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2 as an Original article

3 **Achieving clinical pictures of melanocytic skin neoplasms**

4 **before the histopathologic examination**

5 **does not introduce a bias in the diagnostic process**

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39 **Abstract**

40 **Background** – The *a priori* knowledge of the clinical picture of melanocytic skin
41 neoplasms (MSN) introduces a potential bias in the histopathologic examination.

42 **Methods** – Histologic slides from 99 MSN were circulated among ten histopathologists
43 with clinical expertise: five histopathologists had clinical images available after a ‘blind’
44 examination (Group 1); the other five had clinical images available before microscopic
45 examination (Group 2). Data from the two groups were compared regarding consensus
46 diagnosis (CD: a diagnosis in agreement by ≥ 4 histopathologists/group), chance-corrected
47 interobserver agreement (Fleiss’ *k*), and level of diagnostic confidence (LDC: a 1 to 5
48 arbitrary scale indicating ‘increasing reliability’ of any given diagnosis).

49 **Results** – Compared with Group 1 histopathologists, Group 2 achieved a lower number of
50 CD (84 vs. 90) but a higher *k* value (0.74 vs. 0.69) and a greater mean LDC value (4.57
51 vs 4.32). The same CD was rendered by the two groups in 81/99 cases. Spitzoid MSN
52 were most frequently controversial for both groups.

53 **Conclusions** – The histopathologic interpretation of MSN seems to be not influenced by
54 the knowledge of the clinical picture before histopathologic examination..

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56 Introduction

57 Whether any diagnostic test should be read together with clinical information has
58 been debated since 1963, when Schreiber¹ suggested the clinical information as a way to
59 improve the accuracy of chest X-ray evaluation. Nonetheless, the impact of the clinical
60 information in diagnostic cytohistopathology has been addressed by very few studies.²⁻⁵ A
61 commonly used argument against the 'interdisciplinary' approach is that clinical
62 information may bias the reading:⁶⁻⁷ in order to minimize such a bias, the microscopic
63 examination should be carried out first blind to the clinical information and then in light of
64 them:^{4,5,8} thus, *perception* (identification of abnormal areas and their features) would result
65 unbiased by the clinical information, whereas the latter should help the final *interpretation*
66 (attribution of the abnormalities to an entity). By following such a methodology, two recent
67 studies performed in the field of dermatopathology have shown that the dermatopathologic
68 diagnosis starts as a perception of microscopic criteria which can work as such, but is
69 finally a clinically-aided interpretation.⁴⁻⁵ A major problem, however, is the potential bias
70 born by an *a priori* knowledge of the clinical picture, as happens when clinical
71 dermatologists evaluate the histologic specimens from their own patients.^{7,9-11}

72 In a previous study,⁴ the histologic slides from 99 clinically atypical melanocytic skin
73 neoplasm (MSN) were submitted to ten histopathologists, five of these with clinical
74 expertise ('clinical histopathologists'); in order to evaluate the diagnostic impact of the
75 single clinical data, clinical information were given with a five-step procedure (no
76 information; age/sex/location; clinical diagnosis; clinical image; dermoscopic image). Steps
77 1-3 of such a procedure excluded the bias of the knowledge of the clinical picture before
78 histopathology. We now introduced such a bias by submitting the same dataset from the
79 previous study⁴ to five clinical histopathologists who were requested to look at the
80 histologic slides only after having all pertinent clinical information. The new data were
81 compared with those given by the former five clinical histopathologists.

82 **Methods**

83 After an *ad hoc* authorization obtained by the patients or their guardians, 99 consecutive
84 cases of clinically/dermoscopically atypical MSN were submitted to two groups of clinical
85 histopathologists:

86 **Group 1** (ZA, RC, LC, HK, HPS): histopathologists having a stepwise access to clinical
87 information in the course of their microscopic evaluation;

88 **Group 2** (GAn, HB, CC, SS, CMS): histopathologists having full knowledge of the clinical
89 picture before the microscopic examination.

90 Each panelist is almost equally involved in routine clinical and histopathologic work.
91 Only two of the above panelists (LC and HPS) had worked for several years at the same
92 Institution.

93 For each case, a single hematoxylin-eosin stained slide, accurately checked for its
94 technical and diagnostic adequacy, was provided to each panelist.

95 All the clinical information concerning the selected cases was included into a
96 FileMaker Pro 7™ (FileMaker Inc.)-generated database. For each case, Group 1
97 histopathologists were requested to evaluate the microscopic slide according to a five-step
98 procedure: i) no information; ii) knowledge of age and gender of the patient and location of
99 the lesion; iii) clinical diagnosis; iv) clinical image; v) dermoscopic image. Group 2
100 histopathologists had all information available before microscopic examination.

101 The influence derived on the diagnosis of MSN from the knowledge of the full
102 clinical information before the histopathologic examination was checked by comparing the
103 data provided by Group 2 histopathologists with the data provided by Group 1
104 histopathologists. The parameters evaluated were: the consensus diagnosis (CD), the
105 chance-corrected interobserver agreement, and the mean level of diagnostic confidence
106 (LDC). For statistical analysis, all the diagnoses were grouped into two ratings: 'melanoma'
107 and 'nevus'.

108 CD was defined as a diagnosis made in agreement by at least four out of five
109 panelists per group. This have been recently proposed as a 'surrogate' gold standard
110 when follow-up data can give little information (as in this case: see the Results
111 section).^{12,13} Unanimous diagnoses were a subgroup of CDs; the comparison between the
112 number of both unanimous diagnoses and CDs given by Group 1 and Group 2
113 histopathologists was performed with McNemar's test.¹⁴ The given p -value is one-tailed
114 and a p -value of <0.05 indicates statistical significance.

115 Case by case, the histopathologists were asked to log into the database also a *level*
116 *of diagnostic confidence* (LDC), namely, the probability, as scored according to an
117 arbitrary scale, that they 'subjectively' attributed to the given diagnosis.¹⁵ The LDC scale
118 was structured into five levels:

119 **LDC 1** – No diagnostic certainty: no diagnosis can be made.

120 **LDC 2** – Low diagnostic certainty: a diagnosis is felt as slightly more likely.

121 **LDC 3** – Moderate diagnostic certainty: a diagnosis is favoured, but with some
122 elements of doubt.

123 **LDC 4** – High diagnostic certainty: a diagnosis is strongly favoured.

124 **LDC 5** – Absolute diagnostic certainty: no other diagnosis is possible.

125 The interobserver agreement among the observers was calculated using the k
126 statistics for multiple ratings introduced by Fleiss.¹⁶⁻¹⁸ Given $n=5$ as the number of
127 panelists, k values range between +1 (perfect agreement) and <0 (perfect disagreement);
128 values greater than 0.75 represent an excellent agreement; values lower than 0.40 a poor
129 For the comparison of LDC values a Normal z -test for dependent samples was used.¹⁹
130 The given p -value is 2-tailed and a p -value <0.05 indicates statistical significance.

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133 **Results**

134 The study included 99 cases from 96 patients (M:F=0.6:1; age range: 10-78 years; mean
135 age: 43.3 years; median age: 42 years). The most common location was the back (40
136 cases), followed by the lower limbs (16 cases) and by the upper limbs (12 cases). The
137 referring histopathologist had diagnosed 54 cases as 'nevus' and 45 cases as 'melanoma'.
138 Follow-up (range: 24-96 months; mean: 54.5 months) was available in 65 cases, 30 of
139 which originally diagnosed as melanoma. Ten of these cases underwent sentinel node
140 biopsy, which was negative in all instances; an adverse clinical outcome was recorded in
141 five cases (four sentinel node negative cases in which distant metastases developed; one
142 0.80 mm-thick melanoma in which a nodal metastasis detected 40 months after excision).
143 All the metastasizing cases received a CD of melanoma from both groups of observers.

144 Within Group 1 histopathologists, 65 cases had a unanimous diagnosis and 25
145 cases had only one discrepant diagnosis, with a CD obtained in 90/99 cases. The k value
146 was 0.69 and the LDC 4.32 ± 0.59 .

147 Group 2 histopathologists diagnosed 75/99 MSN in unanimity and 9 MSN with only
148 one discrepant diagnosis: therefore, a CD was achieved in 84/99 cases. The k value was
149 0.74; the LDC was 4.57 ± 0.39 . Thus, compared with data from Group 1, there was a lower
150 number of CD, but a greater chance-corrected interobserver agreement and a greater
151 mean LDC value. Remarkably, the differences among the number of unanimous
152 diagnoses as well as the number of CDs generated by the two groups was not statistically
153 significant (McNemar's test: $p=0.078$ for the differences in the number of unanimous
154 diagnoses; $p=0.18$ for the differences in the number of CDs), whereas the difference
155 between the mean LDC values was highly significant (Normal z-test $p<0.001$).

156 By comparing case by case the CD generated by the two groups of observers, 81
157 cases resulted with the same CD; five cases were controversial for both groups; six cases

158 were controversial only for Group 1; and seven cases were controversial only for Group 2.
159 The five most controversial cases showed Spitzoid (3/5; Fig. 1) or lentiginous (2/5; Fig. 2)
160 features. Overall, the most common morphologic patterns of controversial cases (Table 1)
161 were Spitzoid (8/18 cases), lentiginous (3/18), and regression(-like). Among these
162 controversial cases, there was no association between a given morphologic pattern and
163 the protocol of microscopic observation followed.

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167 **Discussion**

168 This study demonstrates that the histopathologist who knows the clinical picture of MSN
169 before the histopathologic examination is not biased in the final interpretation and is
170 actually strengthened in the diagnostic process.

171 It has been demonstrated that full clinical information provided after a first
172 microscopic examination accomplished blind to the clinical data can aid the final
173 interpretation for both MSN⁴ and inflammatory dermatoses.⁵ It is still disputable, however,
174 whether a bias is introduced in the diagnostic process when the full knowledge of the
175 clinical picture is achieved before histopathologic examination. This issue also involves the
176 neverending debate regarding the histopathologic practice by dermatologists and the level
177 of training required them to sign out dermatopathology cases.^{7,20}

178 We have compared some parameters (CDs, chance-corrected interobserver
179 agreement, mean LDC) provided in a series of 99 MSN by two groups of histopathologists
180 with clinical expertise: one of these (Group 1) had clinico-dermoscopic images available
181 before the microscopic examination, whereas the other (Group 2) had all clinical
182 information available *a priori*. Within the Group 2 there was a lower number of CDs: this
183 finding, although not statistically significant, could suggest that a *perception* influenced by
184 the knowledge of the clinical picture does necessarily translate into a more homogeneous
185 *interpretation*. Therefore, the extreme scenario of a clinical prejudice forcing the
186 histopathologic diagnosis²¹ is unlikely. Instead, the *k* value generated by Group 2
187 histopathologists was greater than Group 1: this means that the influence of the clinical
188 pictures is similar, regardless the moment in which they are introduced into the diagnostic
189 process.

190 A further interesting finding is the greater LDC found within Group 2
191 histopathologists, a finding which was statistically significant. This could imply that the
192 clinical picture, albeit being unable to bias the final *interpretation*, can aid the *perception*

193 and give greater strength to the diagnostic process. Parenthetically, among controversial
194 cases, there was no association between a given morphologic pattern and the protocol of
195 microscopic observation followed. As expected, controversies in Spitzoid MSN^{4,22} (an
196 example is given in Fig. 1) were found to be sizable, independent from the moment in
197 which the histopathologist is aware of the clinical picture. Along with the results of our
198 previous study,⁴ we also found some diagnostic controversy regarding lentiginous MSN
199 (an example is given in Fig. 2): all the disputable lesions of this category were removed
200 from the back of middle-aged patients (data not shown). It has been previously
201 demonstrated that the differential diagnosis between lentiginous 'dysplastic' nevus and
202 lentiginous melanoma can be significantly aided by the clinico-dermoscopic digital
203 monitoring of the lesions, since lentiginous melanoma continuously, but slowly grows and
204 remains 'in situ' over years or even decades.²³⁻²⁵ In the present study, however, data
205 regarding the 'E' (=evolution) criterion of the ABCDE clinical alphabet of melanoma²⁶ were
206 not provided, and this must be underlined as a limitation in the clinicopathologic evaluation
207 made by the panelists. Lesions with regression(-like) features^{24,27,28} have been found
208 somewhat controversial, but to a lesser extent than expected. This can be due to the fact
209 that all the MSN included in the present study had undergone macroscopic sampling
210 according to their dermoscopic features, a procedure which can help the diagnostic
211 evaluation of these lesions by highlighting their most atypical features.²⁴

212 In conclusion, there is evidence that clinical pictures of MSN can aid their
213 *interpretation* and that the latter is not biased if the clinical pictures are available before the
214 microscopic examination. Good lines of communication between dermatologists and
215 histopathologists are always desirable; when the dermatologist and the histopathologist
216 are the same person, the communication is best and, if intellectually honest, is probably
217 not misleading.

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291 Table 1 – Morphologic features of the most controversial cases of the present study

292 distributed according to the group

293

Panelists	Main morphologic pattern						
	<i>Spitzoid</i>	<i>Lentiginous</i>	<i>Regression(-like)</i>	<i>Nested</i>	<i>Halo</i>	<i>Congenital nevus-like</i>	Total
All	3	2	0	0	0	0	5
Group 1	2	0	2	1	1	0	6
Group 2	3	1	1	1	0	1	7
Total	8	3	3	2	1	1	18

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295

296 **Figure legends**

297

298 **Figure 1:** A melanocytic lesion of the thigh in a 58-year-old woman. Dermoscopy is
299 characterized by a striking asymmetry, with a reticular depigmentation associated with a
300 dotted vascular pattern in its upper portion (A). Histopathologically, the neoplasm is
301 compound, with a moderate epidermal hyperplasia (B), lack of circumscription (C), and
302 with a Spitzoid cytomorphology (D). The differential diagnosis is between a Spitz nevus
303 and an early invasive Spitzoid melanoma.

304

305 **Figure 2:** A flat melanocytic lesion of the back in a 58-year-old man.
306 Dermoscopically there is an atypical pigment network with features of regression (A);
307 histopathologically, the lesion is large, with partially preserved retiform epidermal
308 hyperplasia (B), a prevailing single cell proliferation at the junction, involvement of the
309 adnexal epithelium (C) and cytologic features of 'severe dysplasia' (D). The differential
310 diagnosis is between a 'severely dysplastic' (Clark) nevus and a lentiginous melanoma in
311 situ.²³

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