Nuclear pseudoinclusions in melanocytic naevi and melanomas

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Abstract

Melanocytes in melanocytic naevi and melanomas can display great variation. The presence of nuclear pseudoinclusions (NPI) is said to be useful in the histological and cytological differential diagnosis of malignant melanoma. The prevalence and characteristics of NPI in a series of 493 naevi and 50 melanomas are described. NPI were found in 31% of adult naevi, 30% of congenital naevi from children, 42% of Spitz naevi, 20% of dysplastic naevi, and 56% of melanomas. The presence of NPI is not a reliable criterion for differentiating melanoma from benign melanocytic lesions, although it is useful in distinguishing melanocytic from non-melanocytic tumours.

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The presence of nuclear pseudoinclusions (NPI) is a sufficiently common and consistent¹ feature of malignant melanomas to attain the status of a "characteristic". The current study found NPI in 56% of 50 malignant melanomas, but also in 31% of benign melanocytic lesions. In practice the diagnosis of malignant melanoma requires a constellation of histological features in which the presence of NPI is a minor criterion.^{2,3} Although NPI may be of value for separating malignant melanomas from other tumours,⁴ NPI do not distinguish melanoma from melanoma simulants or from common acquired naevi.

Methods

Consecutive melanocytic lesions were retrieved from the files of three hospitals. There were 327 intradermal naevi (IDN), 101 compound naevi (CMN) and 20 junctional naevi (JMN) from adult patients, and 23 congenital melanocytic naevi (all greater than 1.5 cm in diameter) from children, 10 dysplastic naevi and

12 Spitz naevi. Fifty malignant melanomas or melanoma deposits were obtained. All tissues had been fixed in 10% formalin/buffered saline, processed, cut, and stained in the conventional manner.

For each lesion, a single cross-section (4 µm thick) was examined. NPI were defined as wholly intranuclear inclusions which occupied more than half of the cross-sectional nuclear area, had a well defined smooth rim, and contained material similar to that of the cytoplasm. Cells with multivesicular nuclei were not included. To determine whether NPI were associated with specific cytoarchitectural patterns, the presence of melanin and the type, location and numbers of cells with pigmented NPI were noted.

Results

Naevi (figure) and melanomas contained NPI (table). In benign lesions NPI were most commonly present in large epithelioid cells (Meisner and Von Albertini⁵ type A cells) although they were found in type B and rarely in type C melanocytes. In common acquired naevi epithelioid melanocytes are most abundant in the superficial dermis of IDN, especially IDN with a papillomatous or raised profile, and the frequency of NPI in IDN reflects this. Of the IDN, 21% contained pigmented NPI, usually in the superficial epithelioid cells in which cytoplasmic pigment is most common. Within a naevus, non-pigmented NPI outnumbered pigmented NPI by a factor of about 10:1. NPI containing pigment may be the only part of a lesion where melanin can be seen on light microscopy in sections stained with haematoxylin and eosin. This characteristic can be useful in establishing that a lesion is melanocytic.²

Apart from cell morphology and the (related) architecture of the naevus, there was no correlation between NPI and the age or sex of the patient or other variables studied. These were artefactual, degenerative or maturational changes, pseudovascular space formation, neurotisation, and the presence of multinucleated cells, lipocytes, cytoplasmic inclusions, and balloon cells (data not shown). Spitz naevi often contained NPI in epithelioid and spindle cells. Dysplastic naevi occasionally showed NPI in large atypical junctional melanocytes. In addition to the benign lesions listed in the table, four cellular blue naevi (two with NPI) and three examples of naevus cell rests in axillary lymph nodes (none with NPI) were examined. Among the melanomas there was wide variation in the percentage with NPI according to histological subtype, with in situ and superficial

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NPI in benign and malignant melanocytic lesions

Lesions	No. of cases	Percentage with NPI
Common naevi	(448)	(31)
intradermal naevus	327	35
compound naevus	101	25
junctional naevus	20	10
Congenital naevus	23	30
Spitz naevus	12	42
Dysplastic naevus	10	20
Malignant melanoma	(50)	(56)
nodular	16	88
superficial spreading with vertical growth	12	42
superficial spreading	9	22
in situ	5	20
subcutaneous or nodal metastasis	8	75

Superficial portion of a papillomatous intradermal melanocytic naevus. NPI are present in several cells. Inset—Oil immersion detail from an intradermal naevus. A melanocyte showing a well defined NPI containing melanin pigment is also present.

spreading variants much less likely to contain NPI than the deeply invasive or metastatic lesions (table).

Discussion

NPI are established as a feature of malignant melanoma^{1-3,6} but, with the exception of Spitz naevi, NPI in naevi have not been studied extensively. The two major points for discussion are whether NPI in naevi should be dismissed as an artefact and whether their presence is of any relevance to the diagnosis of melanoma.

Even if NPI in naevi are regarded as an artefact, they are a consistent finding, being present in naevi and melanomas from three hospitals, and they have been described previously in a few cases.^{4,6,7} If an artefactual feature is consistently expressed by a pathological entity, it is of diagnostic importance. Examples of useful artefacts include characteristic nuclear features of papillary thyroid carcinoma and the subepidermal retraction spaces seen in Spitz naevi.⁸ NPI are a manifestation of nuclear membrane complexity and are not confined to melanocytes. Occasional unpigmented NPI may occur in a wide range of normal tissues and tumours (personal observations)^{4,7} and they have excited study previously. In the early part of the century there was debate as to whether cytoplasmic material was synthesised by the nucleus and secreted via inclusions or was produced in the cytoplasm. Ludford⁹ described the distribution of melanin in an equine melanoma, found pigmented nuclear inclusions and concluded that melanin was produced at both sites. From the 1950s, electron microscopists described true nuclear inclusions and NPI in various tissues, including a small number of melanocytic naevi.⁷ Apart from three small sur-

veys,^{4,6,7} most authors either do not mention NPI in naevi, or regard them as an artefact. By contrast, NPI are established as a feature of malignant melanoma, sometimes in quantitative studies^{1,7} or in general descriptions of melanoma cell morphology.^{2,3}

Despite the stress laid on NPI in melanomas, NPI in naevi are not likely to cause over-diagnosis of malignancy. Firstly, most difficulties occur in interpretation of superficial lesions (junctional, compound, or dysplastic naevi and superficial spreading melanoma). These are the lesions that are least likely to contain NPI, which are usually found in IDN and nodular malignant melanoma. Thus, NPI are largely absent from the lesions in which they would be most confusing. The Spitz naevus, cellular blue naevus and the deep penetrating naevus are exceptions to this rule, as, in addition to the finding of NPI in 42% of Spitz naevi in the current study, they have been described previously in Spitz naevi^{2,4} and in a deep penetrating naevus.¹⁰ Secondly, the differential diagnosis of malignant melanoma relies on a combination of clinical, architectural and cytological criteria, and, in practice, NPI are relegated to a minor role. In cytology architectural features are lost, so cytological features such as nuclear morphology become more important. However, clinicians are unlikely to aspirate benign naevi, and whilst axillary lymph node capsular naevus cell rests can show NPI (illustrated but not discussed in¹¹) they are too rare to cause confusion, especially in the absence of other cytological criteria of malignancy.

In conclusion, experienced pathologists will not make misdiagnoses of melanocytic lesions on the basis of NPI, but their presence in benign lesions has received little attention. They are found in melanoma simulants such as dysplastic, Spitz and cellular blue naevi, as well as in obviously benign congenital and common acquired melanocytic naevi.

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- 1 Layfield LJ, Ostrzega N. Fine needle aspirate smear morphology in metastatic melanoma. *Acta Cytol* 1989;33:606-12.
- 2 Mooi WJ, Krausz T. *Biopsy pathology of melanocytic disorders*. London: Chapman and Hall, 1992.
- 3 Elder DE, Murphy GF. Melanocytic tumours of the skin. In: *Atlas of tumor pathology*. Third series. Fascicle 2. Washington: Armed Forces Institute of Pathology, 1991.
- 4 Barr RJ, King DF. The significance of pseudoinclusions within the nuclei of melanocytes of certain neoplasms. In: Ackerman AB, ed. *Masson monographs in dermatology*. Vol 1. *Pathology of malignant melanoma*. New York: Masson, 1981:269-72.
- 5 Miescher MG, Von Albertini A. Histologie de 100 cas de naevi pigmentaires d'après les méthodes de Masson. *Bull Soc Fr Dermatol Syph* 1935;42:1265-73.
- 6 Apitz K. Über die Pigmentbildung in den Zellkernen melanotischer Geschwülste: I. Beitrag zur Pathologie des Zellkernes. *Virchow Arch A Pathol Anat* 1937;300:89-112.
- 7 Sobel HJ, Schwarz R, Marquet E. Nonviral nuclear inclusions. 1. Cytoplasmic invaginations. *Arch Pathol* 1969;87:179-92.
- 8 Weedon D, Little JH. Spindle and epithelioid cell nevi in children and adults. A review of 211 cases of Spitz nevus. *Cancer* 1977;40:217-25.
- 9 Ludford RJ. II. Nuclear activity during melanosis: With special reference to melanin formation in a melanotic sarcoma. *J R Microbiol Soc* 1924:13-28.
- 10 Seab JA, Graham JH, Helwig EB. Deep penetrating nevus. *Am J Surg Pathol* 1989;13:39-44.
- 11 Ridolfi RL, Rosen PP, Thaler H. Nevus cell aggregates associated with lymph nodes: estimated frequency and clinical significance. *Cancer* 1977;39:164-71.