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Malignant Melanoma in Childhood: A Clinicopathologic Study of 13 Cases and Comparison with Spitz Nevi

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The clinical and histological features of 13 malignant melanomas in children <13 years of age in New South Wales, Australia, were compared with those in a control group of children with 15 Spitz nevi, 4 of which were considered atypical, and 2 unusual compound nevocellular nevi. Six of the controls had been previously diagnosed histologically as malignant melanoma. The objective observations made by one or more histopathologists experienced in reporting melanocytic lesions, and the clinical details, mainly from the Sydney Melanoma Unit files, were entered on a detailed protocol. Evaluation was assisted by the use of SPSS-X software on a mainframe VAX computer. Six of the 13 children with malignant melanoma died with their disease. The most frequent clinical features found in the malignant melanomas were bleeding, ulceration, itching, and black or variegated color. Recent enlargement and darkening were noted in the majority of both the malignant melanomas and the Spitz nevi. Histological features favoring malignancy in this series were mitoses within 0.25 mm of the dermal margin of the melanoma, a dermal mitotic rate exceeding 2/mm^2, ulceration, surface exudate, large pigment granules, and clear-cell differentiation. The median thickness of the malignant melanomas was 1.3 mm but in the 4 children who died with melanoma the median thickness was 2.9 mm. Absence of mitoses, predominance of spindle cells, and diffuse maturation favored Spitz nevus. The median thickness of the Spitz nevi was 0.7 mm.

Pigmented skin lesions are common in childhood. A survey of schoolchildren in Queensland, Australia in 1989 showed a mean of 28 moles per child [1]. Most pigmented skin lesions on children are benign nevocellular nevi. Childhood malignant melanomas are rare [2, 3]. Despite this rarity, it is important that clinicians be aware that malignant melanoma does occur in childhood.

Difficulties persist in the histological distinction between malignant melanomas and benign nevi such as Spitz nevi. The purposes of this study are to record further cases of childhood malignant melanomas and assess both their clinical and histological features.

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Material and Methods

From the files of the Department of Morbid Anatomy, Sydney Hospital, from 1960 to 1983, and the files of the Department of Anatomical Pathology, Royal Prince Alfred Hospital, Sydney, from 1950 to 1989, the 19 cases listed as malignant melanoma in patients ≤13 years of age at diagnosis were reviewed. The clinical notes and follow-up data were obtained from the records of the Sydney Melanoma Unit and from the histopathology reports. The cases reviewed include the 10 children under the age of 13 years mentioned by Shaw and associates [4]. Three of these 10 cases had been previously reported by McGovern and Goulston (their cases V, VII, VIII) [5].

The tissue sections in all cases were stained or restained with hematoxylin and eosin. In a few lesions a complete cross-section of the lesion was not available. In 2 cases (cases 12 and 13), sections of primary melanoma were unavailable so the recurrences were stained for S-100 protein, neurone specific enolase, and HMB-45 for confirmation. Because of the general difficulty in obtaining paraffin blocks or spare sections, PAS stains were not done to substantiate the presence of Kamino bodies [6]. The 11 patients selected as controls were 2 to 13 years of age and cases listed as Spitz nevus, juvenile melanoma, or atypical nevus in the Sydney Hospital files. The histological material in each case was objectively studied by one or more histopathologists with extensive experience in melanocytic lesions. When absolute or numerical values could not be allocated for the histological features, semiquantitative estimates were made. Where the reviewing histopathologists made differing assessments, a consensus was reached over a multiheaded microscope. The data were entered on a comprehensive protocol of 320 clinical and histological variables. The data

Table 1. Childhood malignant melanomas.

Case	Sex/age	Site	Clinical stage at presentation	Original pathology diagnosis	Study review diagnosis	Maximum diameter (mm)	Thickness (mm)	Clark's level	Rec/mets (mos.)	Follow-up (mos.)
1	F/10	Shoulder	1	SSM	SSM	7.0	0.6	4	nil	A & W, 63
2	M/12	Upper leg	1	SSM	SSM	5.5	0.5	2	nil	A & W, 44
3	M/4	Chest	1	MM in DN	SSM	3.6	0.7	4	nil	A & W, 17
4	F/10	Shoulder	1	"In situ MM" with nevus	SSM	3.5	0.5	2	Scar, 12	A & W, 84
5	M/12	Ear	1	SSM	SSM	7.0	1.3	3	nil	A & W, 40
6	F/6	Buttock	1	Nod MM	MM	9.0	2.6	4	RN, 39; Liver, 158	Dead, 158
7	F/8	Upper arm	1	MM	MM	NA	2.1	NA	RN, 3	A & W, 114
8	F/8	Face	2	MM	MM	3.0	5.5	5	RN, 8; DSN, 8	Dead, 11
9	F/12	Heel	2	Nod MM	ALMM	17.0	3.1	4	Scar, 14	Dead, 36
10	M/12	Chest	1	MM	BMM	4.0	0.8	4	Scar, 18	A & W, 72
11	F/5	Upper leg	1	MM	? Spitz (90%)	5.2	1.6	4	Ovaries, 144 Omentum, 144	Dead, 146
12	F/12	Lower leg	2	MM	NA	NA	NA	NA	DSN, 30	Dead, 36
13	M/8	Upper leg	1	SSM	NA	NA	NA	NA	Scar, 7	Dead, 14

Stage 1 = local skin disease only; Stage 2 = regional lymph node metastases; Stage 3 = distant disease.

Rec = recurrence(s); Mets = metastases; F = female; M = male; SSM = superficial spreading melanoma; MM = malignant melanoma, not otherwise specified; Nod MM = nodular malignant melanoma; DN = dysplastic nevus; Scar = site of excision of primary melanoma; RN = regional nodes; NA = not assessable/available; DSN = distant skin nodule; ALMM = acral lentiginous malignant melanoma; BMM = borderline malignant melanoma; CN = combined nevus (compound and blue); UCN = ulcerated compound nevus; AS = atypical Spitz nevus; Spitz = Spitz nevus; A & W = alive and well; LTF = lost to follow-up; and B nevus = benign nevus.

Table 2. Childhood Nevi.

Case	Sex/age	Site	Original pathology diagnosis	Study review diagnosis	Maximum diameter (mm)	Thickness (mm)	Clark's level	Follow-up (mos.)
14	M/5	Shoulder	MM	CN	4.5	1.4	4	A & W, 160
15	M/12	Face	MM	UCN	5.0	4.5	4	A & W, 27
16	M/10	Upper back	MM	AS	3.0	0.7	2	A & W, 200
17	M/12	Heel	ALMM	Spitz	4.5	0.4	1	LTF
18	F/13	Upper arm	MM	Spitz	4.0	2.0	4	LTF
19	M/12	Upper leg	SSM	Spitz	5.5	0.5	2	A & W, 86
20	F/2	Upper arm	Spitz	AS	2.5	0.2	1	LTF
21	F/2	Lower arm	Spitz	AS	5.5	0.6	3	LTF
22	M/8	Shoulder	Spitz	AS	5.0	1.6	4	LTF
23	F/2	Upper leg	Spitz	Spitz	2.5	0.4	3	LTF
24	F/12	Face	Spitz	Spitz	3.0	NA	NA	LTF
25	M/12	Lower back	Spitz	Spitz	2.2	0.4	2	A & W, 36
26	F/7	Upper arm	Spitz	Spitz	3.5	NA	NA	LTF
27	M/10	Lower leg	Spitz	Spitz	4.5	0.8	3	LTF
28	F/12	Foot	Spitz	Spitz	8.5	4.5	4	LTF
29	F/13	Upper leg	B nevus	Spitz	8.0	0.7	3	LTF
30	F/3	Lower leg	Spitz	Spitz	5.0	1.8	4	LTF

See Table 1 for definitions.

were then transferred to SPSS-X software on a VAX mainframe computer.

Results

On objective histological review of the 17 lesions that were originally reported to be malignant melanoma, 10 were still considered to be malignant, 1 was equivocal (case 11), and 6 were benign. Based on follow-up data, case 11 proved to be malignant and was included in the malignant melanoma group (Table 1). The 6 cases in which the diagnosis was changed to benign are included in Table 2 together with the 11 randomly selected controls.

Of the 6 lesions originally diagnosed as malignant melanoma and reclassified as benign, 4 lesions (cases 16 to 19) were considered to be Spitz nevi because of good symmetry, "rain-down" pattern, Kamino bodies, and absence of dermal mitoses. One of the remaining reclassified lesions (case 15) was an ulcerated compound nevus with mild reactive cellular atypia. The other lesion (case 14) was a combined blue and nevocellular nevus. Thus 13 malignant melanomas and 17 nevi formed the basis of this comparative study.

Four of these 6 children with lesions reclassified as benign remained alive and well without recurrence for at least 2 years (Table 2) and 2 children were lost to follow-up. No follow-up was available on 10 of the 11 other children with Spitz nevi.

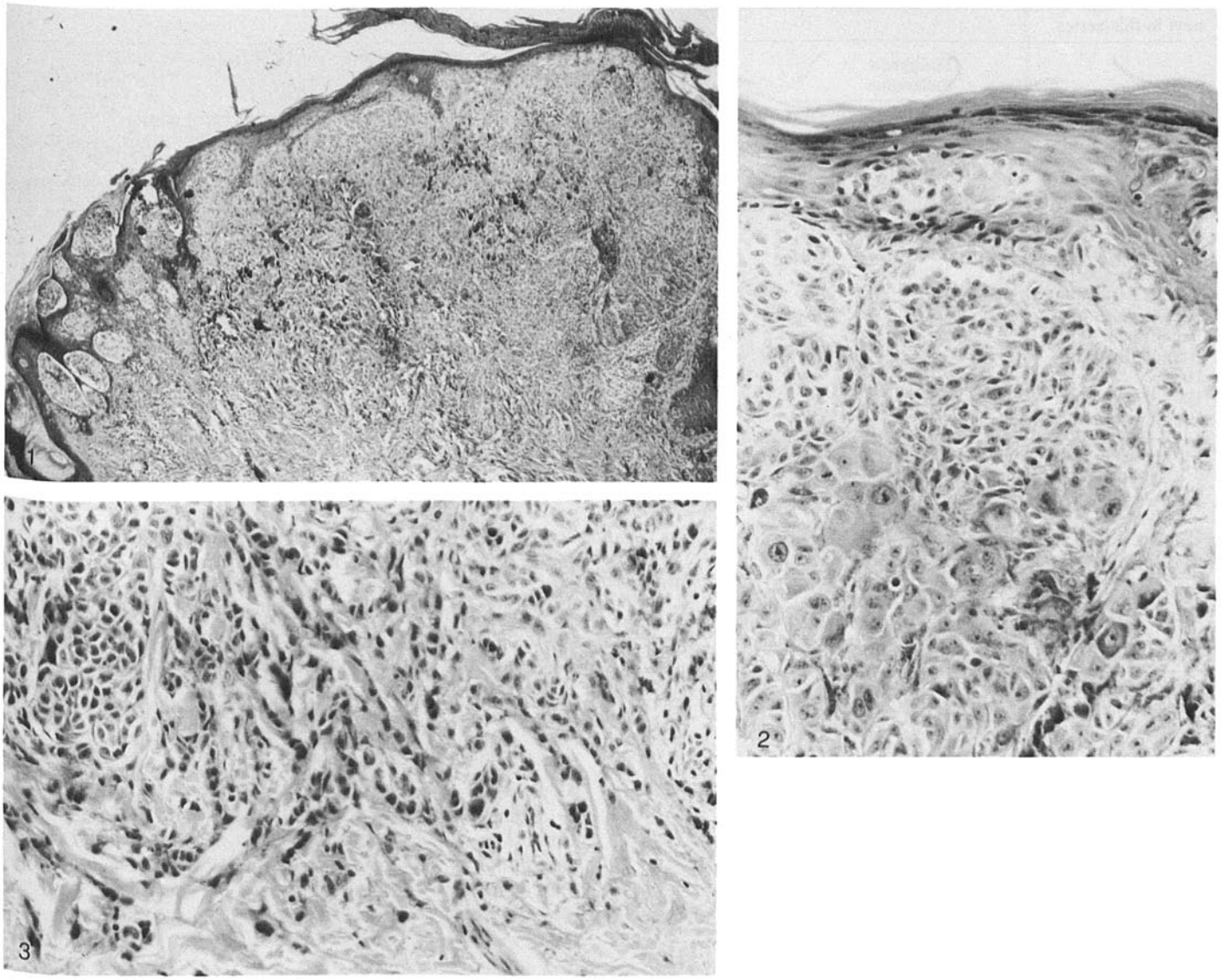

Fig. 1. Malignant melanoma with some features of Spitz nevus (case 11). The photomicrograph includes about 75% of the lesion. There is epidermal hyperplasia at the edges (one shown) and thinning of the epidermis centrally. There is little evidence of single cell epidermal invasion. Melanin pigment is patchy. Original magnification ×3.2.

Fig. 2. Near the center of this malignant melanoma (case 11) there are small somewhat spindle shaped melanocytes in the subepidermal zone. Deeper there are abnormal large epithelioid melanocytes many with atypical nuclei and an occasional mitosis. Some of the nucleoli have an irregular shape. Original magnification ×66.

Fig. 3. At the base of this malignant melanoma (case 11) there is an infiltrating pattern and variable maturation. Original magnification ×66.

Case 11 was of most interest. In November, 1971, the mother of this 5 year old girl first noticed a pale brown freckle on the child's right thigh. About 8 months later, a small black spot appeared on the lesion, gradually spread over it, and became slightly raised. On these clinical grounds malignant melanoma was suspected, despite the age of the child. Biopsy of the lesion was performed in November, 1972 and 2 of the authors (S.W.McC. and A.A.P.) as well as the late Professor V.J. McGovern reported this to be a 1.4 mm thick malignant melanoma. A radical elective lymph node dissection of her right groin, in continuity with the primary lesion site, was performed at this time. The lymph nodes proved to be free of tumor. The child was followed at regular intervals and apart from persistent keloid scarring in her groin, she remained well until November, 1984 when she complained of chronic abdominal pain. At laparotomy, widespread metastatic melanoma was found to be infiltrating the omentum, liver, and both ovaries. She died 2 months later. The original diagnosis of malignant melanoma was therefore substantiated by her death from metastatic melanoma. On the present review, however, the diagnosis was equivocal. The primary lesion (Figs. 1–3) was composed predominantly of epithelioid melanocytes and three histopathologists considered it most likely to be a Spitz nevus, with 10% doubt, on the basis of good symmetry, epidermal hyperplasia,

Table 3. Main clinical features of malignant melanomas and Spitz nevi in this series.

Clinical feature	Malignant melanoma		Spitz nevi
	Total	Died	
Bleeding	6/9	3/4	3/14
Ulceration	5/10	3/4	1/13
Recent enlargement	5/8	3/4	9/11
Itching	4/8	2/4	2/13
Black color	4/11	1/4	0/14
Variegated/mottled	4/11	2/4	1/14
Warty surface	3/10	1/4	0/15
Recent darkening	3/8	2/4	11/15
Recent pale change	2/8	1/4	0/13
Recent pain	2/8	1/4	0/13
Irregular margin	2/9	1/4	6/8
Halo	2/10	1/4	0/16
Dark brown color	1/11	0/4	2/15
Light brown color	1/11	0/4	5/15
Grey color	0/11	0/4	3/15

Number with feature/total number.

Table 4. Main histological features of malignant melanomas and Spitz nevi in this series.[a]

Histological feature	Malignant melanoma		Spitz nevus	
	Total	Died	Atypical	Typical
Median thickness mm (Breslow)	1.3	2.9	0.7	0.7
Marginal mitoses[b]	9/11	4/4	0/3	0/8
Mitoses >2/mm^2 (Clark levels II–V)	7/11	4/4	0/4	0/11
Ulceration	3/11	2/3	0/4	0/11
Surface exudate	5/11	4/4	0/4	0/11
Large pigment granules[c]	4/11	3/4	0/4	0/11
Clear-cell differentiation	4/11	1/4	1/4	0/11
Necrosis	1/11	0/4	0/4	0/11
Dusty pigment	9/11	3/4	1/4	2/11
Abnormal mitoses	3/11	2/4	0/4	1/11
Associated benign nevus	3/11	1/4	0/4	1/11
≥1 mitoses in papillary dermis	10/11	4/4	1/3	3/11
Asymmetry	4/8	1/3	1/4	1/9
Epithelioid cells predominant	10/11	4/4	1/4	4/11
Epithelioid melanocytes in granular layer	9/9	3/3	2/4	4/11
Junctional melanocyte mitoses	9/9	3/3	3/4	4/11
Junctional component beyond dermal component	7/11	2/3	1/4	3/11
Diffuse maturation in dermis	1/11	1/4	2/4	4/11
Spindle cells predominant	1/11	0/4	3/4	5/11
Absence of mitoses levels II–V	0/11	0/4	2/4	7/11

Number with feature/total number.

[a]Those features that favor malignant melanoma are towards the top of the table. Those that favor Spitz nevus are towards the bottom.

[b]Mitoses within 0.25 mm of margin of lesion (Clark levels II–V).

[c]>1/3 size red blood cell.

hyperkeratosis, and sharp edges bounded by junctional nests. There was no central epidermal hyperplasia and deep maturation was only patchy. The original correct diagnosis of malignancy was based on the cytological features of high mitotic rate (up to 6/mm^2), foci of large melanocytes with nuclear atypia, and some dusty cytoplasmic melanin pigment.

Though many variables were not significant in this small series, those that were either significant, most numerous, or unique were selected for inclusion in Tables 3, 4 and 5. The main clinical features recorded in the clinical notes are given in Table 3. The features proportionally more common in malignant melanomas were bleeding, ulceration, itching, black color, and variegated or mottled color. The height, contour, pink color, presence of hairs, and duration of the lesion were not helpful.

Table 5. Histological features considered unhelpful in differentiating malignant melanomas from Spitz nevi in this series.

Epidermal hyperplasia—central, peripheral, patchy, uniform
Hypergranulosis
Subepidermal clefts—central, peripheral
Lentiginous, pagetoid or nesting melanocytes at edges
Melanocytes on walls, tips of rete ridges and at the apex of dermal papillae
Variable proportion of nests and single cells in junctional zone
Epidermal invasion pattern by nests and small single cells
Pushing and/or infiltrating margins
The amount and size of nests in dermis
Fibrosis
Capillary proliferation
Melanocyte size
Patchy maturation in dermis
Melanocyte nuclear size and shape
Nuclear hyperchromatism
Nucleolar size and shape in junctional zone and dermis
More than 1 nucleolus/cell in dermis
Kamino bodies seen in H & E sections
Pattern of inflammatory infiltrate

In Table 4 the main histological features of the malignant melanomas and the nevi are listed. Those features proportionally in favor of the melanomas are placed at the top of the table. They include mitoses within 0.25 mm of the dermal margin of the melanoma, a dermal mitotic rate exceeding 2/mm^2, ulceration, surface exudate, large pigment granules, and clear-cell differentiation. Similarly, those features proportionally favoring Spitz nevi are at the bottom of the table. They include absence of mitoses, predominance of spindle cells, and diffuse maturation in the dermis. Some of the features of the melanomas and nevi are illustrated in Figures 1–5. In Table 5 are listed the histological features not found to be diagnostically helpful in this series.

One child with malignant melanoma and 1 child with atypical Spitz nevus had a family history of melanoma. Of the 13 children with malignant melanoma in this series, 6 died with their disease 1 to 13 years after diagnosis. The thickness of the 4 fatal primary melanomas available for study ranged from 1.6 mm to 5.5 mm (median 2.9 mm).

Discussion

The true incidence and biological behavior of childhood malignant melanomas have been difficult to determine because of the uncertainty of the diagnostic criteria. In 1948, Sophie Spitz reported that many childhood lesions which had been diagnosed histologically as malignant melanoma had proved to be benign. She used the term "juvenile melanoma" to describe these lesions [7]. This lesion has since been called Spitz nevus or Spitz's nevus [8]. A review of the Mayo Clinic files in 1954 confirmed that an optimistic prognosis for childhood malignant melanoma was due to the inclusion of Spitz nevi [9].

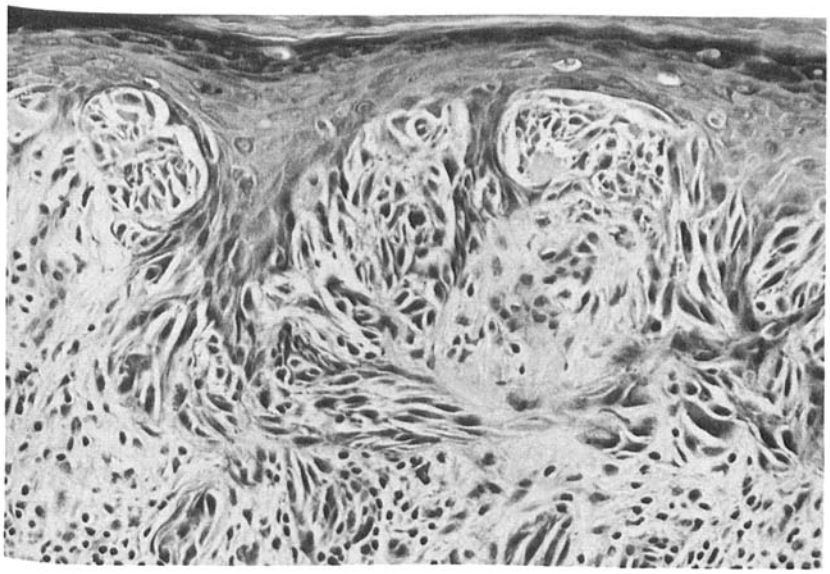

Fig. 4. One of the Spitz nevi (case 23) with spindling cells and a Kamino (eosinophilic) body in the central nest to the right of center. Original magnification ×66.

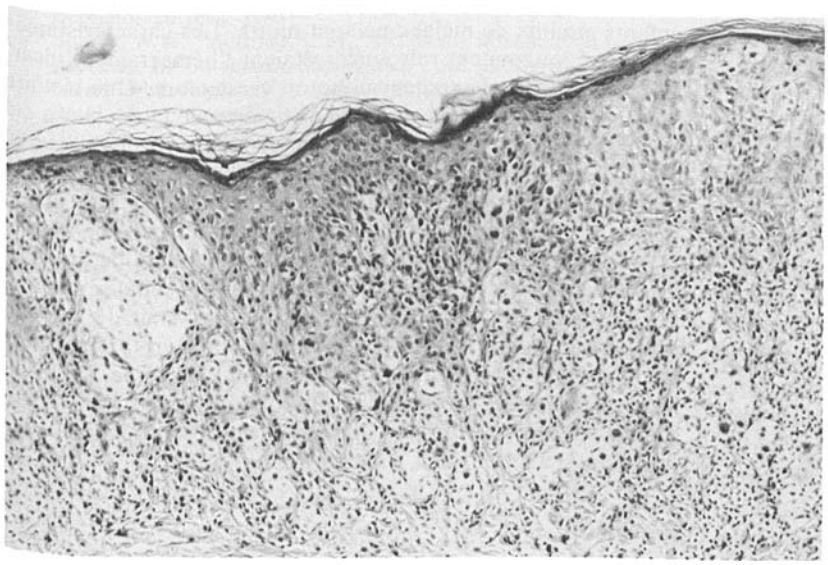

Fig. 5. The main feature of this malignant melanoma (case 10) was foci of ballooned melanocytes in the junctional zone and dermis. Original magnification ×33.

In 1963, McGovern and Goulston [5] stated that childhood malignant melanoma had a similar biological course to that of adult malignant melanoma. They reported 8 cases of malignant melanoma in children under 12 years of age at diagnosis, 4 of whom had died with melanoma. In 1966, Skov-Jensen and associates [10] reported 2 further cases and reviewed 43 cases of metastatic malignant melanoma in children ≤14 years of age. In 1975, Trozak and colleagues [11] reviewed 68 cases of metastatic malignant melanoma in children <15 years of age at diagnosis. In 1989, Smith and associates [12] reported that metastases to regional lymph nodes from some large and atypical spindle and epithelioid nevi, several of which had been reported as malignant melanoma, were not followed by further dissemination. Their series included 13 children <15 years of age. In view of this finding, some of the children in earlier series who had only regional node metastases may not have had potentially lethal malignant melanomas. Similarly, on the basis of monoclonal antibody studies, large histologically malignant nodules in giant congenital nevi may not metastasize [13].

Two recent reports [14, 15] of malignant melanoma in children and adolescents <20 years of age discussed the response to current therapy. Reintgen and coworkers [14] found that actuarial disease-free intervals and survival rates for malignant melanoma were similar in both juvenile and adult populations. Rao and associates [15] reported 33 cases of malignant melanoma in patients <20 years of age, at least 15 of which appear to have been <13 years of age. Of their patients treated with chemotherapy, the response appeared to be better than in adults.

In the present series, 6 of the 13 children with malignant melanoma died with their disease from 1 year to 13 years after diagnosis. The fact that these children had relatively thick

melanomas emphasizes the importance of early recognition and radical treatment of their disease. The surgical approach to the treatment of childhood malignant melanoma at the Sydney Melanoma Unit is similar to that of adult malignant melanoma.

There are several risk factors for the development of malignant melanoma at a young age. These include children born to mothers with metastatic melanoma (probably transplacental spread, a rare phenomenon), children with giant hairy nevi, children with xeroderma pigmentosum, and children with a family history of dysplastic nevus syndrome or malignant melanoma [2, 3]. In the present series, 1 patient with malignant melanoma and 1 patient with an atypical Spitz nevus had a family history of melanoma.

In contrast to the findings of Sybert [16], the clinical features of the childhood melanomas in the present series resembled those of melanomas in adults and adolescents in that there was often bleeding, ulceration, itching, and black or variegated color. Recent enlargement was also common but this feature was more frequent in the Spitz nevi. Almost half of the nevi had a pale color but the only pink lesion in the series was a malignant melanoma.

In a detailed review of 211 cases of Spitz nevus in 1977, Weedon and Little [17] stated that in borderline cases the features which suggest malignancy include presence of atypical mitoses, prominent epidermal invasion, particularly by single cells without overlying hyperkeratosis, lack of maturity at the base of the lesion, nuclear hyperchromatism and coarse chromatin in mononuclear tumor cells, and destruction of collagen. Of these features only atypical mitoses and lack of maturity at the base of the lesion were more frequent in the melanomas in the present series. Peters and Goellner [18] reviewed 33 cases of Spitz nevus and 19 cases of malignant melanoma in patients aged 20 years or less. They studied 25 histological criteria and concluded that malignant melanomas had a higher degree of pagetoid spread, cellular pleomorphism, nuclear hyperchromasia, and mitotic activity. They added that spindle cells were more prominent in Spitz nevi. In comparing the present series, only mitotic activity and prominence of spindle cells were helpful criteria.

In childhood nevi, epidermal invasion by melanocytes appears less significant than in adults [19, 20]. Mérot and Frenk [20] found that single cell epidermal invasion was minimal in Spitz nevi and always associated with nesting and transepidermal elimination. In the lesions of this series epithelioid melanocytes were found in the granular layer of all 9 malignant melanomas with assessable overlying epidermis; 6 of the 15 Spitz nevi had similar epidermal invasion. The pattern of epidermal invasion by nests and single cells was unhelpful. The histological features most strongly in favor of malignancy were marginal mitoses, dermal mitotic rate $>2/mm^2$, ulceration, surface exudate, large pigment granules, and clear-cell differentiation.

It is not surprising that anaylses of the different relatively small series of cases of childhood melanoma reported in the literature do not all highlight the same diagnostic histological criteria since the histological features of malignant melanoma vary considerably from lesion to lesion. Furthermore, reliable diagnosis depends on recognition of a constellation of features, two or more of which are mandatory. To assess the multiple features the entire lesion should always be presented for histopathological examination.

The approach employed in this study using a large number of variables aided by computer technology further refined the important morphological features such as the distribution of mitotic activity near the dermal-tumor junction. This approach may also be useful in the study of adult melanocytic lesions and other tumors.

Résumé

Les caractéristiques cliniques et histologiques de 13 cas de mélanome malin chez des enfants âgés de moins de 13 ans dans la région de New South Wales, Australie, ont été comparées à celles d'un groupe contrôle de 15 naevi de Spitz, dont quatre atypiques et deux de composante naevocellulaire. Six de ces lésions avaient été classées auparavant comme malignes. Les observations objectives effectuées par un ou plusieurs anatomopathologistes, expérimentés dans les lésions mélanocytiques, et les faits cliniques, recueillis à partir des dossiers de l'Unité de Soins pour Mélanome de Sydney, ont été entrées dans un protocole d'analyse détaillé. L'analyse a été effectuée avec un logiciel SPSS-X sur un ordinateur VAS. Six des 13 enfants atteints de mélanome sont morts. Les caractéristiques les plus fréquemment retrouvées étaient l'hémorragie, l'ulcération, le prurit et la couleur noire ou versicolore. Une histoire récente d'élargissement ou d'intensification de la couleur a été notée dans la majorité des mélanomes malins et des naevi de Spitz. Dans cette série, les critères de malignité ont associé des mitoses à moins de 0.25 mm de la marge dermique du mélanome, une fréquence de mitoses supérieure à $2/mm^2$ de derme, la présence d'ulcération, d'un exsudat de surface, de granules pigmentés larges et une différenciation de cellules claires. L'épaisseur médiane des mélanomes malins était de 1.3 mm mais, chez quatre des six enfants qui sont morts, l'épaisseur médiane était de 2.9 mm. En faveur d'un naevi de Spitz, on retenait l'absence de mitose, la prédominance de cellules fusiformes et une maturation diffuse. L'épaisseur médiane des naevi de Spitz était de 0.7 mm.

Resumen

Se compararon las características clínicas e histológicas de 13 melanomas malignos en niños menores de 13 años en New South Wales, Australia, con un grupo control de 15 nevus de Spitz, 4 de los cuales fueron considerados atípicos, y 2 raros nevus compuestos novocelulares. Seis de los controles habían sido histológicamente diagnosticados previamente como melanoma maligno. Las observaciones objetivas realizadas por uno o mas histopatólogos expertos en reportar lesiones melanocíticas, junto con la información clínica, principalmente emanados de los archivos de la Unidad de Melanoma de Sydney, fueron ingresados a un minucioso protocolo, y la evolución fue analizada con ayuda de computación (SPSS-X Software y computador mainframe VAX). Seis de los 13 niños con melanoma maligno murieron por causa de la enfermedad. Los signos clínicos hallados con mayor frecuencia fueron el sangrado, la ulceración, el prurito y el color negro o jaspeado. Se observó aumento del tamaño y oscurecimiento reciente de la lesión en la mayoría de los melanomas malignos y de los nevus de Spitz. Las características histológicas que favorecieron el diagnóstico

de melanoma en esta serie fueron las mitosis dentro de un margen de 0.25 mm del melanoma dérmico, una tasa de mitosis dérmica superior a 2/mm^2, ulceración, exudado de superfice, gránulos pigmentados grandes y diferenciación de células claras. El espesor promedio de los melanomas malignos fue 1.3 mm, pero en los 4 niños que murieron por causa del melanoma el espesor promedio fue 2.9 mm. La ausencia de mitosis, el predominio de células fusiformes y la maduración difusa fueron hallazgos que favorecieron el diagnóstico de nevus de Spitz; el espesor promedio de los nevus de Spitz fue 0.7 mm.

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