The Seoul Journal of Medicine
Vol. 30, No. 4: 223–229, December 1989

Angiomyolipoma of the Kidney: Its Positive Expression of Immunohistochemical Markers for Schwann Cell Differentiation

Chong Jai Kim, Seong Hoe Park* and Je G. Chi

Department of Pathology, Seoul National University College of Medicine, Seoul, 110–460, Korea

= Abstract = Ten cases of renal angiomyolipomas were immunohistochemically analyzed for the presence of S–100 protein, neuron specific enolase (NSE) and desmin using the avidin–biotin complex method. The composition of histologic constituents differed in each case. The cases with predominantly smooth muscle–like solid spindle cell proliferation showed unexpected positive reaction to S–100 protein and NSE. Among 10 cases, five were both S–100 protein positive and NSE positive. The reaction pattern of S–100 protein and NSE was similar. Relatively weak or minimal positive reactions to desmin were observed in the cases and the distribution of positive reaction was different from those of S–100 protein and NSE. The result demonstrated immunohistochemical evidence of neural or Schwann cell differentiation in a significant proportion of renal angiomyolipomas, and its histogenesis was speculated.

Key words: ***Angiomyolipoma, Immunohistochemistry, S–100 protein, Neuron specific enolase, Desmin, Neural differentiation***

INTRODUCTION

The angiomyolipoma is a relatively rare benign tumor of the kidney which is characterized by the proliferation of a variable mixture of blood vessels, smooth muscle and adipose tissue. This lesion is known to be frequently associated with tuberous sclerosis but isolated cases also have been reported (McCullough *et al.*, 1971; Perou and Gray, 1960; Wong *et al.*, 1981; Stillwell *et al.*, 1987). Angiomyolipoma has been generally regarded as a hamartomatous neoplasm (Perou and Gray, 1960) and as the name implies, general agreement on the participation of three basic components–blood vessels, smooth muscle and adipose tissue–is still widely accepted. But there have been some studies suggesting participation of neurilemmoblastic elements in the renal angiomyolipoma (Mori *et al.*, 1984), and Yum *et al.* (1984) observed juxtaglomerular cells on ultrastructural examination of a case of angiomyolipoma. Recently, we observed a case of renal angiomyolipoma that showed strong positive reaction to S–100 protein, one of the representative markers for Schwann cell origin neoplasms, in its smooth muscle cell–like spindle cell elements. Based on this observation, we have studied the immunohistochemical properties of 10 cases of renal angiomyolipomas to elucidate the possibility of participation of neural elements in the angiomyolipoma.

METERIALS AND METHODS

Ten cases of histologically proven renal angiomyolipomas, for which surgical resections of main masses were done during the period of July, 1982 to November, 1988, were collected from the files of the Department of Pathology of Seoul National University Hospital. Only one patient, a 27–year–old female, was associated with clinical evidence of tuberous sclerosis and had multicentric angiomyolipomas with involvement

Received 4/11/89; revised 9/12/89; accepted 11/12/89
*Author for correspondence
**This study was supported by Clinical Research Grant of Seoul National University Hospital (1987)

of one hilar lymph node. Among 10 cases, two cases were misdiagnosed as liposarcoma and benign peripheral nerve sheath tumor on the frozen biopsy duing operation. The patients' ages ranged from 27 years to 69 years, and eight patients were female. The maximal diameters of the masses were between 7 cm and 19 cm.

In every case, paraffin blocks were available, and from all cases, sections showing predominant solid spindle-cell proliferation were selected for both histochemical and immunohistochemical examination. A case of neurilemmoma in thoracic spinal nerve root, a section of normal gastric smooth muscle and five cases of uterine leiomyomas were used for the controls. For the light microscopic examination, besides routine hematoxylin and eosin staining, elastic staining (Weigert), phosphotungstic acid-hematoxylin (PTAH) and Masson's trichrome stainings were applied on 5 μm thick serial sections. For immunohistochemistry, serial paraffin sections were deparaffinized and hydrated through xylene, graded ethyl alcohol and phosphate buffered saline. Then, after sequential incubation with 0.3% hydrogen peroxide to block endogeneous peroxidase activity and nonimmune goat serum to block nonspecific background staining, sections were incubated overnight with three kinds of primary antibodies to S-100 protein, neuron specific enolase and desmin (1:50 dilution, from Bio Genex Laboratories). Biotinylated goat anti-rabbit immunoglobulin and peroxidase conjugated Strept Avidin were used as the linking antibody and labeling agent, respectively (Str Avi Gen B-SA, Bio Genex Laboratories, California, U.S.A.).

RESULTS

Light microscopic findings

Histologic examination of routine H & E staining in 10 cases revealed a variable mixture of vessels with thickened, tortuous and hyalinized walls, rather solid spindle-cell proliferation, and both mature and immature adipose tissue. The vessels usually had perivascular palisading of the spindle cells. Some of the spindle cells had elongated nuclei and slightly wavy or more plump cytoplasm than usual smooth muscle cells. They were arranged as densely packed interlacing bundles or fascicles. The spindle-cells around the blood vessels showed a more typical appearance of myogenic differentiation. Fibrous tissues were present as a component of the main mass, though its relative amount was negligible. Three cases showed fresh intratumoral hemorrhage along with patchy necrosis.

Immunohistochemical findings

Focal aggregates or clusters of spindle cells positive to S-100 protein or neuron specific enolase were observed in seven and eight cases, respectively. Among these cases, five cases showed a concomitant positive reaction to both kinds of antibodies. These areas somewhat resembled the histologic features of the benign peripheral nerve sheath tumor. Stainability to anti-S-100 protein was more intense than to the anti-NSE, but the reaction pattern was similar. The positive cells stained for anti-S-100 protein or anit-NSE were patchy or focal in distribution and intermixed with the surrounding non-staining cells, and the surrounding solid spindle cells were only weakly positive to desmin in four cases. The small nests of spindle-cells among adipose tissue were also occasionally positive to NSE or S-100 protein antibodies (Fig. 1, 2), though the usual positive elements were found among areas of solid spindle cells which were regarded as a myogenic component (Fig. 3). The pattern of reaction for desmin was rather discrete or patchy in solid areas, and a relatively weak positive reaction was observed in four cases of angiomyolipoma.

Normal entrapped small peripheral nerve trunks were stained positive for both antibodies. The neurilemmoma in control showed strong positive reaction to both S-100 protein and NSE but was completely negative to desmin. The gastric smooth muscle and uterine leiomyomas were completely negative to antibodies to NSE and S-100 protein, while there showed an intense positive reaction to desmin. Entrapped ureteral smooth muscle was also strongly positive in one case of angiomyolipoma. The profile of the 10 cases and their immunohistochemical findings are summarized in Table 1.

DISCUSSION

The angiomyolipoma has been regarded as a benign hamartomatous mesenchymal neoplasm of the kidney whose major histologic consti-

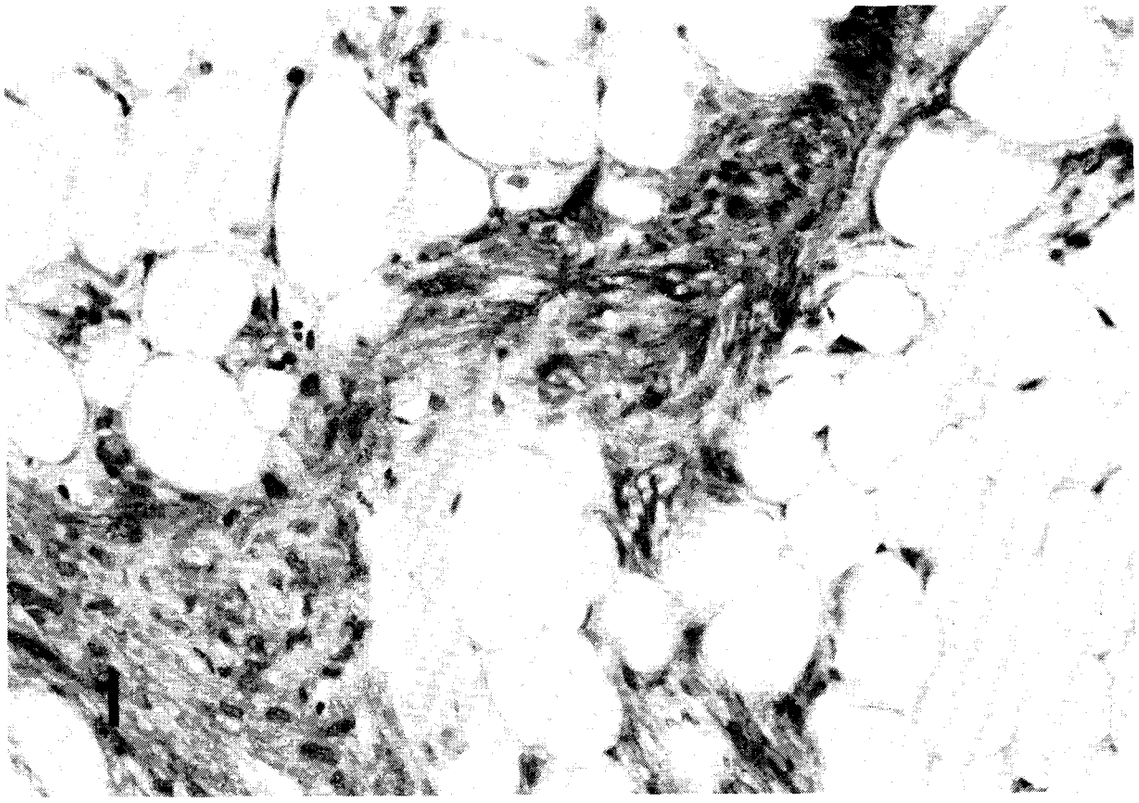

Fig. 1. Focal area of positive reaction to S-100 protein in the spindle cell component, intermixed with adipose tissue in Case 7. (× 200)

Table 1. Profile and Immunohistochemical Findings of 10 cases

Case No.	Age/Sex	Location	Size(cm)	S-100	NSE	Desmin	Remarks
1.	39/F	left	10×10	+	+	+	
2.	46/F	right	7× 6	+	+	+	
3.	49/F	left	8× 5	+	−	−	
4.	27/F	left	13×10	+	−	+	Tuberous sclerosis
5.	50/F	right	13×10	−	+	−	*
6.	69/F	left	9× 4	+	+	−	
7.	45/F	left	19×10	−	+	−	
8.	53/M	right	9× 8	+	+	−	#
9.	41/F	left	7× 6	+	+	+	
10.	52/M	left	8× 8	+	−	−	

*: The case was diagnosed as liposarcoma on frozen biopsy.

#: The case was diagnosed as benign peripheral nerve sheath tumor on frozen biposy.

tuents are abnormal vessels, smooth muscle and adipose tissue. Previous ultrastructural examination confirmed these three elements in the neoplasm (Chalvardjian *et al.*, 1978). Besides these three elements, fibrous tissue can join as a component, and Yum *et al.*, demonstrated typical juxtaglomerular cells in a case of renal angiomyolipoma and speculated its origin from a common precursor cell present in the perivscular space (Yum *et al.*, 1984).

This study was carried out to elucidate the presence of neural elements in renal angiomyolipomas, particularly among their spindle cell components which were conventionally regarded undoubtedly as smooth muscle cells on light microscopic level. The event that led us to organize

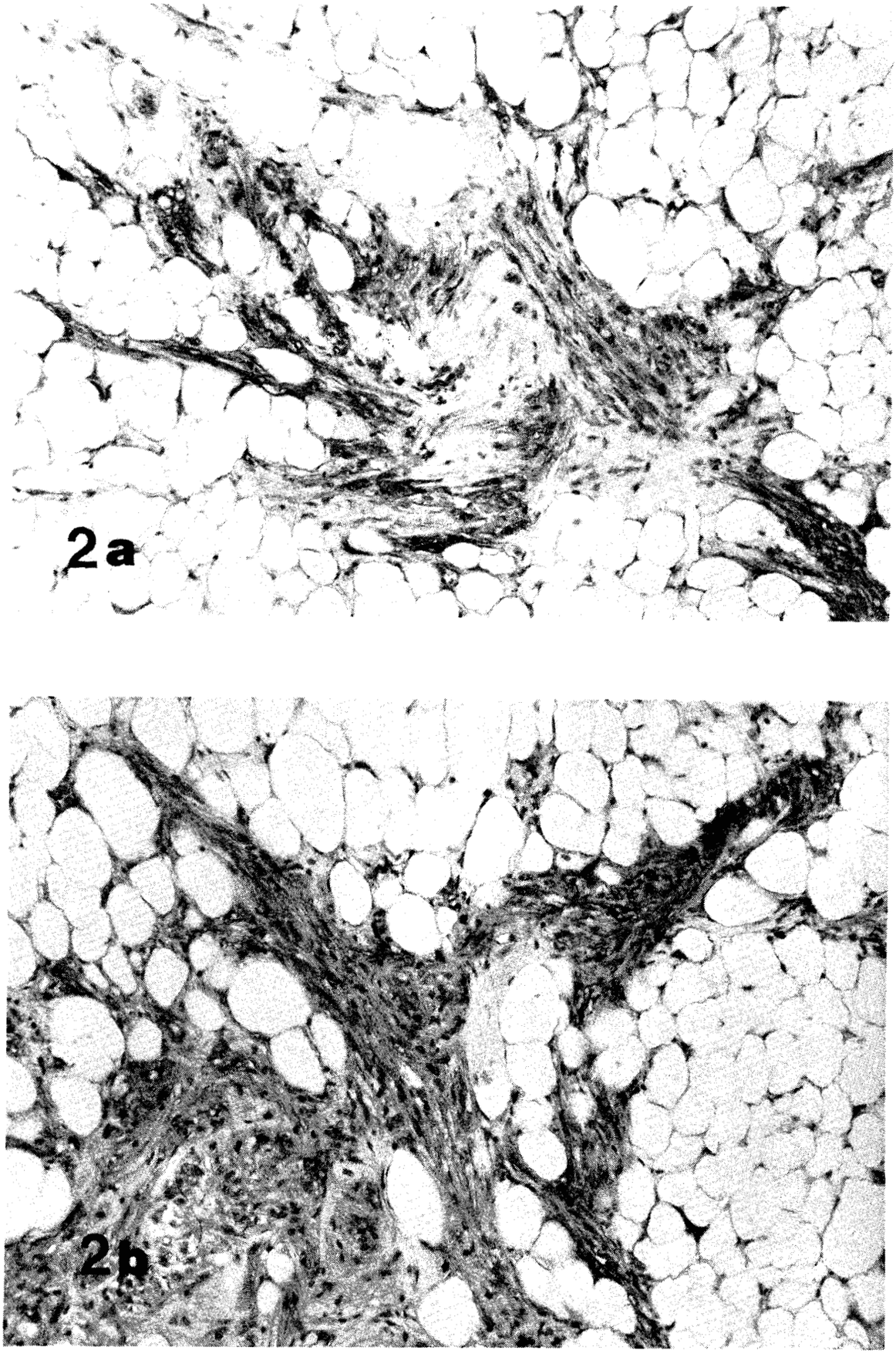

Fig. 2. Patchy areas of positive reaction to both S–100 protein (a) and NSE (b) in Case 1. (× 100)

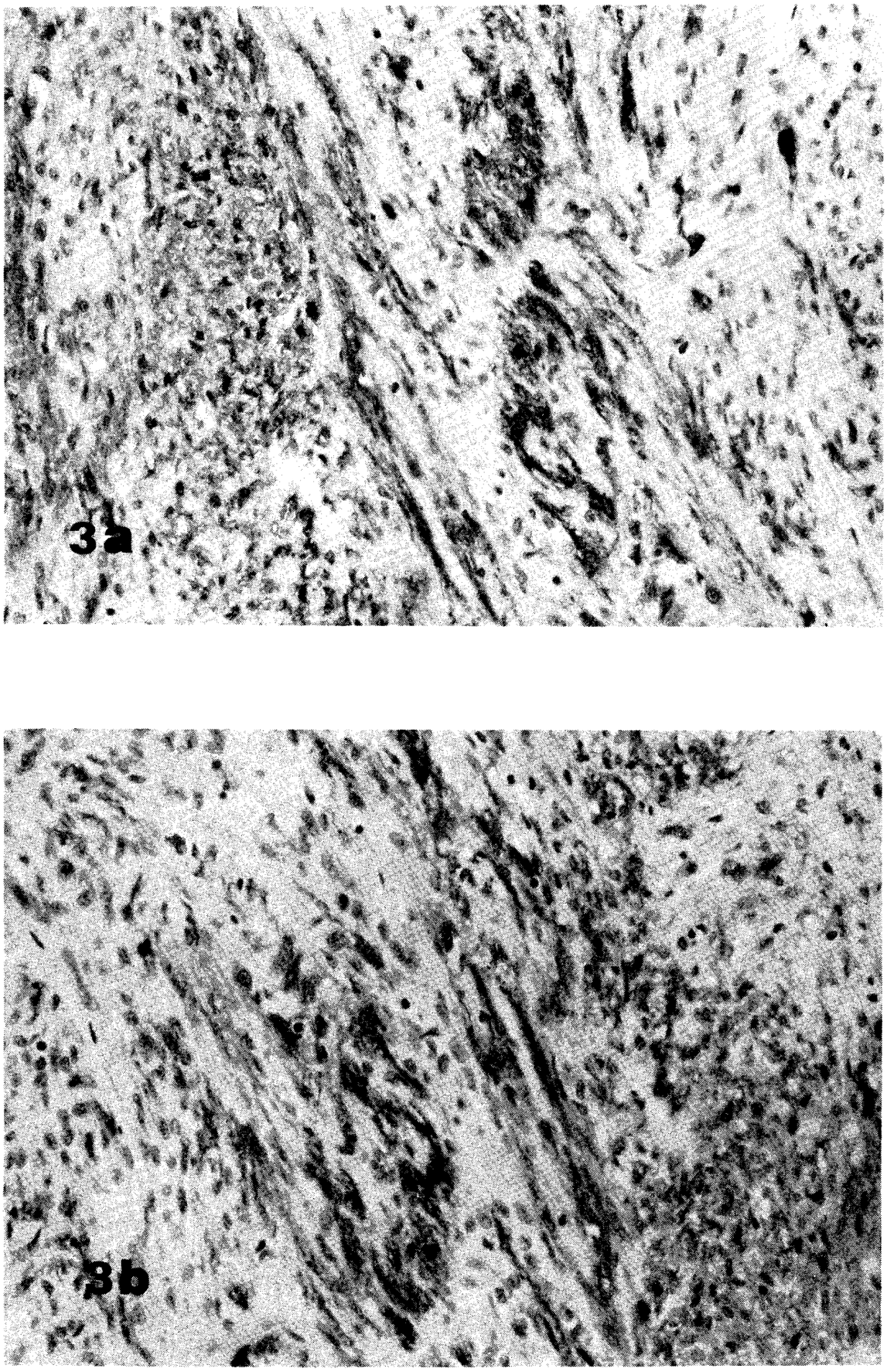

Fig. 3. Similar pattern of positive reaction to S-100 protein (a) and NSE (b) in the smooth muscle-like spindle cell component of the tumor in Case 8. (× 200)

this study was our recent experience of misdiagnosing a case of renal angiomyolipoma as benign peripheral nerve sheath tumor on forzen biopsy. The diagnosis was corrected on permanent sections, but subsequent immunohistochemical staning for S–100 protein demonstrated strong positivity, though patchy in distribution in its solid compartment composed of smooth muscle cell–like spindle cells.

An immunohistochemical examination was performed on three different kinds of antigens (S–100 protein, NSE, desmin) using the Biotin–Strept Avidin amplified system (Bio Genex Laboratories) to investigate immunohistochemical evidence of neural or Schwann cell differentiation. The S–100 protein and NSE are two different antigens used as diagnostic immunohistochemical markers for various peripheral nerve sheath tumors and for some other types of tumors or cells (Weiss *et al.*, 1983; Nakzato *et al.*, 1982; Nakajima *et al.*, 1982; Simpson *et al.*, 1984; Vinores *et al.*, 1984). These markers are not exclusively specific for those nerve sheath cells, and it may be argued that the S–100 protein is present in nonneural tissue, including adipose tissue origin tumors, and that NSE is also nonspecific. However, based on the largely concomitant expression of both S–100 protein and NSE in the areas of negative desmin expression and the histologic difference of S–100 protein and NSE positive spindle cell elements from tumors of adipose tissue origin, we cautiously excluded the possibility of nonspecific reaction.

The 10 cases in this study showed significant difference in the proportion of histologic constituents, while positive reactions to two antibodies (S–100 protein and NSE) were observed mainly in the cases which were predominantly composed of smooth muscle cell–like spindle cells.

The result of immunohistochemical examination of this study strongly suggests the participation of Schwann cell elements in some proportion of renal angiomyolipomas. Though there are previous reports regarding blastic Schwann cell elements or pericytes as part of angiomyolipoma (Mori *et al.*, 1984; Inglis, 1960), as far as we know, there has been no immunohistochemical study done to evaluate Schwann cell differentiation in renal angiomyolipomas. Recently, however, an immunohistochemical analysis of gastrointestinal stromal tumors has been done, and spindle cells positive to S–100 protein have been found in the cases classified as leiomyomas and leiomyosarcomas. The histogenetic origin of cells was postulated as 1) myenteric nervous system, a source for perineurial and mesenchymal nerve sheath cells, or 2) the presence of complex mixed differentiation pattern between smooth muscle and neural elements (Miettinen, 1988; Mazur and Clark, 1983; Pike *et al.*, 1986).

We believe that basically the same speculations can be made to explain the presence of S–100 protein or NSE positive spindle cells in renal angiomyolipomas, as in the case of gastrointestinal stromal tumors, even though the circumstances are different in that the angiomyolipoma is generally regarded as a hamartoma. Peripheral nerve trunks are normally present in and around the kidney, and it is possible to assume their participation as a component of hamartoma. Another possible explanation would be the presence of mixed differentiation between smooth muscle cells and Schwann cells as found in the cases of gastrointestinal stromal tumors (Miettinen, 1988). In our opinion, the latter explanation seems to be more reasonale because the positive reactions were among smooth muscle cells, and there also was transition between the S–100 or NSE positive and negative cells. It is very unlikely that the positive elements are the entrapped nerve sheath elements because the reactions were found in tumorous spindle cells even when normal nerve trunks were not present in the proximity.

In conclusion, we observed that there is immunohistochemical evidence of Schwann cell differentiation in renal angiomyolipomas, especially in the cases with predominant spindle cell proliferation. Though at present the histogenesis of these elements can only be speculated, we believe that further accumulated case studies on angiomyolipomas with thorough ultrastructural and immunohistochemical analysis will yield a clue to its basic histogenesis and histologic composition.

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= 국문초록 =

신의 혈관근지방종에 있어서의 슈반세포형 면역조직화학적 표지의 발현

서울대학교 의과대학 병리학 교실

김종재 · 박성회 · 지제근

저자들은 10례의 신의 혈관근지방종을 대상으로 S-100 단백, neuron specific enolase (NSE) 및 desmin에 대한 면역조직화학적 검색을 시행하였다. 이들 10례중 5례는 S-100 단백과 NSE에 대하여 각기 양성반응을 보였다. 이러한 신의 혈관근지방종에서의 기대치 못한 S-100 단백이나 NSE등 신경조직에서 관찰될 수 있는 면역조직화학적 표지의 발현은 이 종양이 지금까지 알려진 혈관, 평활근, 지방등의 조직 이외에 신경 혹은 슈반세포성 분화를 보이는 조직으로 구성되어 있을 가능성을 시사하여 그 가능한 조직학적인 기원을 유추하여 보았다.