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Original article

Comparison between retroperitoneal leiomyosarcoma and dedifferentiated liposarcoma

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ABSTRACT

It is important to distinguish between leiomyosarcoma (LMS) and dedifferentiated liposarcoma (DDLS) in the retroperitoneum. The dedifferentiated component of DDLS shows an LMS-like morphology in some cases; thus, detailed evaluation is necessary to achieve an accurate diagnosis. Immunohistochemically, MDM2 and myogenic markers provide clues for the diagnoses. However, immunoreactivity for MDM2 and myogenic markers has not been well studied in retroperitoneal LMS and DDLS. Here, we compared the clinicopathological data of 20 retroperitoneal tumors initially diagnosed as LMS with that of 36 cases of retroperitoneal DDLS and conducted an immunohistochemical study. Four (20%) of the cases initially diagnosed as LMS were immunoreactive for MDM2. Fifteen cases (41.7%) of DDLS showed positive expression of two or more myogenic markers. The patients with LMS with MDM2 overexpression were older than the patients with LMS without MDM2 overexpression ($P = 0.0328$). LMS with MDM2 overexpression showed a worse prognosis than DDLS ($P = 0.0408$). No significant difference in prognosis was found between LMS without MDM2 overexpression and DDLS with myogenic differentiation. In conclusion, we recommend that systemic MDM2 expression analysis be performed in cases of retroperitoneal sarcoma. Overdependence on the expression of myogenic markers could lead to misdiagnosis in distinguishing LMS from DDLS.

1. Introduction

Retroperitoneal sarcomas represent approximately 16% of all soft tissue sarcomas [1]. The most common histologic subtypes of sarcomas in the retroperitoneum are well-differentiated/dedifferentiated liposarcoma (WD/DDLS) and leiomyosarcoma (LMS) [2]. WDLS and DDLS share the same genetic abnormality characterized by giant chromosomes wherein *MDM2* (12q15) is consistently amplified. In contrast, LMS usually shows a highly complex karyotype [3]. WD/DDLSs often recur in the retroperitoneum, whereas LMSs are prone to both local recurrence and distant metastasis. It is important to obtain an accurate diagnosis in order to determine the patient prognosis and make a treatment plan with which to follow-up after surgery.

It is sometimes difficult to distinguish between LMS and DDLS. The histological feature of DDLS is the transition from WDLS to non-lipogenic sarcoma as the dedifferentiated component. In some cases, the dedifferentiated component shows LMS-like morphology; thus, detailed evaluation is necessary to obtain an accurate diagnosis. The presence of a well-differentiated (lipogenic) component is the key difference between LMS and DDLS; however, it is difficult to obtain an accurate diagnosis of DDLS without a well-differentiated component [4–6].

Immunohistochemical and molecular analyses are applied to distinguish between LMS and DDLS. The presence of immunoreactivity for two myogenic markers is supportive of LMS. MDM2 expression is a key feature of DDLS [3]. However, *MDM2* amplification can be observed in LMS [7,8], and myogenic differentiation is not a rare event in DDLS [9]. Therefore, the relationship between LMS with *MDM2* amplification and DDLS with myogenic differentiation in cases of retroperitoneal sarcoma must be investigated.

Herein, we compared 20 retroperitoneal tumors initially diagnosed as LMS, including 4 cases, which were later shown by

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immunohistochemistry (IHC) to overexpress MDM2, with 36 cases of retroperitoneal DDLS using clinicopathological data.

2. Materials and methods

2.1. Materials

Twenty cases and 36 cases of previously diagnosed retroperitoneal LMS and DDLS, respectively, were retrieved from the registry file of the Department of Anatomic Pathology, Kyushu University (Fukuoka, Japan) between 1976 and 2015. Thirteen and 36 formalin-fixed, paraffin-embedded (FFPE) specimens of LMS and DDLS were available, respectively. The median number of slides we assessed in performing the diagnosis was 21.5 (range: 1–90) for DDLS and 8 (range: 1–27) for LMS. All DDLS cases were accompanied by a well-differentiated liposarcoma-like component. These components were not observed in LMS cases.

The histological grade was evaluated according to the grading system of the French Federation of Cancer Centers (FNCLCC) [10]. Clinical details and follow-up information were obtained by reviewing the patients' medical charts.

This study was approved by the Ethics Committee of Kyushu University (No. 27-77).

2.2. IHC

Immunohistochemical staining was performed in the cases for which it was available. FFPE tissue was cut at 3 μm. The primary antibodies, clones, dilutions, and sources are listed in Table 1. The immune complex was detected with the DAKO EnVision Detection System. Immunoreactivity for MDM2 was assessed in all cases. Immunoreactivity for myogenic markers, α-smooth muscle actin, desmin, calponin, and h-caldesmon were assessed in the dedifferentiated component of DDLS.

2.3. Fluorescence in situ hybridization (FISH)

Among the LMS cases in which MDM2 expression was confirmed by IHC, FISH analysis was performed on tissue sections using the MDM2 (TexRed)/CEN1q (FITC) Dual Color FISH Probe (Abnova, Taipei, Taiwan). Each FFPE block was cut at 4 μm. FISH analyses were conducted according to the manufacturer's instructions and according to the method described in a previous report [11].

2.4. Statistical analysis

Clinicopathological and immunohistochemical data were described using the median and range for quantitative data and the frequency and percentage for qualitative data. The Fisher exact test and Student's *t* test were applied to evaluate the association between two variables for the qualitative and quantitative data, respectively. Survival data were presented in terms of 2-year survival rates and analyzed using the log rank test. The data analyses were conducted with JMP statistical software (ver. 9.0.2, SAS Institute, Cary, NC).

3. Results

Among the 20 cases previously diagnosed as LMS, 4 cases were immunoreactive for MDM2. We named this cohort "LMS with MDM2 overexpression." (Figs. 1 and 2) The remaining 16 LMS cases were named "LMS without MDM2 overexpression." Among the 4 cases in the former cohort, FFPE specimens were available in 3 cases. These 3 cases were further analyzed by FISH and confirmed to have *MDM2* amplification (Fig. 3). In addition, immunohistochem-

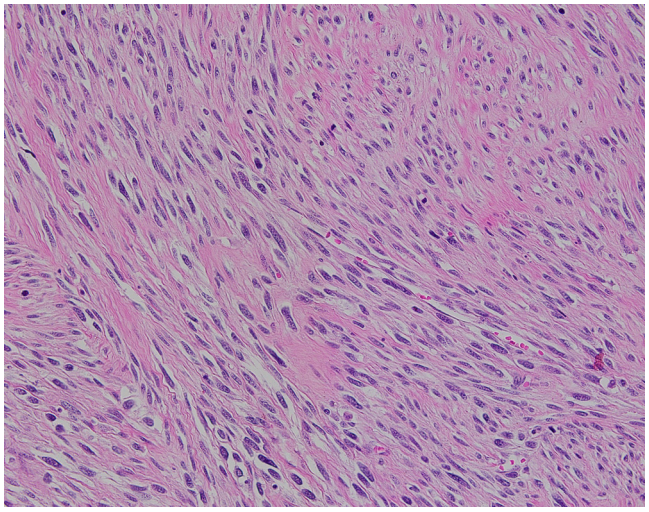

Fig. 1. Representative H&E stain of leiomyosarcoma with *MDM2* overexpression.

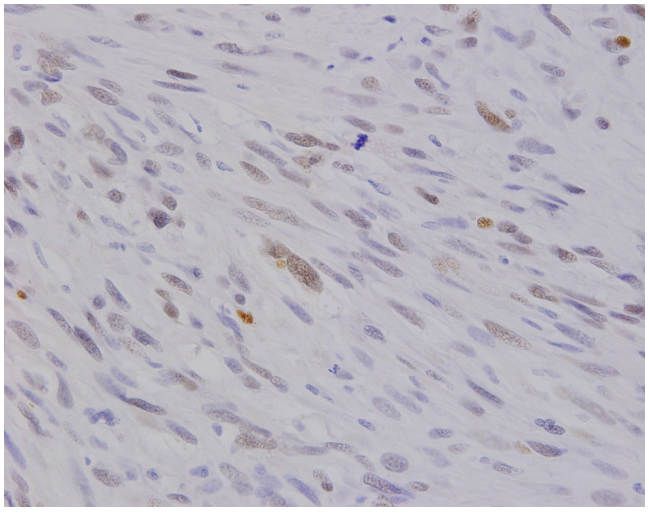

Fig. 2. The immunohistochemical result of leiomyosarcoma, indicating nuclear staining for MDM2.

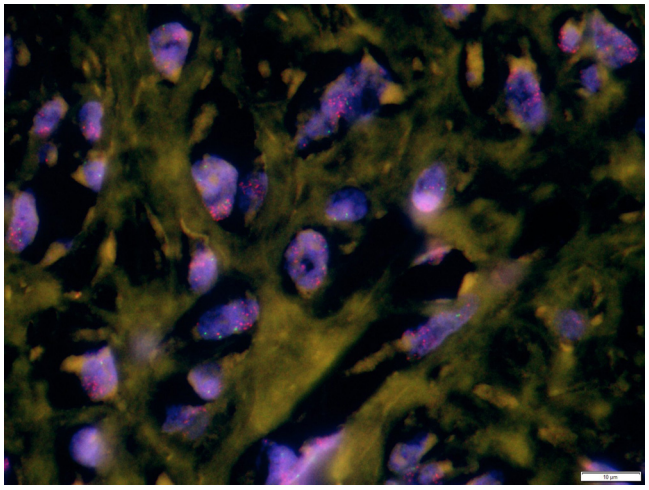

Fig. 3. A cluster of red signals (MDM2) present in a cluster in a tumor cell nucleus (green: centromere of chromosome 12).