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Expression profiles in malignant fibrous histiocytomas: Clues for differentiating ‘spindle cell’ and ‘pleomorphic’ subtypes

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ARTICLE INFO

Article history:

Received 10 August 2007

Accepted 9 October 2007

Available online 4 December 2007

Keywords:

Malignant fibrous histiocytoma

MMP-1

MMP-9

p27(kip1)

ABSTRACT

We analysed 21 samples of malignant fibrous histiocytoma (MFH) distinguished into the two principal morphological categories (‘spindle cell’ and the ‘pleomorphic’ subtypes). The aim of our study was to verify if a distinction between the two subclasses of MFH in terms of expression/activation of protein profiles could support and extend the morphological criteria. For this purpose, we carried out an immunohistochemical and immunoblotting analysis of proteins that could be relevant in sarcoma biology and potential diagnostic and therapeutical targets such as matrix metalloproteinases (MMPs) and molecules related to adhesive and proliferative properties. Our analysis revealed that MMP-1, MMP-9 expression and p27(kip1) cytoplasmic localisation can be considered valid parameters in the classification and potential explanation of the aggressive behaviour of this non-homogeneous group of MFH.

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1. Introduction

Soft tissue sarcomas (STS) comprise a heterogeneous group of mesenchymal tumours. Malignant fibrous histiocytoma (MFH) has been regarded as the most common STS in adult life but it has been plagued by controversy in terms of both histogenesis and validity as a clinicopathological entity.^{1,2} The trend for some pathologists to diagnose MFH less frequently than other subtypes may result from different diagnostic criteria reflecting the concept of MFH as a common morphological manifestation of a variety of poorly differentiated STS, resulting in the diagnosis of MFH after a process of exclusion. A schematic morphological approach to STS considers a final distinction into three categories on the basis of cell shape: round cell morphology, spindle cells admixed

with other mesenchymal elements (pleomorphic) and predominantly spindle cell morphology.³ MFHs can be found within the ‘spindle cell’ and the ‘pleomorphic’ subtypes.³ These two principal morphological categories result useful as they indicate different clinical outcomes, being the pleomorphic type the more aggressive form of the tumour. MFHs are tumours consisting of an admixture of fibroblastic, histiocytic and undifferentiated cells arranged in a storiform growth pattern. The undifferentiated cell may represent a progenitor with capacity to differentiate into histiocytic and fibroblastic cells but the relationship between histiocytic-like cells and true macrophages/histiocytes remains debatable. In fact, some authors consider histiocytic-like cells present in MFH as normal infiltrating macrophages induced by chemo-attractants.⁴ By sharpening the distinction between sarcoma

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doi:10.1016/j.ejca.2007.10.012

Table 1 – Patient clinical features

Case number	F/M	Age	Extent of disease	Site of primary
'Pleomorphic' MFH				
17	M	71	Local recurrence	Extremity
40	M	85	Local recurrence	Extremity
117	F	67	Local recurrence	Extremity
127	F	63	Metastases (sub cutis)	Extremity
129	M	69	Primary disease	Extremity
139	F	33	Metastases (lung)	Extremity
147	M	30	Local recurrence	Retroperitoneal
148	M	50	Metastases (lung)	Extremity
158	M	70	Metastases (lung)	Extremity
175	F	64	Local recurrence	Extremity
209	F	34	Metastases (back)	Extremity
212	F	34	Metastases (lung)	Extremity
228	M	71	Metastases (lung)	Retroperitoneal
251	M	58	Primary disease	Extremity
'Spindle' MFH				
31	F	86	Local recurrence	Breast
83	F	87	Local recurrence	Breast
169	M	79	Primary disease	Extremity
182	F	60	Local recurrence	Extremity
183	M	57	Primary disease	Gastric
187	M	80	Local recurrence	Extremity
264	F	33	Local recurrence	Extremity

types and including functional criteria in the classification, it is likely that genes that define biologically specific features can provide a better characterisation of distinct groups. The products of these genes might include diagnostic markers related to tumour histogenesis as well as targets for new therapies.

While certain tumours exhibit fairly consistent and predictable histiotype-specific behaviour, other lesions, in particular MFH, present with a broad range of clinical behaviour not immediately predictable from histological typing alone. New expression profiles of these poorly differentiated adult STS could be very useful to improve our understanding of MFHs and their biology and origin. Recent reports on gene expression profiles of STS using cDNA microarray technologies provided new insights into MFH characterisation^{5–7} and suggested MFHs as a pleomorphic subtypes amongst STS.

Tumour growth and metastasis involve molecular interactions between tumour cells and the surrounding normal tissues. Several steps are involved in this process, but degradation of the extracellular matrix (ECM) is an essential prerequisite for expansive growth of primary tumours, metastatic spread and neoangiogenesis. In particular, amongst the proteases involved, the MMP family is frequently implicated in the process of ECM degradation.^{8,9} The proper management of the ECM represents a specialised function of mesenchymal cells and includes cell proliferation and migration required for ECM restoration in physio- and pathological situations. While MMP activity is very important in many malignancies such as carcinomas,¹⁰ little is known on the role of MMPs in STS and in particular in MFHs.

The aim of our study was to verify if a distinction between the two major subclasses of MFH ('spindle cells' and 'pleomorphic') in terms of expression/activation of MMPs

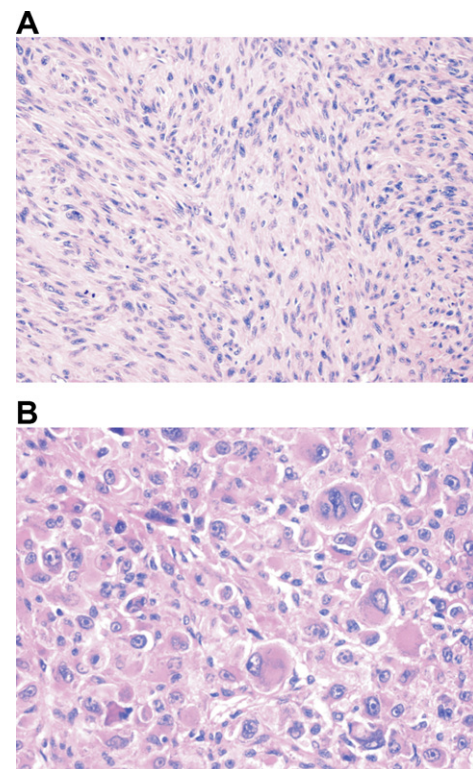


Fig. 1 – MFHs display marked pleomorphism, often with bizarre giant tumor cells, admixed with spindle and rounded histiocyte-like cells, sometimes with foamy cytoplasm. The spindle cells are prominent in (A) whereas the pleomorphic cells prevail in (B). Haematoxylin–eosin staining. Original magnification 100× (A), 200× (B).

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