J. Endocrinol. Invest. 34: 417-421, 2011
DOI: 10.3275/7110

Experience with adrenal schwannoma in a Chinese population of six patients

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ABSTRACT. ***Objectives:*** **Benign adrenal schwannoma is an extremely uncommon cause of incidentaloma. This article describes our experience with the diagnosis and treatment of adrenal schwannoma in a Chinese population of 6 patients. To our knowledge, this is the largest series of this uncommon adrenal tumor treated in a single center.** ***Methods:*** **From May 1999 to May 2009, 6 patients with incidentally discovered adrenal schwannoma were operated on at a tertiary referral hospital in Eastern China. Clinical details, radiographic features, laboratory examinations, pathological findings, and follow-up data of these patients were analyzed.** ***Results:*** **Of the 6 patients, 4 were females (F) and 2 were males (M), with a mean age of 40.5 yr (range: 30-47, M:F=2:1). The 6 patients were managed with open unilateral adrenalectomy; 5 patients had schwannomas on the left side, and 1 on right side. Abnormal urine catecholamine was detected in 1 patient. The mean pathological size of these tumors was 4.3±1.1 cm. The diagnosis of schwannoma was based on classic histological findings, and supported by immunohistochemistry of S-100, vimentin, and ABC positivity. In the follow-up of 47.5±32.3 months, no recurrence and metastasis were observed.** ***Conclusions:*** **Although there may be some clues for radiological diagnosis of adrenal schwannoma, preoperative misdiagnosis is not infrequent. Those tumors may occasionally have endocrine function. Histological examination is the key of diagnosis, and surgical resection is the treatment of choice once malignancy cannot be excluded by preoperative analyses.**

(J. Endocrinol. Invest. 34: 417-421, 2011)

INTRODUCTION

Schwannoma is a benign nerve sheath tumor composed of neoplastic cells exhibiting features of constituent Schwann cells of the normal peripheral nerve. The incidence of adrenal schwannoma is very low. As most cases of schwannoma lack specific clinical manifestations, radiographic, and endocrine indexes, the diagnosis is often casual and difficult to be determined pre-operatively. Up to now, only 9 cases are reported in the literature (in English) (1-8). This article reports the clinical features of adrenal schwannoma based on the 10-yr experience of a tertiary referral hospital in Eastern China. To our knowledge, this is the largest series of this uncommon adrenal tumor treated in a single center.

PATIENTS AND METHODS

From May 1999 to May 2009, 6 patients with adrenal schwannoma underwent surgery at the department of urology in Changhai Hospital (Shanghai, China). Clinical details, radiological features, endocrine indexes, intervention measures, pathological diagnoses, and follow-up data of these patients were collected. The study protocol involving human materials was approved by the institutional Ethics Committee of Changhai Hospital.

The medical and family histories of these 6 patients were unremarkable. At the initial examination, blood pressure was normal in all patients. They were referred with ultrasonography and computerized tomography (CT) scan initially or during residence. Dynamic contrast-enhanced CT examination was performed with a multislice helical CT scanner before and after iv iodinated contrast medium administration. CT images were reviewed by a radiologist blinded to the results of the pathological examination. The size, shape, and density of the tumors were measured, and the pattern of enhancement was defined. Density of the tumors on CT images presented as low attenuation (<20 HU), intermediate attenuation (20-40 HU), and high attenuation (>40 HU). As no informed consent was obtained from the patients, additional magnetic resonance imagings (MRI) were not performed.

Endocrine indexes and reference range were showed, which included: 1) serum potassium; 2) 24-h urinary epinephrine, norepinephrine, and dopamine; 3) upright and decubitus plasma aldosterone; 4) upright and decubitus plasma renin activity; 5) plasma cortisol, and 6) serum DHEA.

No patient agreed to receive image-guided fine needle aspiration (FNA) biopsy before surgery due to concern about complications. The tumors were successfully resected and paraffin-embedded for gross pathologic, light microscopic, and immunohistochemical evaluation. In our 6 cases the sections examined were 4, 5, 4, 6, 7, and 3, respectively. All the sections were reviewed by a single pathologist who was informed of the diagnosis.

RESULTS

The mean age of the 6 patients was 40.5 yr [range 30-47 yr; male (M):female (F)=1:2]. Five patients had unilateral lesions on the left side, and the other one on the right side. All the 6 cases of adrenal schwannoma in this series were detected during routine medical examinations, or during check-ups for various complaints or clinical onsets associated with the urogenital or general systems.

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Key-words: Adrenal, diagnose, schwannoma, treatment.

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Accepted March 12, 2010.

First published online June 11, 2010.

Table 1 - *Basic clinical characteristics of 6 patients with adrenal schwannoma.*

Case	Age/sex	Side	Clinical presentations	Serum potassium	Abnormal endocrine indexes	Tumor size	Pre-operative diagnosis
1	38/F	Left	Medical examination	Normal	Normal	3.5 cm	Adrenal adenoma
2	46/F	Left	Medical examination	Normal	Normal	4.5 cm	Adrenal adenoma
3	39/M	Right	Right waist pain	Normal	Normal	3.5 cm	Adrenal adenoma
4	43/F	Left	Left abdominal pain	Normal	Normal	5.1 cm	Adrenal adenoma
5	47/M	Left	Medical examination	Normal	Urine catecholamine E:23.21 μg/24 h NE:126.21 μg/24 h DA:489.45 μg/24 h	6.0 cm	Adrenal pheochromocytoma
6	30/F	Left	Medical examination	Normal	Normal	3.0 cm	Adrenal adenoma

M: male; F: female; E: epinephrine; DA: dopamine; NE: norepinephrine.

As shown in Table 1, routine medical examination was the main chance (4/6, 67%) of revealing clinical onsets leading to the discovery of adrenal schwannoma.

An overview of the history and physical findings revealed that all the 6 cases were initially found by transabdominal ultrasonography. Ultrasonographic imagings of the abdomen showed a well-circumscribed hypoechoic mass located on the adrenal region (Fig. 1). On pre-contrast images, tumor density was homogeneous with low attenuation in all cases. Two tumors had a high attenuated thin capsule and were centrally calcified (Fig. 2A). On postcontrast images, slight early-enhancement heterogeneity was seen in 1 patient (Fig. 2B), and slight late-enhancement heterogeneity was seen in all tumors.

Biochemical and baseline hormonal evaluation revealed that urine catecholamine level was high in 1, and normal in the other 5 patients. All the 6 patients presented with normokalemia (Table 1).

All the 6 patients underwent open unilateral adrenalectomy. Indications for surgery were one or more of the following: tumor size ≥4 cm (no.=3), suspected pheochromocytoma (no.=3), or patient's fear of malignancy (no.=4). All these 6 adrenal tumors were successfully resected by surgery. In case 5, the whole left kidney was resected, because the tumor was large and adhered with the renal artery so that it was difficult to separate it completely from the lefty kidney and the artery.

The diagnosis of adrenal schwannoma was finally confirmed by pathology. The largest tumor measured 6.0 × 5.0 × 5.0 cm, and the smallest 3.0 × 2.5 × 2.0 cm. The

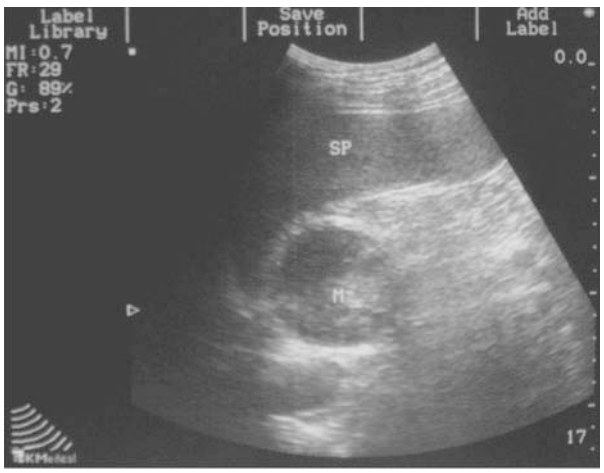

Fig. 1 - *Ultrasonographic images of the left abdomen showing a well-circumscribed hypoechoic mass cystic components measuring 6 cm in diameter.*

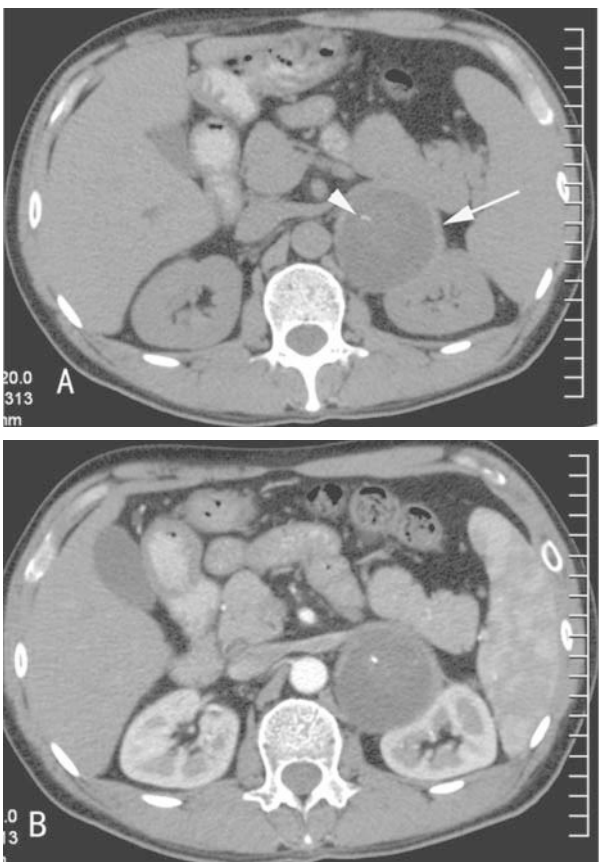

Fig. 2 - *Computerized tomography scan image of the abdomen demonstrating a well-circumscribed low-density mass with central calcification, approximately 6 cm in size, located in the region of the left adrenal gland. (A) Pre-contrast image; (B) Post-contrast image.*

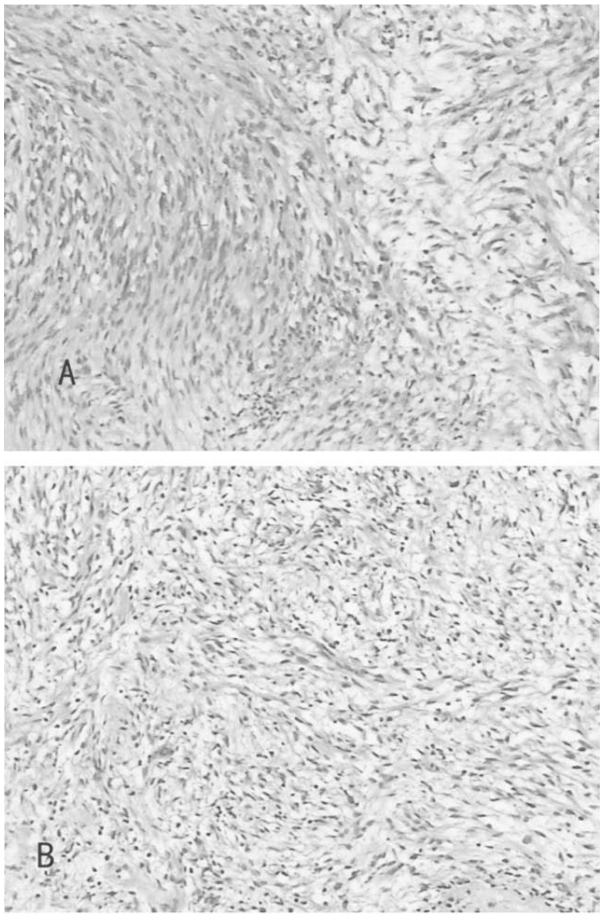

Fig. 3 - *The tumor exhibits Antoni A areas composed of ill-defined fascicles of spindle cells (A) and loosely organized Antoni B areas (B) (original magnification ×100) .*

mean size of the tumors resected by adrenalectomy was 4.3±1.1 cm. The cross-section of the tumors looked tan to pale yellow, surrounded by a fibrous capsule. Microscopically, the tumors had typical schwannoma presentations, including cellular Antoni A areas, and hypocellular Antoni B areas (Fig. 3A-B). The tumor cells showed diffuse expression of S-100 protein and also displayed positive immunoreactivity for vimentin and ABC protein (Fig. 4A-C). The tumor cells were negative for smooth muscle actin in immunohistochemistry.

The patients were followed up for a mean of 47.5±32.3 months (range: 9-103), during which no recurrence or metastasis was observed. The hormone level of the patient whose endocrine index was abnormal before surgery returned to normal at 6 months.

DISCUSSION

The majority of neoplasms of the adrenal gland are derived from the constituent of cortex, chromaffin, or nerve cells. Nerve sheath tumors occurring in the adrenal gland are comparatively uncommon. As well-documented cases of schwannoma originating from the adrenal gland are rare (5), misdiagnosis is most likely.

Nine cases of schwannomas were reported in the literature, the ratio of women to men was 2:1 (F:M=6:3), which

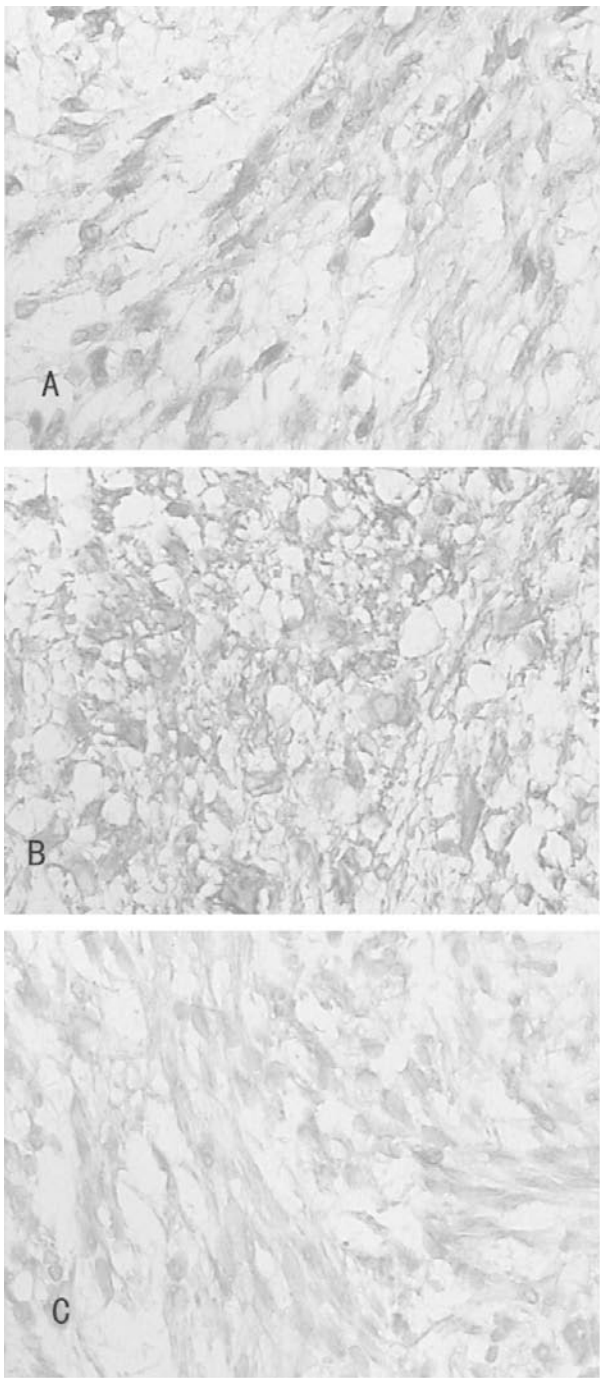

Fig. 4 - *On immunohistochemical examination, tumor cells are positive for S-100 protein (A); tumor cells are positive for vimentin protein (B); tumor cells are positive for ABC protein (C) (original magnification ×400).*

was coincident as reported in our center. Age of the patients in our series ranged from 30-47 yr, with female to male ratio about 2:1 (F:M=4:2). The 6 cases of schwannoma in this series were discovered in a 10-yr period, and 4 of them were discovered accidentally by health examination, indicating that schwannoma is undetectable in many asymptomatic patients without undergoing routine physical examination for other medical reasons.

The incidence of adrenal schwannoma is low, and differential diagnosis by imaging is difficult. Most adrenal schwannomas, including adrenal adenoma, adrenocortical carcinoma, adrenal metastasis, adrenal myelolipoma, and groups of neuroblastomas, present as non-functioning solid tumors. Ultrasonographic imagings of all the 6 tumors showed a well-circumscribed hypoechoic mass; also CT scan is not specific, as reported in the literature (7). Unenhanced CT often shows schwannomas as well-circumscribed homogeneous masses in the adrenal region. Schwannomas is slightly enhanced after iv administration of the contrast material. Although MRI was not performed in these patients, schwannomas, according to the literature, showed low signal intensity on T1-weighted images and heterogeneously high signal intensity on T2-weighted images. Many adrenal tumors share some of these radiological features, such as ganglioneuroma which contain ganglions and schwann cells in varying proportions. This seems to partly explain why MRI and CT scan features vary from tumor to tumor, depending upon their specific compositions (9). A schwannoma, when it grows large, often displayed such degenerative changes as cyst formation (about 66%), calcification, hemorrhage, and hyalinization as reported in our center (10). Differential diagnoses of adrenal schwannomas include neurogenic adrenal ganglioneuromas and neurofibromas, which are imageologically similar to adrenal schwannomas. Ichikawa et al. (7) reported delayed heterogeneous enhancement of ganglioneuromas on contrast-enhanced CT, while neurofibromas originate from nerve sheath and have a homogeneous, smooth, and round appearance with a distinct contour on CT imaging. Neurofibromas often contain multiple cystic spaces of varying size due to myxoid degeneration. Neurofibromas and schwannomas occasionally demonstrate a target-like enhancement pattern, and their attenuation or signal intensity in the central portion is different from that in the periphery on CT imaging (16).

Pre-operative diagnosis of adrenal schwannomas, especially those asymptomatic ones, remains difficult despite some radiological clues. Therefore, we recommend complete surgical resection once malignancy cannot be excluded by pre-operative analyses (11).

Schwannoma and pheochromocytoma shared some imaging features (3, 12). Intriguingly, as shown in 1 of our 6 patients, schwannoma may also have an endocrine function, which may lead to misdiagnosis of pheochromocytoma. However, how can the phenomenon be explained?

These tumors macroscopically arose from the medulla of the gland as reported (8). Furthermore, schwannoma cells also possess phagocytic function and may stimulate undifferentiated chromaffin cells or pheochromoblasts to maturate and replace injured chromaffin cells (13). As the tumor grows large, schwannoma may have secretary function like some adrenal ganglioneuroma (14, 15).

Adrenal medulla and sympathetic ganglion are both derived from neural crest cells in the period of embryonic development. By their development, biochemistry, and physiology, chromaffin cells are closely related to sympathetic neurons. Both cell types possess the machineries to synthesize, store, release, and take up catecholamines. Extra-adrenal chromaffin cells are most degraded or disappear after birth, but there are still chromaffin cells located in the sympathetic ganglion (17). Schwannomas come from the nerve system, where chromaffin cells may possibly remain. These remaining chromaffin cells may secrete catecholamine, presenting as catecholaminuria. This may be another reason for schwannomas to have endocrine function.

FNA biopsy should be avoided if pheochromocytoma or echinococcal parasitic cyst are suspected, since the procedure can be harmful (2). We do not advocate the use of FNA biopsy as a routine examination, for the role of FNA biopsy in evaluation of adrenal tumors remains controversial with respect to diagnostic accuracy and potential hazard. In our series, no patient agreed to receive CT-guided FNA biopsy.

The final diagnosis of schwannoma is confirmed by pathology. Gross features of adrenal schwannoma have been essentially identical to those found in most other anatomical sites. The tumor is typically well-circumscribed as an encapsulated round mass. The cut surface often consists of glistenting firm white-tan tissue with an occasional focus of yellow discoloration. Microscopically, there was a prominent spindle-cell population within a collagenous stroma. The architectural pattern is typical for schwannoma including cellular Antoni A areas, hypocellular Antoni B areas, and numerous well formed Verocay bodies. It is important that ancient changes, especially associated nuclear atypia, be not misinterpreted as signs of malignancy (1).

On immunohistochemical examination, the tumor cells were positive for S-100 protein. Furthermore, the protein of vimentin and ABC was also found to be positive in the tumor cells. Positive vimentin indicates that the tumor derives from mesenchymal tissue, not from epithelial tissue. Both positive ABC and positive S-100 may indicate that the tumor is a neurogenic tumor, not a pheochromocytoma. Although vimentin and ABC may not be the marker for schwannoma as specific as S-100, they may be used for auxiliary diagnosis of schwannoma.

However, it should be emphasized that there are some limitations of this study. First, the retrospective nature of this study may lead to potential bias in data collection. Second, the study included only a cohort of patients from one of the biggest tertiary care centers in China and might not be representative of all cases in the whole country. Third, there might be referral bias based on the tertiary nature of the medical center. Despite these limitations, we believe that our data truly represented valuable information related to adrenal schwannomas in China.

To our knowledge, this is the largest series of cases of adrenal schwannoma in the literature. Although there have been some clues for radiological diagnosis of

adrenal schwannoma, pre-operative misdiagnosis is not infrequent. Those tumors may occasionally have endocrine function. At present, surgical resection is the treatment of choice once malignancy cannot be excluded by pre-operative analyses.

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