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Histological and Cytological Criteria in the Diagnosis of Malignant Melanomas by Cryostat Sections***

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Summary. Although cryostat sections in general allow a distinction to be made between malignant melanomas and other pigmented lesions in clinically doubtful cases, the differential diagnosis may be difficult. The histological and cytological criteria taken into account can be classified as major, minor, and insufficient. Knowing the diagnostic value of each makes a conventionally established diagnosis safer. Variance analysis does not contribute to the problem but it can nevertheless be shown that the evaluation of six major criteria makes a quick and reliable cryostat section diagnosis possible. If these results are confirmed in a prospective study it would be a decisive step on the way to a quicker and safer cryostat section diagnosis of malignant melanoma, even for the less experienced histopathologist.

Key words: Malignant melanomas – Cryostat sections – Major diagnostic criteria – Variance analysis

Introduction

Diagnostic accuracy in the clinical assessment of malignant melanoma is no better than 64.4 p.c. (Kopf et al. 1975). In many cases therefore, doubtful lesions cannot be directly subjected to radical surgical removal. In other skin lesions, such as basal cell carcinoma, a biopsy would be taken to confirm the clinical diagnosis, but in malignant melanoma incisional biopsy is unwise (Braun-Falco 1975) and even excisional biopsy is subject to debate. Intraoperative diagnosis by cryostat sections has recently won broad support (Braun-Falco and Konz 1980; Steigleder and Plümmer 1980) although it is not generally accepted (Kopf et al. 1978). It must be admitted that the differential diagnosis of malignant

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melanoma and nevus cell nevus by cryostat sections can still raise problems. The value of the histological and cytological criteria taken into consideration will therefore be analyzed and a new concept for this special task developed.

Materials and Methods

Cryostat sections of 158 cases clinically suspicious for malignant melanoma, dating from 1978 and 1979, were available for this study. They had been prepared intraoperatively using a Damon Minotome cryotome. In 11 cases a definite diagnosis could not even be established from the paraffin sections, 147 thus remained for further analysis, of which 81 were finally considered to be malignant melanoma (m.m.) and 33 nevus cell nevus (n.c.n.). Former routine cryostat section diagnosis had established all diagnosis of nevus cell nevi correctly; once m.m., however, had been taken for n.c.n. from the frozen section, so the overall accuracy of the method amounted to 99.1%.

The cryostat sections of all 114 cases were reexamined without any knowledge of the former results and were checked for a variety of criteria considered relevant for differential diagnosis. Their frequency was initially examined in both diseases and the data subjected to variance analysis. In addition, efforts were made to establish certain combinations of criteria typical of either m.m. or n.c.n. Finally calculations were done to test if a certain number of fulfilled criteria correlates with a distinct diagnosis. In general, histological differentiation of melanocytes and nevocytes was not intended.

Results

The criteria sought in all cases are listed in the Tables 1, 2, and 3, separating histological features referring to the epidermis and to the cutis/subcutis and cytological features. The first two columns deal with the frequency of the criteria in m.m. and n.c.n. The third one shows how often cases positive for the criteria belong to the m.m. group. A criterion only usually fulfilled in cases of *either* the m.m. or n.c.n. group can be considered to be especially useful in distinguishing between the two groups in unknown cases. In this connection the overall frequency of a criterion in all cases of m.m. and n.c.n. together is of minor importance. So ulceration (see Table 1) turns out to be highly selective criterion. Although it will not be expected to be present in most cases of m.m. it is a very strong argument in favour of a diagnosis of m.m. if present. In our material it is found exclusively in cases of m.m., but general experience leaves no doubt that no single criterion allows the establishment of the diagnosis of m.m. or n.c.n.

The data collected were then subjected to *variance analysis* a well known statistical method, distinguishing between members of two related groups. Four criteria were relevant to that aim: infiltrative growth, number of mitoses, pleomorphism in general, and pagetoid cells in the epidermis. On the basis of their evaluation 93.0% of all cases of m.m. and n.c.n. could be diagnosed correctly, 3 of the 81 cases of m.m. would be taken for n.c.n., 5 of 33 cases of n.c.n. for m.m. The dominant role of these criteria in the differential diagnosis of m.m. and n.c.n. by cryostat sections is thus obvious. However, diagnostic accuracy cannot be increased on the basis of variance analysis.

Consequently we looked for the *diagnostic value of combinations of criteria* relatively specific for m.m. Initially these *criteria* were reckoned to be the group which were found in 90% or more of cases of m.m., that is: ulceration/erosion;

Table 1. Frequency of certain histological criteria in the epidermis of malignant melanoma (m.m.) and nevus cell nevus (n.c.n.) lesions and the proportion of cases of m.m. of the total frequency of the criterion

Criterion	Frequency in m.m. lesions	Frequency in n.c.n. lesions	Proportion of cases of m.m. of the total frequency
Transepidermal elimination of			
1. Pigment	77.8%	84.8%	69.2%
2. Naevo-/Melanocytes	84.0%	45.5%	81.9%
Acanthosis			
1. in the marginal area of the lesion	79.0%	45.5%	81.0%
2. throughout the lesion	46.9%	36.4%	76.0%
Epidermal atrophy	25.9%	15.2%	80.8%
Ulceration	12.3%	0.0%	100.0%
Erosion	9.9%	0.0%	100.0%
Epidermal spread of nevo-/melanocytes	84.0%	51.5%	80.0%

Table 2. Frequency of certain histological criteria in the cutis of malignant melanoma (m.m.) and nevus cell nevus (n.c.n.) lesions and proportion of cases of m.m. of the total frequency of the criterion

Criterion	Frequency in m.m. lesions	Frequency in n.c.n. lesions	Proportion of cases of m.m. of the total frequency
Spread of cells:			
1. junctional	88.9%	72.7%	75.0%
2. corial	100.0%	100.0%	71.0%
3. adnexial	21.0%	3.0%	94.4%
4. infiltrative	85.2%	6.1%	97.2%
Stroma reaction:			
1. present at all	91.4%	45.5%	83.1%
2. lateral	85.2%	39.4%	84.1%
3. central	69.1%	42.4%	80.0%

Table 3. Frequency of certain cytologic criteria in malignant melanoma (m.m.) and nevus cell nevus (n.c.n.) lesions and proportion of cases of m.m. of the total frequency of the criterion

Criterion	Frequency in m.m. lesions	Frequency in n.c.n. lesions	Proportion of cases of m.m. of the total frequency
Aspect of cells			
1. uniform (1 cell clone)	67.9%	90.0%	64.7%
2. multiform (several clones)	30.9%	9.1%	89.3%
Number of mitoses per field of view (at a magnification of 40)			
1. 0	32.1%	87.9%	47.3%
2. 1–3	61.7%	12.1%	92.6%
3. 4–7	6.2%	0.0%	100.0%
Pleomorphism			
1. general	95.1%	15.2%	93.9%
2. special (pagetoid cells)	17.3%	0.0%	100.0%

Table 4. Frequency and specifity of typical combinations of criteria

Criterion	Combinations of criteria							
Ulceration	−	−	−	+	−	−	−	−
Erosion	−	−	+	−	−	−	−	−
Infiltration	+	+	+	+	+	+	−	−
Adnexial involvement	−	+	−	−	−	−	−	−
Mitoses: 1–3	−	+	+	+	+	−	−	−
Mitoses: 4–7	−	−	−	−	−	−	−	−
General pleomorphism	+	+	+	+	+	+	+	−
Pagetoid cells	+	−	−	−	−	−	−	−
Frequency (n)	4	5	3	5	24	12	5	24
Specifity (M = m.m.; N = n.c.n.)	M	M	M	M	M	M/N (11/1)	N/M (4/1)	N/M (22/2)

infiltrative growth and involvement of adnexia; mitoses (at maximum 1–3 or 4–7 respectively per field of view at a magnification of 40×); pleomorphism in general, and the formation of pagetoid cells. Of 192 combinations theoretically possible 30 were realized, 14 of which registered more than once and 8 more than twice. The latter are shown in Table 4. Three of the more frequent combinations of criteria therefore appear in both cases of m.m. and n.c.n., in our material 41 cases are involved.

The other 73 cases show either one of the 5 more frequent combinations unequivocally linked with m.m., or one of the 6 twice and 16 once realized combinations totally specific for either m.m., *or* n.c.n. in the present material. The criteria applied to cryostat sections thus make an accurate diagnosis at a 100 p.c. level possible in 63.2% of the cases. In the other cases a highly reliable diagnosis is also possible, as one diagnosis – m.m. or n.c.n. – is far more frequent in association with each of the by principle equivocal combinations of criteria (see Table 4). Taking the more frequent diagnosis in all cases in which such a combination is found, 96.5% of cases would be diagnosed correctly, a false positive rate of 0.9% for m.m.

Although the results obtained by correlating the criteria fulfilled in a given case to any *combination* of *criteria* belonging to the thesaurus established here seem encouraging, the procedure itself would be *laborious*. Therefore we analyzed whether the *number of criteria fulfilled* allows good correlation with the diagnosis to be established. *Considering the 6 major histological and cytological criteria* laid down in Table 5 we can also diagnose *96.5% of cases correctly*, providing that *all cases with two or more major criteria fulfilled are looked upon as m.m., and all those with 0 or 1 criteria fulfilled as n.c.n. The number of false positive diagnoses of m.m.* again amounts to *0.9%*, the *number of false negatives* to *2.6%*. From Table 6, all cases with 3 or more criteria fulfilled *always* belong to the m.m. group, in these 55.3% of cases diagnostic accuracy amounts to 100%. Figure 1 graphically demonstrates the different distribution of the number of criteria fulfilled in cases of m.m. and n.c.n. The 6 criteria applied so far clearly deserve to be considered *major ones*.

Table 5. Major, minor, and insufficient criteria for the diagnosis of malignant melanoma by cryostat sections

Major criteria	Minor criteria	Insufficient criteria
Ulceration/erosion	Transepidermal elimination of cells	Transepidermal elimination of pigment
Adnexial spread of cells	Acanthosis in the marginal area	Acanthosis all over the lesion
Infiltrative spread of cells	Atrophy of epidermis	Junctional spread of melano-/nevocytes
Demonstration of mitoses	Epidermal spread of melano-/nevocytes	Corial spread of melano-/nevocytes
Pleomorphism	Multiform aspect of cells (several clones)	Uniform aspect of cells
Pagetoid cells	Stroma reaction: at all present	Lack of mitoses
	Stroma reaction: lateral	
	Stroma reaction: central	

Table 6. Number of major criteria fulfilled in malignant melanoma ($n=81$) and nevus cell nevus ($n=33$) lesions

Number of criteria fulfilled	Number of malignant melanoma lesions	Number of nevus cell nevus lesions
5	5	0
4	20	0
3	38	0
2	15	1
1	1	10
0	2	22

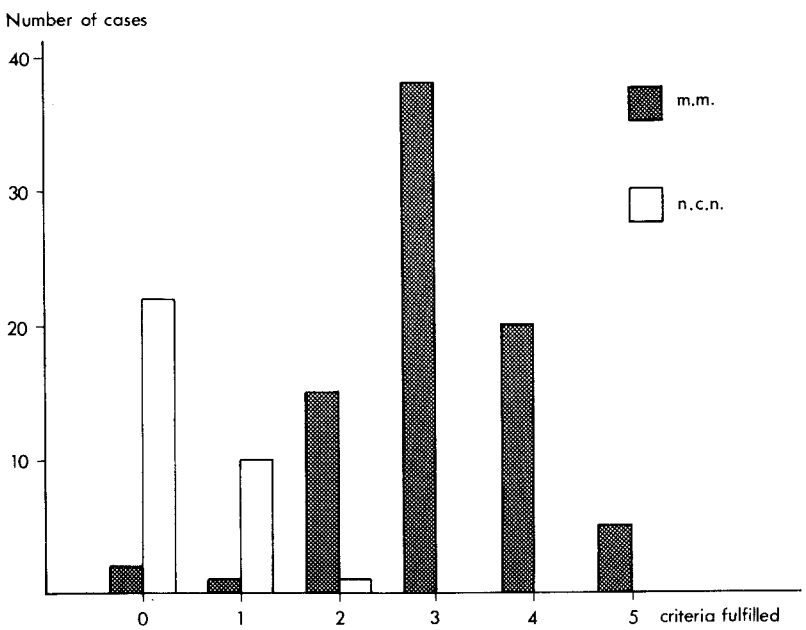

Fig. 1. Frequency distribution of the numbers of major criteria fulfilled in cases of malignant melanoma and nevus cell nevus

In order to judge whether the consideration of additional criteria could advance diagnostic accuracy further, sections with less than 3 major criteria fulfilled were checked for those criteria which are listed in the second column of Table 5. These are called *minor criteria* as *80 to 90%* of the cases in which they are present at all belong to the m.m. group. The only case of n.c.n. of the 16 positive for 2 major criteria proved positive for 6 minor ones. A rule to define cases of m.m. thus had to read: a case with 2 major and 7 or more minor criteria fulfilled represents a m.m. If this is adopted however, all but 4 of the 15 cases of m.m. showing 2 major criteria would be diagnosed as n.c.n. The situation in the cases showing 1 or 0 major criteria was similar, demonstrating that the number of minor criteria fulfilled does not contribute to differential diagnosis. The use of combinations of major and minor criteria, however, further improved diagnostic accuracy. This is especially true of the cases with 1 major criterion fulfilled, but not of these with 2 major criteria. In face of the low frequency of equivocal combinations of major criteria a final judgment in this field must be postponed.

For reasons of completeness the criteria evaluated but not yet discussed are listed in Table 5, they are called *insufficient* as less than 80% of cases where they are present belong to the m.m. group.

Discussion

To diagnose m.m. intraoperatively by frozen sections is a widely approved procedure (Hermanek and Bünte 1972; Davis and Little 1974; Braun-Falco and Konz 1980; Steigleder and Plümmer 1980). Its aim is to make definite surgical treatment by a single operation possible when the diagnosis of m.m. is presumed but not established clinically (Little and Davis 1974). Judgment of frozen sections, however, poses specific problems which are solved only in part by the new technique of cryostat sectioning. No single criterion is diagnostic alone, and due to the method applied the sections must be examined with special care (Lund and Kraus 1962). In general the differential diagnosis of clinically similar pigmented lesions such as m.m., basal cell carcinoma or thrombosing angioma by cryostat sections is easy but the differentiation between m.m. and n.c.n. can be difficult in some cases (Hermanek and Bünte 1972; Davis and Little 1974). The histological and cytological criteria usually applied for the diagnosis of m.m. must be evaluated to find out to which extent they can be applied to cryostat sections and whether the evaluation of groups of criteria can guarantee optimal diagnostic accuracy.

On the basis of our findings the criteria considered comprise major, minor, and insufficient ones. While variance analysis proved ineffective a search for certain combinations of major criteria is rewarding. An even simpler method, the determination of the number of major criteria fulfilled, makes a highly reliable diagnosis possible. Thus cryostat section diagnosis of m.m. in clinically doubtful pigmented lesions seems to be easier even for the histopathologist infrequently confronted with this problem.

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