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Clinical Pathological Analysis of Synovial Sarcoma

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OBJECTIVE To investigate the clinical diagnosis and differential diagnosis of synovial sarcoma (SS).

METHODS A total of 41 paraffin-embedded synovial sarcoma samples were examined by H&E staining, immunohistochemistry staining and the reverse transcriptase polymerase chain reaction (RT-PCR), in order to provide a scientific bases for diagnosis and differential diagnosis.

RESULTS Twelve cases were a biphasic type, 22 cases were a monophasic fibrous type, and 7 cases were a poorly differentiated type. Thirty-six cases were both CK (and/or EMA) and Vim positive. Five cases were only Vim positive. A SYT-SSX fusion gene was detected in 18 cases by RT-PCR.

CONCLUSION By observation of the histomorphology, immunohistochemistry markers and detection of a SYT-SSX fusion gene, we can make a clinical pathological diagnosis of synovial sarcoma.

KEYWORDS: synovial sarcoma, clinical pathology, diagnosis.

INTRODUCTION

Synovial sarcoma is a type of malignant soft tissue tumor, the origin of which is still unknown. It accounts for 5%~10% of sarcomas[1]. Based on biphasic differentiation and clinical findings, it can be diagnosed clinically. But some cases occur in old patients and in unusual parts of the body, for example: larynx and throat, lung, kidney, skull base, pleura, major pectoral muscle and heart etc. Diagnosis is difficult in some without an obvious biphasic differentiation. In order to provide a diagnostic bases for clinical and differential diagnosis, we have conducted the study of SS at three levels: histomorphology, immunohistochemistry and molecular biology.

MATERIALS AND METHODS

Clinical samples

A total of 41 synovial sarcoma samples were collected from 1994~2003 in the JiangSu People's Hospital. All samples were fixed by 10% formalin, and paraffin embedded. Following routine H&E staining, all slides were observed microscopically.

Immunohistochemistry

Slides were stained by SP methods. The following mouse monoclonal antibodies(McAb) against human antigens were used: CK, EMA, Vim, SMA, Des, s-100, PGP and PCNA. Products of the DAKO Co. were all purchased from the Fujian Maixin Co.

Assessment of positive expression was conducted by considering the strength of positive staining and number of positive cells. First a score for strength of positive staining was given: no colour was 0, light yellow was 1, brown was 2, deep brown was 3. Second a score for the percentage of positive cells was given: negative was 0, positive cells ≤ 10% was 1, 11%~50% was 2, 51%~75% was 3, >75% was 4. If multiplication of these two scores was >3, the immunohistochemical staining was considered to be positive.

Reverse transcriptase-polymerase chain reaction (RT-PCR)

RNA extraction was conducted using a Trizol kit. The PCR amplication primer sequences were: the forward primer (FP): 5'-CCAGCAGGCCTTATGGATA-3', the reverse primer (RP): 5'-TTTGTGGGCCAGATGCTTC-3', both lengths were 98 bp. Amplication conditions: denaturation at 94℃ for 50 s, annealing at 58℃ for 30 s and extension at 72℃ for 1 min, totally 40 cycles. The PCR product was electrophoresed on a 3% agarose gel and stained with ethidium bromide.

Statistical analysis

The χ^2 test was conducted with SPSS statistical software, designed for the experimental groups.

RESULTS

Clinical data

The cases were comprised of 24 males and 17 females with a ratio of 1.4:1, ranging in ages 9 to 67 years old, with an average of 35.4. The tumors occured in the following locations: head-neck 1 (2.4%), trunk 5 (12.3%), upper extremities 6 (14.6%), and lower extremities 29 (70.7%). Clinical complaints were localized palpable swelling or mass, associated with pain and limitation of joint motion.

Histomorphology

Gross findings

Tumors were round or multilobular, poorly circumscribed, and having a size between 1× 2 × 2 cm to 5 × 12 × 16 cm. On section they were gray-yellow, and exhibited a rather variegated appearance with cyst formation, hemorrhage, and necrosis.

Microscopic findings of the cases

Twelve (29%) were biphasic type, 22(54%) were monophasic fibous type and 7 (17%) were poorly differentiated type. Spindle-shaped cells were uniform with little cytoplasm, not well outlined, with oval dark-staining nuclei and oriented. Some areas appeared with myxoid degeneration and hemangiopericytomatous vasculature changes (Fig.1). Epithelial cells were oval, distinctly outlined, with abundant pale-staining cytoplasm and large vesicular nuclei. They were disposed in solid cords, nests, or glandular structures (Fig.2). Mast cells could obviously be seen infiltrated in 8 cases (Fig.3).

Immunohistochemistry

CK was cytoplasm positive (Fig.4). EMA was positive in the cytoplasm or on the cell membranes. Vim was cytoplasm positive (Fig.5). Des, α-SMA, s-100, PGP were all cytoplasm positive. PCNA was nuclei positive.

Statistical results showed that there were no significant differences between the expression of CK and EMA (P>0.01). Both could serve as antibodies for epithelial markers. On the contrary, there were significant differences between the positive expression of Des, SMA, s-100 and Vim, CK, and EMA (P<0.01), demonstrating that Des, SMA, s-100 are not the significant markers for synovial sarcomas.

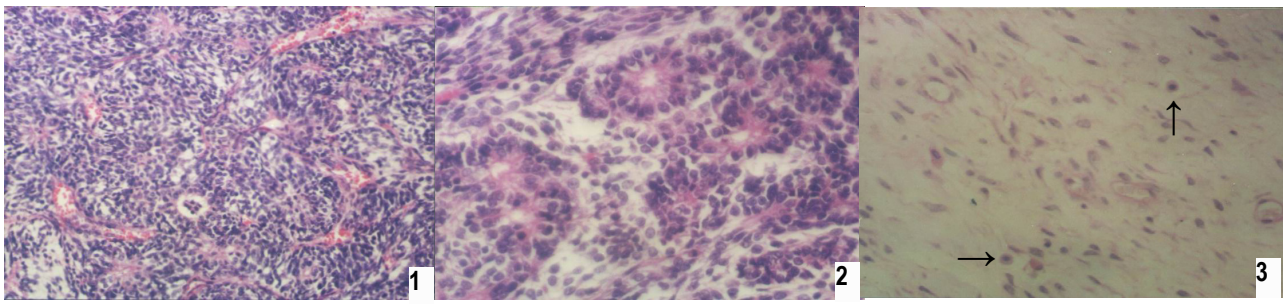

Fig.1. Hemangiopericytomatous vasculature in synovial sarcoma (×200). Fig.2. Epithelial cells appear glandular in structure (×400). Fig.3. Myxoid degeneration area with mast cells infiltrated (×400).

Table 1. Results of immunohistochemistry and the positive ratio expression.

	Negative	Positive	Positive ratio (%)
CK	5	36	87.8%
EMA	6	35	85.4%
Vim	0	41	100.0%
Des	40	1	2.5%
SMA	41	0	0.0%
s-100	35	6	14.6%
PGP	10	31	75.6%
PCNA	3	38	92.7%

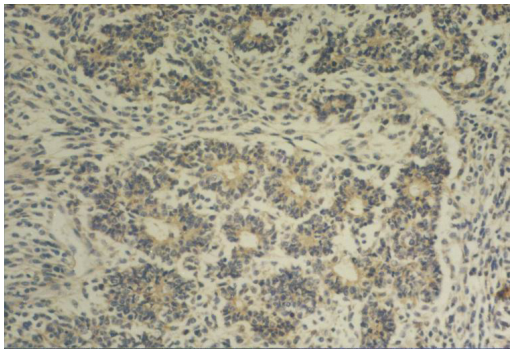

Fig.4. CK positive expression in a glandular structure area (×200).

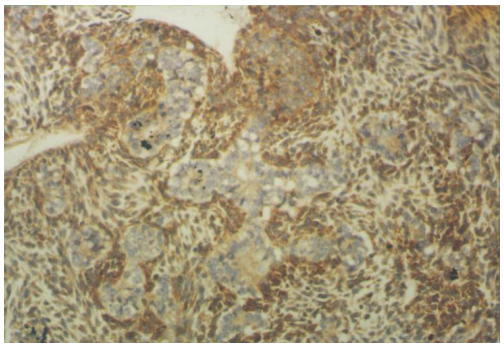

Fig.5. Vim positive expression in a spindle cell area (×400).

RT-PCR

Using 20 cases of paraffin-embedded tumors with less hemorrhage and necrosis, (the samples with hemorrhage and necrosis were not examined in order to avoid contamination), the expression of the SYT-SSX fusion gene was detected in 18 cases (90%). Two cases were negative (Fig.6).

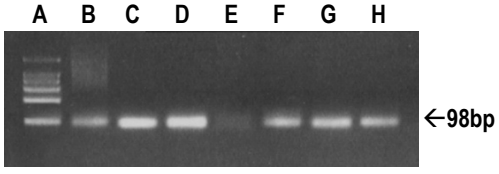

Fig.6. Results of detection of the SYT-SSX fusion gene. Lane A represented the marker. Lane B, C, D, F, G and H represented samples. Lane E represented the negative control.

DISCUSSION

Origin of the tumors

Studies of molecular genetics have demonstrated that synovial sarcomas are a unique type of soft tissue tumor, with a chromosome translocation and formation of a SYT-SSX fusion gene[1].

Pathological features

According to the data from the Armed Forces Institute of Pathology(AFIP), synovial sarcomas rank fourth in malignant soft tissue tumors, but in China these tumors rank second in malignant soft tissue tumors[2]. In typical biphasic tumors, epithelial cells deposit in mass or have a trend for a glandular structure; there are transformations between spindle cells and epithelial cells[3]. Monophasic fibrous type tumors consist mainly of spindle cells, and epithelial cells are focal or almost absent; so careful examination and dissection are required to make a diagnosis. Theorically, monophasic epithelial type SSs exists, but they are difficult to diagnose. In our study, poorly differentiated types accounted for 17%, lower than that which has been reported in the literature. Differentiation between poorly differentiated and well differentiated SS is difficult. It is commonly regarded that if at least 5 low scopes appear to be lowly differentiation[4] or if there are 2 or more mitosis per HPF, it indicated a poorly differentiated tumor. In our study mast cells were seen in 8 cases, for a positive ratio of 19.5%. Enzinger and Weiss suggested that[1], mast cells are one characteristic of typical SS, appearing more in spindle cells areas, and it can be regarded as one of the important diagnostic bases for SS. In SS mesenchymal, hemangiopericytomatous changs also can be seen.

Immunohistochemical markers

CK, EMA and Vim positive are sensitive markers for diagnosis of SS[5]. In the biphasic type, Vim is positive in spindle cells areas, and CK or EMA are positive in epithelial areas. In the monophasic fibrous type, CK or EMA can also be expressed in spindle cells areas, which demonstrate that the tumor cells have a similarity to epithelial cells. s-100 is a marker of nerve origin, and sometimes it is expressed in SS. Under such circumstances, there is a need to make a differential diagnosis from a malignant peripheral nerve sheath tumor (MPNST). In our study, the s-100 positive ratio was 14.6%, lower than the 30% which has been reported[1]. In recent research, s-100 has shown a close relationship between PGP expression in SS and YB-1 expression in nuclei, and the latter is regarded as all independent factor for the prognosis of

SS[6]. Y-box-binding protein (YB-1) is one part of the DNA-binding protein family, which has all interaction with inverted CCAAT boxes. YB-1 is thought to be associated with the repair of DNA and DNA injury reaction[7].

Molecular characteristics

Recent findings have shown that all translocations cloned from soft tissue tumors result in production of typical-fusion gene proteins. These proteins have a relationship with tumor pathogenesis, but an understanding of their biochemical role needs more research. Furthermore, many studies have shown that these fusion genes produced by chromosome translocations are almost always transcription factors, suggesting that the joint pathogenesis of SS may be a result of disturbance of gene expression involved in growth and differentiation of the cells. The translocation of chromosome in SS is *t* (X;18) (p11.2; q11.2), which results in the fusion between SYT of 18q11 and SSX of Xp11, thus a SYT-SSX fusion gene formed[8]. In other tumors which require a histomorphologicaliy differential diagnosis from SS, such as hemangiopericytomatous, mesothelioma, leiomyosarcoma and malignant peripheral nerve sheath tumor(MPNST) etc., there are no such translocations or fusion genes. Althought it has been reported by O' Sullivan[9] that a SYT-SSX fusion gene was found in 75% of MPNST, this finding was not verified by other scientists. Then various studies from different laboratories failed to find a SYT-SSX fusion gene in other MPNST tumors[10]. So it is regarded that a detection of a SYT-SSX fusion gene is typical for diagnosis of SS. In our study, the positive value was 90%, almost the same as the literature reported from abroad. In consideration of a SS or for a need to differentiate from spindle cell sarcoma, small round cell sarcoma or epithelial fibrous sarcoma etc., using this method to detect a fusion gene is useful, and valuable[11].

Differential diagnosis

There is a need to differentiate a monophasic fibrous type SS from a fibrosarcoma, leiomyosarcoma, MPNST etc. The spindle cells of fibrosarcoma appear in a binds of interlaced arrangement, mitotic figures are common, and epithelial markers are negative. The spindle cells of leiomyosarcoma have a dark-eosinophilic cytoplasm and SMA or Des are positive. MPNST is of neural origin, so the spindle cells are more wave-shaped, and one end of the nucleis is bulged, and s-100 is positive but epithelial markers negative. Biphasic SS must be differentiated from malignant mesothelioma, which always occurs in older males who have had a history of contact with asbestos. These always are focused in the pleura or peritoneum, and furthermore by detection of the SYT-SSX fusion gene they can be diagnosed. Hemangiopericytomatous also need to be differentiated from SS. These tumors have vascular changes in all of the tumor area, are not focal, the tumor cells are polygon in shape, CD34 positive, and negative for epithelial markers.

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