Artigo Original

Proliferações Melanocíticas de Potencial Maligno Incerto: Um Estudo Retrospetivo de 23 Doentes

J. Lopes[1], C. Sousa[1], D. Teixeira[1], D. Tente[2], A. Baptista[1], A. Moreira[1]
[1]Dermatology Department, Vila Nova de Gaia/ Espinho Hospital Center, Portugal
[2]Pathology Department, Vila Nova de Gaia/ Espinho Hospital Center, Portugal

RESUMO – **Introdução**: As lesões melanocíticas podem apresentar características histológicas que impossibilitam a sua classificação de forma dicotómica como benignas ou malignas. Estas lesões, designadas proliferações melanocíticas de potencial maligno incerto, frequentemente apresentam características limítrofes entre nevo benigno e melanoma maligno, o que reflete o seu potencial biológico indeterminado. **Métodos**: Com o objetivo de caracterizar a população de proliferações melanocíticas de potencial maligno incerto diagnosticadas no nosso centro entre 2007 e 2017, foram analisados relatórios histopatológicos de lesões melanocíticas classificadas, neste período, como displásicas ou malignas. **Resultados**: Identificaram-se 23 lesões (4,3%) com características histopatológicas *borderline* ou de potencial maligno incerto. A média de idades dos doentes foi de 34,8 anos. Dezasseis lesões (69,6%) foram observadas por um segundo patologista, com discordância interobservador em 25% dos casos. O tratamento mais frequentemente realizado foi a excisão alargada, com grande variabilidade no que concerne às margens cirúrgicas. Realizou-se biopsia de gânglio sentinela em dois doentes, que se viriam a revelar negativas. O tempo de *follow-up* mediano foi de 22 meses, não se verificando recidiva de nenhuma lesão tratada. **Discussão**: A controvérsia do tema estende-se desde a natureza e classificação destas lesões até ao seu tratamento. Com este trabalho foi possível observar a variabilidade quanto à caracterização histológica destas lesões, assim como ao seu tratamento. No entanto, a inexistência de recidivas ou mortes atribuíveis à doença corrobora o seu frequente carácter benigno e excelente prognóstico.
PALAVRAS-CHAVE – Lesões Pré-Cancerosas; Melanocitos; Melanoma; Neoplasias da Pele; Nevo Pigmentado.

Melanocytic Proliferations of Uncertain Malignant Potential: A Retrospective Study of 23 patients

ABSTRACT – ***Introduction:*** *Melanocytic lesions may present with several histologic features that make them impossible to classify in a dichotomous way, as benign or malignant. Such lesions, designated as melanocytic proliferations of uncertain malignant potential, frequently show borderline features between benign nevus and malignant melanoma, reflecting their undetermined biological potential.* ***Methods:*** *In order to characterize melanocytic proliferations of uncertain malignant potential diagnosed at our center between 2007 and 2017, histopathological reports of melanocytic lesions classified, in this period, as either dysplastic or malignant were analyzed.* ***Results:*** *Twenty-three lesions (4.3%) with borderline histopathological features or uncertain malignant potential were identified. The mean patient age was 34.8 years. Sixteen lesions (69.6%) were observed by a second pathologist, with an inter-observer disagreement on 25%. The most frequently performed treatment was wide excision, with large variability regarding the surgical margins. A sentinel lymph node biopsy was performed in two patients, both being negative. The median follow-up time was 22 months, and there was no recurrence of any treated lesion.* ***Discussion:*** *The controversy of this subject extends from the nature and classification of these lesions to their treatment. With this study we were able to verify the variability regarding their histologic characterization, as well as their treatment. However, the inexistence of recurrences and deaths attributable to the disease corroborates their frequently benign character and excellent prognosis.*
KEYWORDS – *Melanocytes; Melanoma; Nevus, Pigmented; Precancerous Conditions; Skin Neoplasms.*

Correspondência: Jorge Lopes
Serviço de Dermatologia
Centro Hospitalar de Vila Nova de Gaia/ Espinho
Rua Conceição Fernandes
4434-502 Vila Nova de Gaia, Portugal
E-mail: jorge.lopes@chvng.min-saude.pt
DOI: https://dx.doi.org/10.29021/spdv.77.4.1108

Recebido/*Received* 2019/07/31 | **Aceite/*Accepted*** 2019/10/10 | **Publicado/*Published*** 2019/12/31

Artigo Original

INTRODUCTION

For many years, from a histological point of view, the dominant paradigm was to classify melanocytic lesions in a dichotomous way, either as benign or malignant. However, these lesions may have features that give the diagnosis a certain degree of uncertainty. The pathologist is frequently confronted with lesions with borderline characteristics between benign simulants and malignant melanoma due to ambiguous diagnostic criteria and inter-observer discordance.

We define melanocytic proliferations of uncertain malignant potential (MPUMP) as those that cannot be histologically classified as benign or malignant, presenting ambiguous features that reflect their undetermined biological potential.

These lesions can be divided into two generic categories: superficial - superficial atypical melanocytic proliferations of unknown significance (SAMPUS) and deep - melanocytic tumors of uncertain malignant potential (MELTUMP). In the first category we include predominantly junctional lesions and lesions confined to the epidermis and papillary dermis, without evidence of tumor proliferation or mitoses in the dermal component. As such, the risk of metastasis is expected to be low and the prognosis excellent. The differential diagnosis is made mainly between in situ melanoma and dysplastic junctional nevus. The second category, MELTUMP, consists of lesions with a dermal tumor component, therefore with a potential local and distant metastatic capacity. Due to their atypical characteristics, the diagnosis of invasive melanoma cannot be safely discarded. In this category we include atypical Spitz nevus, deep penetrating nevus, cellular blue nevus and nevoid melanoma.[1]

We henceforth tried to characterize and review MPUMP diagnosed at our department.

METHODS

In this study, we performed a retrospective analysis of MPUMP diagnosed in our department between 2007 and 2017. To perform this task, a search in the database of the Pathology Department of this center was carried out. Histopathological reports coded, according to SNOMED classification, as "Dysplastic Nevus", "Melanoma in situ", "Malignant melanoma" and "Epithelioid or Spindle Cell Nevus" were searched. The lesions described on the histology report as having borderline features, such as cytoarchitectural atypia, pagetoid spread, deep mitosis, asymmetry or loss of vertical maturation were included. By consulting the clinical file and histology report, variables such as demographic characteristics (age and gender), lesion characteristics and its anatomical location, histopathological features, treatment performed, follow-up time and recurrences were extracted.

Categorical variables are presented with absolute and relative frequency and continuous variables with mean and standard deviation (SD) or with median and interquartile range (IQR) for variables that do not follow a normal distribution. The normal distribution was verified using the Shapiro-Wilk test or skewness and kurtosis values.

One-way ANOVA was used to compare patient age and follow-up times for each type of lesion. Chi-square test was used to evaluate the relation between lesion classification and a second pathological observation.

All p values reported are two-tailed, with a p value lower than 0.05 indicating statistical significance. Tests were conducted using SPSS software (IBM Analytics), version 23.0.

RESULTS

Five hundred and thirty nine histopathological reports coded as "Dysplastic Nevus", "Melanoma in situ", "Malignant Melanoma" or "Epithelioid or Spindle Cell Nevus" were analyzed. Twenty three lesions (4.3%) with characteristics of uncertain malignant potential were identified. The majority (60.3%) of these lesions were diagnosed in the last 3 years of analysis.

Lesional features

Eight (34.8%) superficial lesions and 15 (65.2%) deep lesions were identified (Table 1). Most of the superficial lesions were classified by the pathologist as SAMPUS and most of the deep lesions were classified as atypical Spitz nevus. Eleven (47.8%) lesions were reported to have a spitzoid phenotype,

Table 1 - Histologic characteristics of the lesions.

	Superficial	Deep	Total	*p value*
Histologic classification, n (%)				
• Borderline dysplastic nevus	3 (37.5)	0	3 (13.0)	
• SAMPUS	5 (62.5)	0	5 (21.7)	
• Atypical Spitz nevus	0	11 (73.3)	11 (47.8)	---
• MELTUMP	0	3 (20.0)	3 (13.0)	
• Deep penetrating nevus	0	1 (6.7)	1 (4.3	
Histological characteristics, n (%)				
• Cytoarchitectural atypia	5 (62.5)	15 (100.0)	20 (87.0)	
• Pagetoid spread	6 (75.0)	8 (53.3)	14 (60.9)	
• Deep mitosis	0	3 (20.0)	3 (13.0)	-
• Dermal inflammatory infiltrate	6 (75.0)	10 (66.7)	16 (69.6)	
• Loss of vertical maturation	0	2 (13.3)	2 (8.7)	
Second observation, n (%)	2 (25.0)	14 (93.3)	16 (69.6)	0.02

Table 2 - Demographic characteristics and lesion location.

	Superficial	Deep	Total	*p value*
Sex, n (%)				
• Male • Female • Age, Mean (SD), years	4 (50.0) 4 (50.0) 43.0 (14.6)	4 (26.7) 11 (73.3) 30.5 (14.8)	8 (34.8) 15 (65.2) 34.8 (15.6)	0.065
Location, n (%)				
• Head and neck • Trunk • Upper limbs • Lower limbs	0 5 (62.5) 0 3 (37.5)	3 (20.0) 3 (20.0) 2 (13.3) 7 (46.7)	3 (13.0) 8 (34.8) 2 (8.7) 10 (43.5)	

Table 3 - Treatment performed.

	Superficial	Deep	Total
Treatment performed, n (%)			
• Narrow excision • Wide excision with 5 mm margins • Wide excision with 10 mm margins	0 6 (75.0) 2 (25.0)	7 (46.7) 5 (33.3) 3 (20.0)	7 (30.4) 11 (47.8) 5 (21.7)
Sentinel lymph node biopsy, n (%)			
• Positive • Negative	0 0	0 2 (100.0)	0 2 (100.0)

defined as epithelioid or fusiform cellular morphology, and were found exclusively on deep lesions.

The most frequent histopathological features reported by the pathologist were cytoarchitectural atypia in 87.0%, dermal inflammatory infiltrate in 70.0%, pagetoid spread in 60.9%, deep mitoses in 13.0% and loss of vertical maturation in 8.7%.

Sixteen (70.0%) lesions, 14/15 deep lesions (93.3%) and 2/8 superficial lesions (25%) were observed by a second pathologist specialized in melanocytic tumors, who in 25.0% of cases had a different opinion concerning the nature of the lesions (two SAMPUS and one MELTUMP initially classified as dysplastic nevi as well as one atypical Spitz nevus initially classified as spitzoid melanoma).

Population

Eight (34.8%) lesions occurred in male patients and 15 (65.2%) in females (Table 2), with no predilection of gender for any histopathological type of lesion.

The mean patient's age was 34.8 (SD 15.6) years, ranging from 5 to 65 years. The mean age of patients with spitzoid lesion phenotype was 27.2 (SD 11.2) years, while that of non-spitzoid was 41.8 (SD 16.2) years ($p = 0.02$). There was no significant difference on patient's age in the other groups of lesions.

As to lesion location, the most frequent sites were the lower limbs (43.5%), followed by the trunk (34.8%), head and neck (13.0%), with no particular association between the type of lesion and localization.

Treatment

For superficial lesions, wide excision with a 5 mm margin was performed in six out of eight cases (75%) and 10 mm margin in the other two cases. For deep lesions, the most frequent approach was narrow excision (7/15 cases, 47%), followed by wide excision with a 5 mm margin (5/15, 33%) and wide excision with a 10 mm margin (3/15, 20%) (Table 3).

Two patients with deep lesions underwent a sentinel lymph node biopsy, which were negative in both cases.

Follow-up

To date, 10 (43.5%) patients remain under surveillance at our department, three (13.0%) are followed at another center and 10 (43.5%) were lost during follow-up (Table 4). Patients with superficial lesions were followed for a median period of 10.0 months (min. 6 months, max. 36 months),

Table 4 - Follow-up time and recurrences.

	Superficial	Deep	Total	*p value*
Follow-up, median (IQR), months	10.0 (21.0)	22.0 (25.0)	22.0 (20.0)	0.506
Local or distant recurrence	0	0	0	

Artigo Original

while those patients with deep lesions were followed for 22.0 months (min. 0 months, max. 84 months) ($p = 0.23$). Overall, the median follow-up time was 22.0 months (IQR 20.0, range 0 to 84 months).

During the follow-up period, no local, regional or distant recurrences were identified.

DISCUSSION

Although rare, the number of lesions diagnosed as having uncertain malignant potential has been increasing. In our population, 60.9% of the lesions were diagnosed in the last 3 years of the study. In our opinion, the increasing diagnosis does not reflect an increase in the prevalence of these lesions, but rather a greater awareness of these entities.

The mean age of the patients (34.8 years) is in agreement with similar series.[2,3] Furthermore, lesions with spitzoid phenotype were found in significantly younger patients, corroborating the already available data showing their increased prevalence in this population.[4]

Regarding treatment, it was possible to verify a large variability in the approach to these lesions, expressed by the different excision margins used on lesions with similar characteristics, which reflects the absence of studies and guidelines on this subject. Interestingly, superficial lesions and, therefore, with no or low expected metastatic potential, were subjected to more aggressive approaches, such as excision with 5 mm margins. This discrepancy may be related to a greater number of deep lesions that were classified as "melanocytic nevus" at the time of the clinical diagnosis. We presume that under a clinical impression of benignity, clinicians selected less aggressive approaches.

In this study, only two patients underwent sentinel lymph node biopsy. Meyers *et al*[5] performed a sentinel lymph node biopsy in 31 patients with MELTUMP, five (16%) of which were positive. Lallas *et al*[6] have demonstrated that this may be positive in up to 31% of patients with atypical Spitz nevi, although mortality is very low. In essence, a positive sentinel lymph node biopsy does not seem to predict a more aggressive or unfavorable prognosis, and its execution is discouraged by some authors.[7]

During follow-up we found no local/distant recurrences or deaths attributable to the disease. Although with a relatively short follow-up period, this study corroborates previous studies where patients were followed for longer periods, confirming the good prognosis of these entities.[2,5,8]

Only 70% of these neoplasms were observed by a second pathologist, which, in our view, is insufficient. When confronted with a situation of uncertainty, a second observation and consequent discussion may lead to the reduction of its subjective side and diagnostic error. But a second observation is, indeed, associated with a high inter-observer discordance on the nature of the lesion. This is ultimately a reflection of the pathologists' criteria and their experience and a further indicator of the importance of this discussion.[9]

This study is not without limitations. Perhaps the most important ones are the low sample size (n=23). The authors, however, feel these numbers are still significant, as they account for 10 years of MPUMP diagnosed at this center, given their low rate of occurrence. Another important limitation is the fact that the histology report was the sole source of information regarding lesion characteristics, as no slides were reviewed for this study. Other potential weaknesses include the non-detection of some lesions when searching the database, due to coding errors or the complete lack of coding, and the short median follow-up time (22 months). Despite these limitations, this is one of the few studies analyzing the diagnosis and management of MPUMP (both deep and superficial), and the first performed in a Portuguese population.

To conclude, in this study we were able to verify the benign behavior of these lesions within the relatively short term follow-up, given their extremely low rate of recurrences and deaths attributable to the disease. However, the inexistence of clinical guidelines for this subject leads to a high variability on their management, expressed by the different treatment approaches for similar lesions. Further studies are needed to clarify the biologic behavior of these entities as well as their best management strategy.

Conflitos de interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Protecção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.
Consentimento: Consentimento dos doentes para publicação obtido.

Conflicts of interest: *The authors have no conflicts of interest to declare.*
Financing support: *This work has not received any contribution, grant or scholarship.*
Confidentiality of data: *The authors declare that they have followed the protocols of their work center on the publication of data from patients.*
Protection of human and animal subjects: *The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).*
Patient Consent: *Consent for publication was obtained.*

Proveniência e revisão por pares: Não comissionado; revisão externa por pares
Provenance and peer review: *Not commissioned; externally peer reviewed*

REFERENCES

1. Elder D, Xu X. The approach to the patient with a difficult melanocytic lesion. Pathology. 2004;36:428-34. doi: 10.1080/00313020412331283905
2. Pusiol T, Piscioli F, Speziali L, Zorzi MG, Morichetti D, Roncati L. Clinical features, dermoscopic patterns, and histological diagnostic model for melanocytic tumors of uncertain malignant potential (MELTUMP). Acta Dermatovenerol Croat. 2015;23:185-94.
3. Abraham R, Karakousis G, Acs G, Ziober A, Cerroni L, Mihm M, et al. Lymphatic invasion predicts aggressive behavior in melanocytic tumors of uncertain malignant potential (MELTUMP). Am J Surg Pathol. 2013;37:669-75. doi: 10.1097/PAS.0b013e318288ff47
4. Requena C, Requena L, Kutzner H, Yus E. Spitz nevus: a clinicopathological study of 349 cases. Am J Dermatopathol. 2009;31:107-16. doi: 10.1097/dad.0b013e3181934218
5. Meyers M, Yeh J, Deal A, Byerly F, Woosley J, Frank J, et al. Age and Breslow depth are associated with a positive sentinel lymph node in patients with cutaneous melanocytic tumors of uncertain malignant potential. J Am Coll Surg. 2010;211:744-8. doi: 10.1016/j.jamcollsurg.
6. Lallas A, Kyrgidis A, Ferrara G, Kittler H, Apalla Z, Castagnetti F, et al. Atypical Spitz tumours and sentinel lymph node biopsy: a systematic review. Lancet Oncol. 2014;15:e178-83. doi: 10.1016/S1470-2045(13)70608-9.
7. Piccolo V, Moscarella E, Lallas A, Alfano R, Ferrara G, Argenziano G. MELTUMP: how to manage these lesions in the clinical routine. G Ital Dermatol Venereol. 2017;152:266-9. doi: 10.1016/S1470-2045(13)70608-9
8. Green R, Taghizadeh R, Lewis C, Lawrence C, Husain A, Ahmed O. Melanocytic tumours of uncertain malignant potential (MELTUMPs) - a diagnostic and management dilemma. Eur J Plast Surg. 2014;38:13-6. doi: 10.1007/s00238-014-1028-3
9. Cerroni L, Barnhill R, Elder D, Gottlieb G, Heenan P, Kutzner H, et al. Melanocytic Tumors of Uncertain Malignant Potential: results of a tutorial held at the XXIX Symposium of the International Society of Dermatopathology in Graz, October 2008. Am J Surg Pathol. 2010;34:314-26. doi: 10.1097/PAS.0b013e3181cf7fa0