Pathology (February 2016) **48(2)**, pp. 155–165

MELANOCYTIC TUMOUR PATHOLOGY

Paediatric melanoma

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Summary

Cutaneous melanoma occurs only rarely in children under 10 years of age. Mimics of melanoma, including Spitz naevi and proliferative nodules in congenital melanocytic naevi are much more frequent in this age group. Melanoma arising in congenital melanocytic naevus is uncommon, but can show aggressive behaviour. Although spitzoid lesions constitute the majority of 'diagnostically challenging' cases, they are an uncommon cause of mortality in this age group. Among lesions with undoubted metastatic potential, there are biologically distinct tumours which differ significantly in behaviour from the common types of melanoma seen in adults. In patients over 10 years of age and increasingly into the late adolescent years, melanoma is a relatively common neoplasm. Just as in adult patients, care should be taken to exclude melanoma mimics. Particular care is warranted in this older age group in the assessment of lesions with spitzoid morphology as there is significant potential for both over- and under-diagnosis.

Key words: Melanoma; childhood; paediatric; Spitz naevus; atypical Spitz tumour; spitzoid melanoma; congenital melanocytic naevus; proliferative nodule; atypical proliferative nodule; congenital melanoma; adolescent..

Received 13 August, accepted 10 November 2015
Available online 16 January 2016

INTRODUCTION

Melanocytic lesions compose a significant proportion of paediatric dermatopathology practice, and the consideration of melanoma presents an occasional cause of diagnostic difficulty. Melanoma is a relatively common tumour in older adolescents and young adults, accounting for approximately 17% of newly diagnosed malignancies in patients aged 15–39 years in a high incidence population.[1] However, melanoma in patients aged 10 years or less at diagnosis is very uncommon.[2] Nevertheless, given the well known difficulties in this area and the potentially catastrophic results of misdiagnosis, there is justifiable clinical and pathological concern when a biopsy is identified as showing a histologically atypical melanocytic proliferation.

The term 'paediatric melanoma' encompasses a diagnostically and biologically heterogeneous group of lesions. 'Paediatric' is most commonly defined as comprising the group of patients aged less than 18 years at diagnosis. However some authors have included only patients under 10 years,[3] under 15 years,[4,5] under 16 years,[6] or even up to 20[7] or 21 years[8] of age at diagnosis in studies. It is clear that different atypical/malignant melanocytic lesions occur with differing frequencies in patients in various age groups, such that at the extremes of the spectrum there is very little overlap in the type of lesions which occur in elderly patients and those which occur in pre-school aged children. Lesions of 'adult type' (particularly the type unassociated with cumulative sun damage[9]) become increasingly more frequent in the pubertal and post-pubertal years. Furthermore, there appear to be genuine prognostic differences between histologically similar tumours in very young patients when compared with adolescent or young adult patients. In addition, the term 'melanoma' groups clinically, histologically and genetically disparate proliferations, including a subgroup of atypical spitzoid proliferations, lesions arising in congenital melanocytic naevi (CMN) and extracutaneous (e.g., central nervous system and ocular) proliferations.

For these reasons, this review will focus on cutaneous lesions within specific clinical and histomorphological subgroups occurring in two age cohorts: children and adolescents. Since the pubertal status of the patient is typically unknown to the pathologist, but may have important prognostic and diagnostic implications, for the purposes of this discussion childhood will be defined as referring to patients aged 10 years or younger at diagnosis, while adolescence will refer to those aged 11–18 years at diagnosis. It is acknowledged that this separation is imperfect, failing to account for variation in the age of onset of puberty, the complex continuum of physiological changes which characterise puberty, the existence of intermediate age zones at the upper and lower junctions of adolescence and potential differences between lesions in very young and somewhat older children. Furthermore, it is difficult to identify a biological rationale for the importance of this distinction and whether the apparent clinical differences are incremental or discrete. Nevertheless, this separation has clear implications for the appropriate diagnostic approach in many cases and is practically useful, despite these imperfections.[10]

EPIDEMIOLOGY

Although there are numerous epidemiological studies of childhood melanoma, the difficulties described above and diagnostic problems described below indicate that extreme caution is required when interpreting published data in this area. To take but one example, 40% of lesions classified as childhood melanoma in one registry were reclassified as benign lesions after expert histological review.[6] The rate of melanoma diagnosis as a whole increases with age, with the rate per 100,000,000 population reported as 0.7 in the age

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: http://dx.doi.org/10.1016/j.pathol.2015.12.001

group 0–4 years; 1.0 in the age group 5–9 years; 3.0 in the age group 10–14 years and 14.7 in the age group 15–19 years.[11] However, there are very significant differences between the different clinicopathological subtypes of melanoma in a paediatric population, such that melanoma arising in patients with giant CMN often develops before puberty, while conventional superficial spreading melanoma is almost exclusively a disease of white adolescents. A number of studies have indicated a slight increase in the rate of childhood melanoma over recent decades, more prominently in the adolescent age group,[2] though there are conflicting data.[12] As in adult patients, these apparent changes are likely impacted both by genuine epidemiological changes (e.g., variation in sun exposure habits) and shifting diagnostic approaches.[13]

A recent systematic review evaluated the literature for cases of fatal or metastasising (at least stage 3) melanoma in an approach designed to mitigate the impact of diagnostic variation.[14] There is significant potential for reporting bias, given that fatal melanoma is much more likely to be reported in the literature when it occurs in children as opposed to adolescents. In this study 114 cases of fatal cutaneous melanoma unassociated with CMN were identified in patients aged 11–18 years, while 41 cases were identified in children aged 0–10 years. Histological descriptions were provided in 49 cases, with 14 (29%) described as superficial spreading and 22 (45%) described as nodular. Overall eight cases (16%, including three cases also termed nodular) were described with 'spitzoid' or 'Spitz-like' features and five cases (10%) were described as 'small cell melanoma'. More detailed description of the histological subtypes divided by age group was not provided. There were 103 cases of fatal cutaneous childhood melanoma associated with CMN identified (versus 66 CNS melanomas), with 83 cases (80.6%) developing in children aged 0–10.[14]

A family history of melanoma and the presence of multiple melanocytic naevi represent important risk factors for the development of melanoma in patients under 15 years of age.[15,16] Although *CDKN2A* mutations are seen in approximately 10% of adult melanoma patients with a strong family history of melanoma, they are seen in only infrequently (approximately 1%) in patients presenting with melanoma in adolescence.[16,17]

Xeroderma pigmentosum is a rare autosomal recessive disorder of DNA repair associated with photosensitivity and an extreme risk of cutaneous malignancy, including basal cell carcinoma, squamous cell carcinoma and melanoma.[18] Melanoma develops in approximately 5% of patients, with a median age at diagnosis of 17–18 years.[10] While the risk is obviously high in this group of patients, the rarity of the underlying abnormality renders this an uncommon cause of childhood melanoma. In keeping with the mechanisms of carcinogenesis in this group, there appears to be a tendency towards development of lesions more commonly seen in association with chronic sun damage in older patients, including desmoplastic melanoma.[19]

CLINICAL ASPECTS

Cutaneous childhood melanoma can be divided into lesions occurring in the setting of CMN and lesions unassociated with CMN. The former are described in greater detail below. The latter are frequently clinically challenging, with delays in clinical diagnosis being relatively common due to resemblance to naevi or to more common non-melanocytic lesions such as pyogenic granuloma and verrucae. It has been found that the majority of younger children and a significant minority of older children do not present with lesions which meet traditional 'ABCDE' criteria for the recognition of melanoma. Rather, presentation with newly developing amelanotic and bleeding nodules is commonly seen in these groups.[20]

MELANOMA ARISING IN CONGENITAL MELANOCYTIC NAEVI

Melanoma can arise within a CMN both in children and adults.[21] In addition, patients with CMN are at increased risk for presentation with metastatic melanoma of unknown primary site, extracutaneous (principally CNS) melanoma and possibly cutaneous melanoma outside the area of CMN.[22,23] Melanomas arising in CMN in children can develop in both the dermal and subcutaneous portions of the lesion. The risk estimates for developing melanoma associated with CMN vary widely, probably in large part due to referral and reporting bias. An additional problem is presented by variation in diagnostic labelling, both in identifying a naevus as congenital by histopathological assessment and in separating melanoma from specific benign mimics (see below).

A systematic review of the larger studies of this phenomenon, including a total of 6571 patients with CMN, found an overall risk of 0.7%, with mean follow-up ranging from 3.4 to 23.7 years.[22] The risk correlates with the size of the CMN, being highest in large and garment CMN, which account for approximately 75% of CMN associated with melanoma in larger studies. The lifetime risk in large CMN has been estimated at 6% or higher.[21] The risk of melanoma may be higher in CMN associated with satellite lesions, possibly due to a common association with *NRAS* mutations. Indeed, it has been suggested that (fatal) melanoma is rare in the absence of such lesions,[14] albeit that development of melanoma actually within the satellite lesions is apparently rare. It is difficult to accurately evaluate the risk in small CMN, but in population based studies it appears to be very low.[24] The median age of diagnosis of melanoma arising in CMN is around 7 years with fatal cases diagnosed at a median age of 3 years, suggesting that the risk is greatest in children.[14,22] However, it should be noted that many groups are focussed largely on paediatric and adolescent patients with substantial naevi and, even with long follow-up periods, melanoma developing in later adult life and in smaller lesions may be relatively under-reported. The ratio of fatal to non-fatal cases of melanoma arising in patients with CMN is approximately 1:1, with one-third of cases arising within the CMN (as opposed to within the CNS or presenting as metastatic disease with unknown primary) proving fatal.[22] Among fatal cutaneous melanoma arising with CMN, the mean survival is shorter in prepubertal versus older children (14.5 months versus 45 months).[14] Of note, lesions described as rhabdomyosarcoma or melanoma with rhabdomyoblastic differentiation have been reported to develop in CMN.[25]

There is considerable difficulty in determining the appropriate criteria for a diagnosis of malignancy when assessing a cutaneous melanocytic proliferation arising in the setting of a CMN in childhood. These difficulties occur in two major morphological groups: assessment of atypical junctional proliferations overlying CMN and assessment of distinct cellular nodules within the intradermal component of CMN. Each of these will be addressed separately.