

# Extraskeletal Mesenchymal Chondrosarcoma: An Immunohistochemical and Ultrastructural Study

Teiichi MOTOYAMA<sup>1</sup>, Akira OGOSE<sup>1</sup>, Tetsuo HOTTA<sup>2</sup>, Yoshiya INOUE<sup>2</sup>, Toh MATSUBARA<sup>3</sup>  
and Hidenobu WATANABE<sup>1</sup>

<sup>1</sup>Departments of Pathology and <sup>2</sup>Orthopedic Surgery, Niigata University School of Medicine, Asahimachi 1, Niigata 951 Japan;  
<sup>3</sup>Department of Orthopedic Surgery, Tsubame Rosai Hospital, Niigata 959-12, Japan

Received October 3 1994; accepted October 25 1994

**Summary.** This report describes an extremely rare case of extraskeletal mesenchymal chondrosarcoma. The tumor, occurring in the right leg of a male aged 35, was composed of undifferentiated mesenchymal cells and interspersed islands of well-differentiated cartilaginous tissue. Immunohistochemically, S-100 protein was detected in transitional forms between undifferentiated mesenchymal cells and well-differentiated cartilaginous cells as well as well-differentiated cartilaginous cells. Ultrastructurally, the undifferentiated mesenchymal cells had a narrow cytoplasm with a sparsity of organelles. The well-differentiated cartilaginous cells showed many features common to chondrocytes, such as abundant rough endoplasmic reticulum, multiple well-developed Golgi complexes, and microvillous and scalloped cytoplasmic membranes. The differentiation toward cartilaginous cells of undifferentiated mesenchymal cells was indicated by immunohistochemistry and electron microscopy.

## INTRODUCTION

Mesenchymal chondrosarcoma was first described as a distinct entity by Lichtenstein and Bernstein<sup>1</sup> in 1959. This neoplasm has a characteristic histological appearance composed of a sheet of primitive or undifferentiated mesenchymal cells and interspersed islands of well-differentiated cartilaginous tissue.<sup>1,2</sup> Mesenchymal Chondrosarcoma, especially of the soft tissue, is a rare tumor. It is about one-third less common in the soft tissue in the bone.<sup>3</sup> Extraskeletal mesenchymal chondrosarcoma has been encountered in the orbit,<sup>4</sup> cranial and spinal meninges,<sup>5</sup> kidney,<sup>6</sup> lung,<sup>7</sup> mediastinum,<sup>8</sup> trunk and extremities.<sup>3</sup> Because of its rarity and histologic features, diagnosis is occasionally difficult. In this article, we describe the histologic, immunohistochemical and ultrastructural

findings of an extraskeletal mesenchymal chondrosarcoma.

## CASE REPORT

A 35-year-old man, who had been treated with medication for hyperlipemia, complained of a six-month-history of a slow-growing, painless and movable intermuscular mass in the distal portion of his right leg. Roentgenograms of the right leg showed a tumor mass with faint reticular shadow and occasional calcification in the soft tissue (Fig. 1). The tumor was



Fig. 1. Roentgenogram of the patient's right leg.



Fig. 2. The cut surface of the tumor is homogenous whitish yellow except for isolated and irregular calcified or hemorrhagic areas.

resected under the working diagnosis of neurinoma. Although he was treated with anti-cancer chemotherapy of adriamycin and cis-platinum and amputation of the right leg, pulmonary metastasis developed 3 years after surgery.

## MATERIALS AND METHODS

The resected tumor was fixed in 10% neutral buffered formalin and processed for embedding in a routine manner. Sections were cut at a 3-mm thickness and stained with hematoxylin and eosin, periodic acid-Schiff (PAS) reaction with or without diastase digestion, alcian blue (pH 2.5), Azan-Mallory and silver impregnation.

Immunohistochemical studies were performed on paraffin sections with the biotin-streptavidin-peroxidase complex technique. The applied mouse monoclonal antibodies were those of neuron-specific enolase (NSE), desmin and leukocyte common antigen (LCA) (all from Dakopatts, Glostrup, Denmark). A rabbit anti-S-100 protein antibody obtained from Dakopatts was also applied. For negative controls, non-immune mouse or rabbit serum was used in place of the primary antibodies. For comparative studies, we used 3 Ewing's sarcomas of the bone, 3 embryonal rhabdomyosarcomas and 3 malignant lymphomas.

For electron microscopic examination, the tissue cubes were fixed in 2.5% phosphate-buffered glutaraldehyde, post-fixed in 1% osmium tetroxide, and em-

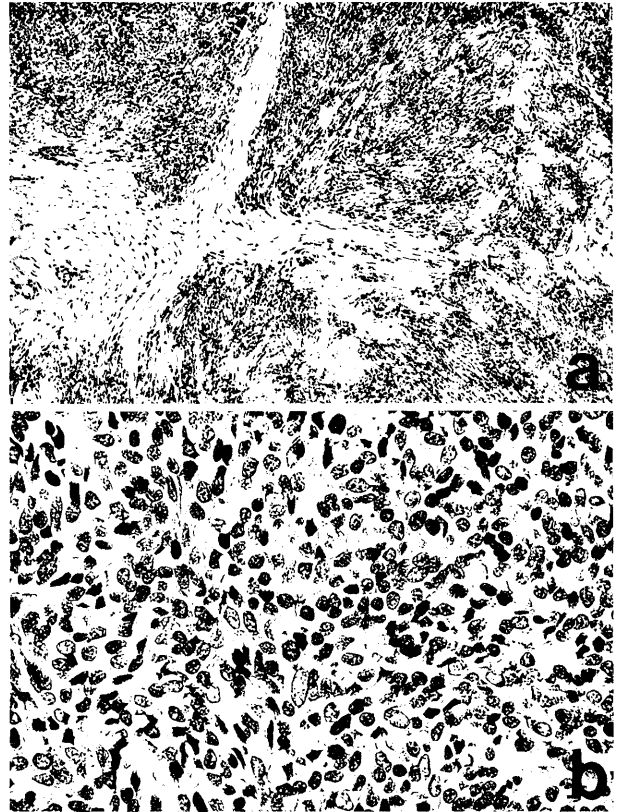


Fig. 3. a. At low magnification, the small cell nests are separated by various-width fibrous septa. b. Higher magnification of a solid area composed of small round to spindle cells. HE.

bedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate.

## RESULTS

### Gross observations

The tumor formed a well-circumscribed, elastic hard mass with a sharply defined margin in the subcutaneous tissue, and measured  $3.0 \times 2.5 \times 1.7$  cm. It was not adherent to the periosteum, bone, nerve or skin. The appearance of the cut section was homogenous whitish yellow, except for isolated and irregular calcified or hemorrhagic areas (Fig. 2).

### Histological findings

Microscopically, the tumor was mainly composed of small round to spindle cells, the nests of which separated by fibrous septa of varying widths (Fig. 3a). The

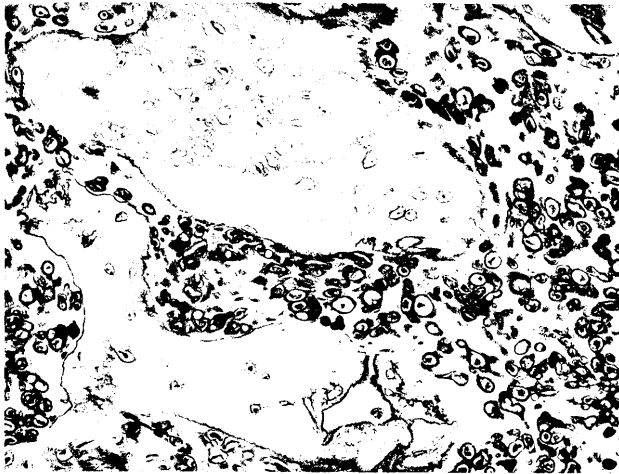


Fig. 4. Well-differentiated cartilaginous tissue with calcification and ossification. HE.

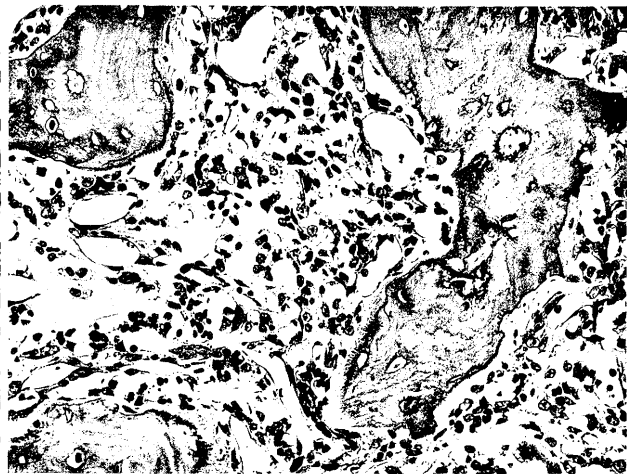


Fig. 5. An area resembling osteosarcoma. However, the bordering cells of bone have little atypia.

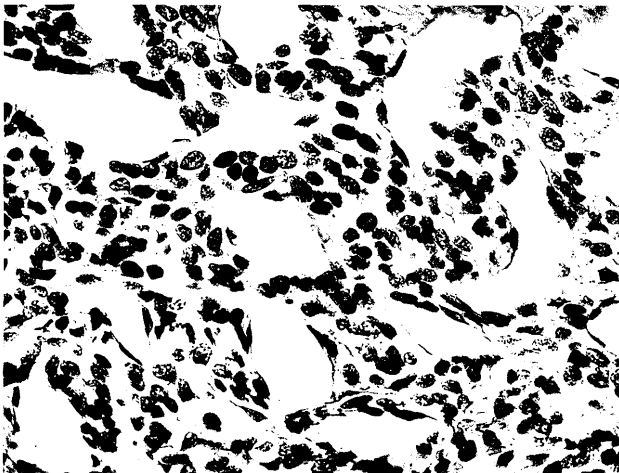


Fig. 6. An area showing the hemangiopericytoma-like arrangement characterized by the clustering of cells around vascular spaces. HE.

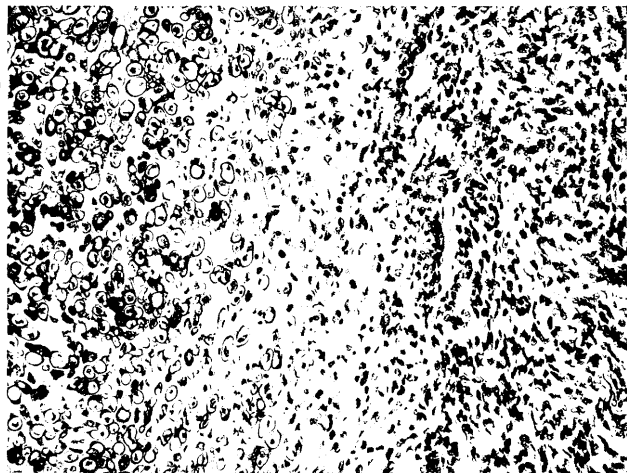


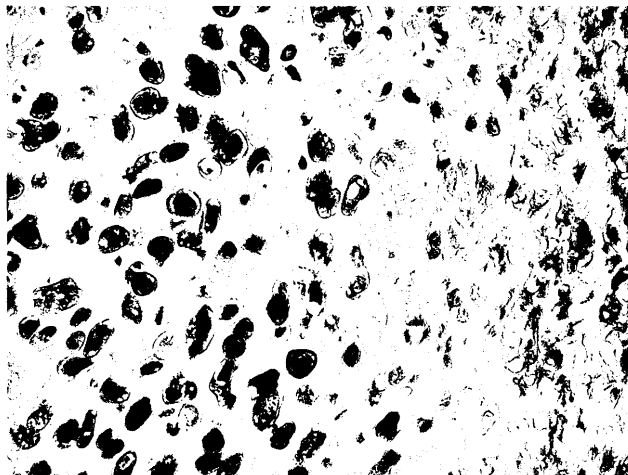
Fig. 7. An area showing histologic transition from undifferentiated small cells to well-differentiated cartilaginous cells. HE.

Table 1. Immunohistochemical findings in small cell neoplasms

Antibody <sup>a</sup> to:	Present case	Positively of other types of small cell neoplasm		
		Ewing's sarcoma	Embryonal rhabdomyosarcoma	Malignant lymphoma
S-100 protein	+ <sup>b</sup>	2/3	0/3	0/3
NSE	-	3/3	0/3	0/3
Desmin	-	0/3	3/3	0/3
LCA	-	0/3	0/3	3/3

a, NSE: neuron-specific enolase; LCA: leukocyte common antigen.

b, +: positive; -: negative.

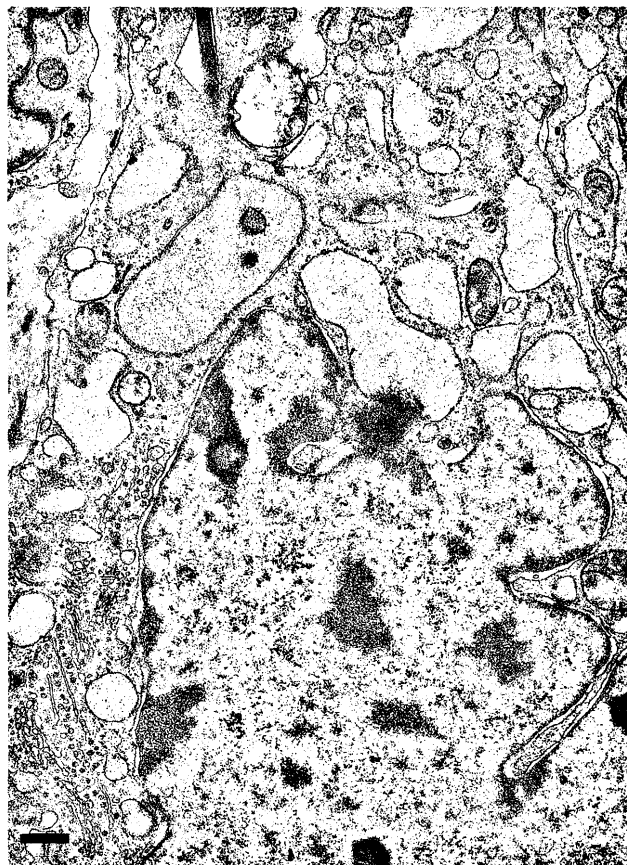


**Fig. 8.** Immunohistochemical staining for S-100 protein. Well-differentiated cartilaginous cells are strongly positive for S-100 protein. A number of poorly differentiated cells are also weakly positive for the antigen.

tumor cells had a scanty cytoplasm and round to oval nuclei with occasional marked hyperchromasia and less conspicuous nucleoli (Fig. 3b). Although a few cells had a little glycogen in the cytoplasm, no significant amount of intracellular glycogen was detected in any tumor cells. No multinucleated osteoclast-like or ganglion-like cells were seen. Horner-Wright rosettes were not observed. There were also considerable areas of well-differentiated cartilaginous tissue with occasional calcification and ossification (Fig. 4). Furthermore, there were some areas resembling osteosarcoma (Fig. 5) or hemangiopericytoma (Fig. 6). However, histologic transitional features between small round to spindle cell tumor areas and well-differentiated cartilaginous area were occasionally found (Fig. 7).

#### Immunohistochemical analysis

Results of immunohistochemical examination are summarized in Table 1. In the well-differentiated cartilaginous and transitional areas, there were many cells strongly positive for S-100 protein. A few cells in the small cell area were weakly positive for S-100 protein (Fig. 8). There were no tumor cells positive for NSE, desmin or LCA in the present tumor. However, all Ewing's sarcoma, all rhabdomyosarcomas and all malignant lymphomas examined showed positive reactions for NSE, desmin and LCA, respectively.



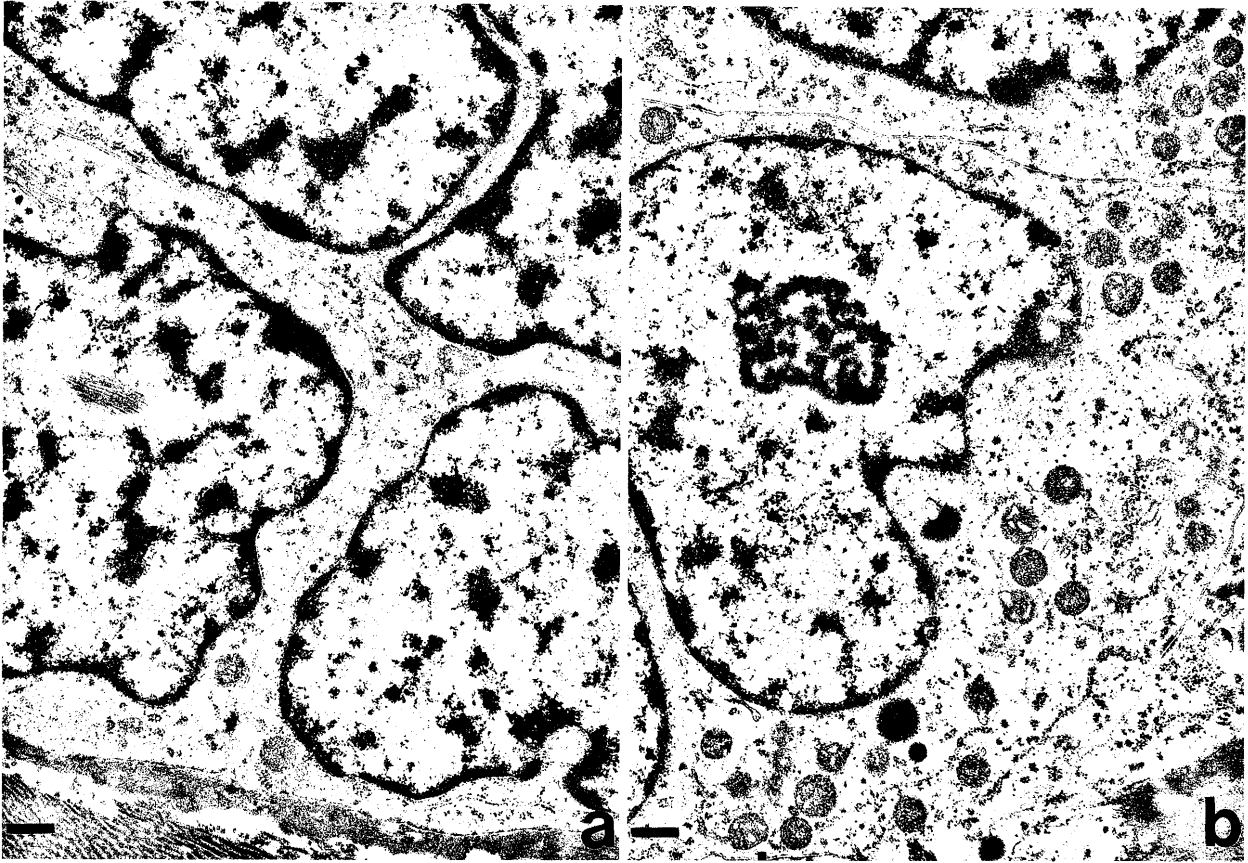
**Fig. 9.** Electron micrograph of well-differentiated cartilaginous cells containing abundant rough endoplasmic reticulum and multiple well-developed Golgi complexes. Bar = 1  $\mu$ m.

#### Ultrastructural findings

The well-differentiated cartilaginous cells contained abundant rough endoplasmic reticulum and multiple well-developed Golgi complexes in the cytoplasm (Fig. 9). Although the majority of undifferentiated small cells usually presented a thin cytoplasm with sparse organelles (Fig. 10a), some cells contained a number of round mitochondria (Fig. 10b). The matrix of the tumor consisted of collagenous fibrils.

#### DISCUSSION

Mesenchymal chondrosarcoma is a cartilaginous tumor of characteristic histological appearance composed of sheets of primitive or undifferentiated mesenchymal cells and interspersed islands of well-differentiated cartilaginous tissue.<sup>1,2)</sup> Immunohistochemical or ultra-



**Fig. 10.** a. Electron micrograph of undifferentiated small cells. Most of the cells have a sparsity of organelles. b. Some cells contain a number of round mitochondria. Bar=1  $\mu$ m.

structural studies have mainly been carried out on mesenchymal chondrosarcomas arising from the bone. Immunohistochemically, the well-differentiated cartilaginous cells of mesenchymal chondrosarcoma are strongly positive for S-100 protein, and transitional cells at the interface of small cells and chondroid foci are variably labeled.<sup>9,10</sup> Ultrastructurally, the well-differentiated cartilaginous cells of mesenchymal chondrosarcoma show many features common to chondrocytes, such as abundant rough endoplasmic reticulum and multiple well-developed Golgi complexes. The undifferentiated mesenchymal cells have a sparsity of organelles.<sup>11,12</sup> Some undifferentiated mesenchymal cells may have a number of mitochondria.<sup>9</sup> The present case of extraskeletal mesenchymal chondrosarcoma principally showed the same features as those of the intraosseous mesenchymal chondrosarcomas reported.

Although typical examples of mesenchymal chondrosarcomas pose no particular problem in diagnosis, correct evaluation may be extremely difficult, with

insufficient numbers of sections showing only one of the two main tissue elements, especially undifferentiated features. Undifferentiated small cells of extraskeletal mesenchymal chondrosarcoma may resemble the tumor cells of other malignant small cell tumors such as extraskeletal Ewing's sarcoma,<sup>13,14</sup> or extraskeletal osteosarcoma,<sup>15-17</sup> especially of small cell variant or chondroblastic variant, and others. These extraskeletal tumors also show the same immunohistochemical and ultrastructural features as those of intraosseous counterparts.<sup>14,17</sup> Embryonal rhabdomyosarcomas and malignant lymphomas have helpful immunohistochemical markers of desmin<sup>18</sup> and LCA,<sup>19</sup> respectively. Mesenchymal chondrosarcomas occasionally show an hemangiopericytoma-like arrangement,<sup>20</sup> while unequivocal hemangiopericytomas have not been reported to show cartilaginous metaplasia or reactive cartilage formation.

The pathogenesis of extraskeletal mesenchymal chondrosarcoma is still obscure, but its origin from primitive mesenchymal cells rather than preformed

cartilage cells appears likely.

Unlike common chondrosarcoma and myxoid chondrosarcoma, mesenchymal chondrosarcoma is a highly malignant neoplasm that easily produces metastasis in most cases.<sup>21</sup> Unfortunately, no effective therapeutic procedures for mesenchymal chondrosarcoma have been established yet. We are conducting research work on the chemosensitivity of mesenchymal chondrosarcoma cells using an original cultured cell line.<sup>22)</sup>

**Acknowledgements.** The authors thank Dr. S. Ushigome of Jikei University School of Medicine, Japan, and Dr. K. K. Unni of Mayo Clinic, USA, for their helpful advice.

## REFERENCES

- 1) Lichtenstein L, Bernstein D: Unusual benign and malignant chondroid tumor of bone: A survey of some mesenchymal cartilage tumors and malignant chondroblastic tumors, including a few multicentric ones, as well as many atypical benign chondroblastomas and chondromyxoid fibromas. *Cancer* 12: 1142-1157, 1959.
- 2) Guccion JG, Font RL, Enzinger FM, Zimmerman LE: Extraskelatal mesenchymal chondrosarcoma. *Arch Pathol* 95: 336-340, 1973.
- 3) Salvador AH, Beabout JW, Dahlin DC: Mesenchymal chondrosarcoma-observations on 30 new cases. *Cancer* 28: 605-615, 1971.
- 4) Jacobs JL, Merriam JC, Chadburn A, Garvin J, Housepian E, Hilal SK: Mesenchymal chondrosarcoma of the orbit. Report of three new cases and review of the literature. *Cancer* 73: 399-405, 1994.
- 5) Lee S-T, Lui T-N, Tsai M-D: Primary intraspinal dura mesenchymal chondrosarcoma. *Surg Neurol* 31: 54-57, 1989.
- 6) Malhotra CM, Doolittle CH, Rodil JV, Vezeridis MP: Mesenchymal chondrosarcoma of the kidney. *Cancer* 54: 2495-2499, 1984.
- 7) Kurotaki H, Tateoka H, Takeuchi M, Yagihashi S, Kamata Y, Nagai K: Primary mesenchymal chondrosarcoma of the lung. A case report with immunohistochemical and ultrastructural studies. *Acta Pathol Jpn* 42: 364-371, 1992.
- 8) Chetty R: Extraskelatal mesenchymal chondrosarcoma of the mediastinum: *Histopathology* 17: 261-263, 1990.
- 9) Ushigome S, Takakuwa T, Shinagawa T, Takagi M, Kishimoto H, Mori N: Ultrastructure of cartilaginous tumors and S-100 protein in the tumors. With reference to the histogenesis of chondroblastoma, chondromyxoid fibroma and mesenchymal chondrosarcoma. *Acta Pathol Jpn* 34: 1285-1300, 1984.
- 10) Swanson PE, Lillemoen TJ, Manivel JC, Wick MR: Mesenchymal chondrosarcoma. An immunohistochemical study. *Arch Pathol Lab Med* 114: 943-948, 1990.
- 11) Steiner GC, Mirra JM, Bullough PG: Mesenchymal chondrosarcoma. A study of the ultrastructure. *Cancer* 32: 926-939, 1973.
- 12) Fu Y-S, Kay S: A comparative ultrastructural study of mesenchymal chondrosarcoma and myxoid chondrosarcoma. *Cancer* 33: 1531-1542, 1974.
- 13) Hashimoto H, Tsuneyoshi M, Daimaru Y, Enjoji M: Extraskelatal Ewing's sarcoma. A clinicopathologic and electron microscopic analysis of 8 cases. *Acta Pathol Jpn* 35: 1087-1098, 1985.
- 14) Llombart-Bosch A, Carda C, Peydro-Olaya A, Noguera R, Perez-Bacete M, Pellin A, Boix J: Soft tissue Ewing's sarcoma. Characterization in established cultures and xenografts with evidence of a neuroectodermic phenotype. *Cancer* 66: 2589-2601, 1990.
- 15) Waxman M, Vuletin JC, Saxe BI, Monteleone FA: Extraskelatal osteosarcoma: Light and electron microscopic study. *Mt Sinai J Med NY* 48: 322-329, 1981.
- 16) Chung EB, Enzinger FM: Extraskelatal osteosarcoma. *Cancer* 60: 1132-1142, 1987.
- 17) Murray AB, Becke H, Taccagni GL: Extraskelatal Osteosarcoma with unusual ultrastructural features. *Ultrastruct Pathol* 14: 335-342, 1990.
- 18) Motoyama T, Watanabe H, Yamamoto T: Embryonal rhabdomyosarcoma in nude mice and *in vitro*. *Acta Pathol Jpn* 36: 1495-1505, 1986.
- 19) Warnke RA, Gatter KG, Phil D, Falini B, Hildreth P, Woolston R-E, Pulford K, Cordell JL, Cohen B, de Wolf-Peeters C, Mason DY: Diagnosis of human lymphoma with monoclonal antileukocyte antibodies. *N Eng J Med* 309: 1275-1281, 1983.
- 20) Nakashima Y, Unni KK, Shives TC, Swee RG, Dahlin DC: Mesenchymal chondrosarcoma of bone and soft tissue. *Cancer* 57: 2444-2453, 1986.
- 21) Enzinger FM, Weiss SW: Soft tissue tumors. Mosby, St. Louis, 1988.
- 22) Fijisawa N, Sato NL, Motoyama T: Establishment of clonal cell lines, with or without cartilage phenotypes, from a hamster mesenchymal chondrosarcoma. *Lab Animal Sci* 41: 590-595, 1991.