanying nevus was ignored Case 1 was also symmetrical; all were pigmented. The asymmetrical melanomas in our series were asymmetrical in both structure and color. In a published series of 33 NMs, 80% were symmetrical and 60.7% were classified as amelanotic [8]. In another published study 64% (n=7/11) of thin NMs (Breslow 2 mm or less) were symmetrical and 18% (n=2/11) were classified as amelanotic [4].

A study of a series of 283 nodular pigmented lesions found that the presence of blue/black color covering at least 10% of the lesion had 78.2% sensitivity for melanoma [14]. The clue of ‘blue-black color’ was present in 60% (n=3/5) of the NMs in our series.

The clues to malignancy of gray or blue structures and polarizing specific white lines (defined as perpendicularly orientated white lines visible only on polarized dermatoscopy) displayed the highest sensitivity for NM in our small consecutive series; each of them (n=5/5) had either one or the other clue and 60% (n=3/5) had both.

Polarizing-specific white lines were first named ‘chrysalis structures’ [15] and were attributed to the presence of increased collagen, which has birefringent properties causing rapid randomization of polarized light thus making the collagen more conspicuous. In a study by Balagula et al. it was found that in non-biopsied lesions these structures were most commonly found in dermatofibromas and scars, but in 265 biopsied lesions including 20 melanomas they were observed...
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image (Figure 3C). In Case 2, polarizing specific white lines are seen peripherally (centrally is structureless white) and vertical collagen bands are seen peripherally in the dermatopathology image (Figure 4D). In Case 3 no white lines are seen in the non-polarizing image—just a white structureless area—but they are seen centrally in the polarized image. Correspondingly, vertical collagen bands, while not conspicuous in the low power view, are seen centrally in the medium-high power view (Figure 5D). In Case 4 the polarizing-specific lines are actually blue/white and there are no white or blue lines in the non-polarized view, just a very prominent structureless blue area. There is an abundance of collagen evident in the dermatopathology images of this case and significant vertical orientation of this is seen in the medium-high power view (Figure 6D). Case 5 is the exception in our series and contains no dermatoscopic white lines in either the polarized or non-polarized images. Of significance, no vertically oriented bands of collagen are seen in any of the dermatopathological images of this case.

We believe this supports the hypothesis that polarizing-specific white lines represent increased collagen production as vertically orientated bands, probably reflecting increased fibroblast activity related to the vertical growth phase of melanoma [16].

Conclusion

NM is a subtype of melanoma distinct from SSM both dermatopathologically and in its biological behavior. The presentation of five consecutive NMs with both polarized and non-polarized dermatoscopy provides a unique perspective on this lesion and supports what is already known: that a significant proportion of nodular melanomas may be dermatoscopically symmetrical but that known clues to melanoma are frequently present. Every one of these five NMs, whether symmetrical or not, had either gray/blue color or polarizing-specific white lines or both. The hypothesis that perpendicular white lines correlate to vertical bands of collagen related to the growth dynamics of invasive melanoma is supported by the fact that the four NMs in our series which displayed dermatoscopic polarizing-specific white lines also displayed dermatopathologic vertical bands of collagen in the dermis, while the one that did not have this feature had no dermatopathologic vertical collagen bands.

We would suggest that more NMs would be diagnosed earlier if nodular lesions with any known clue to malignancy were considered for biopsy regardless of symmetry. In particular, the clue of polarizing-specific white lines should lead to excision unless a confident specific benign diagnosis, for example, of dermatofibroma, can be made on historic and clinical grounds.
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