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Case Report:

Adrenal myelolipoma within myxoid cortical adenoma associated with Conn's syndrome

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Abstract: The coexistence of myelolipoma within adrenal cortical adenoma is extremely rare, for both tumors present usually as separate entities. There are only 16 such cases reported worldwide. To the best of our knowledge, the case we reported here is the first one of myxoid adrenal cortical adenoma associated with myelolipoma reported. A 32-year-old Chinese woman with 4-year history of hypertension was presented in our study. Computed tomography (CT) of the abdomen showed a large heterogeneously-enhancing mass (4.5 cm in diameter) in the left suprarenal region. Clinical history and laboratory results suggest a metabolic disorder as Conn's syndrome. The patient underwent a left adrenalectomy, and a histopathological study confirmed the mass to be a myxoid adrenal cortical adenoma containing myelolipoma. The patient was postoperatively well and discharged uneventfully. In the present case report, we also discuss the etiology of simultaneous myelolipoma and adrenal adenoma associated with Conn's syndrome, and the methods of the diagnosis and differential diagnosis.

Key words: Adrenal gland, Myxoid adrenal cortical adenoma, Myelolipoma, Conn's syndrome, Pathology, Immunohistochemistry
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INTRODUCTION

Adrenal myelolipoma is an uncommon, benign, hormonally non-functioning tumor that is composed of mature adipose tissue and normal hematopoietic tissue. Its pathogenesis remains unclear (Manassero *et al*., 2004). Myxoid adrenal cortical tumor is a very rare neoplasm, and only 17 cases have been reported and its etiology is also unknown (Honda *et al*., 2001). Nevertheless, adrenal myelolipoma occurring within an adrenal cortical adenoma has only 16 cases reported, one of them associated with Conn's syndrome. Here we report a myelolipoma that located in myxoid adrenal cortical adenoma. The diagnosis is made by pathologic examination of the specimen and immunohistochemical findings. Compared with the previous cases, our case is significant in the knowledge about the etiology of myxoid adrenal cortical adenoma and myelolipoma, and the methods of the diagnosis and differential diagnosis.

CLINICAL SUMMARY

A 32-year-old woman with transient hypertension for about 4 years had been presented. Initially, she was found to have asymptomatic hypertension of 166/105 mmHg on a routine physical examination, and later diagnosed as primary hypertension at a local hospital. Her blood pressure (BP) ranged from 162/98 to 175/108 mmHg in the past years without any regular treatments. The patient was referred to our hospital on April 2007. She had undergone cholecystectomy because of gallstones one year before, and all other general physical examinations were within normal limits.

B-ultrasonic diagnosis showed light echo lump of 4.2 cm×3.9 cm in her left adrenal gland, presented a smooth boundary and complete capsule with a calcification spot about 1.0 cm in diameter. Abdominal computed tomography (CT) scan showed that in the left adrenal gland there is a well-

circumscribed mass (4.5 cm in diameter) with small focal areas of high attenuation, which were consistent with calcification spot about 1.2 cm×1.0 cm in size (Fig.1).

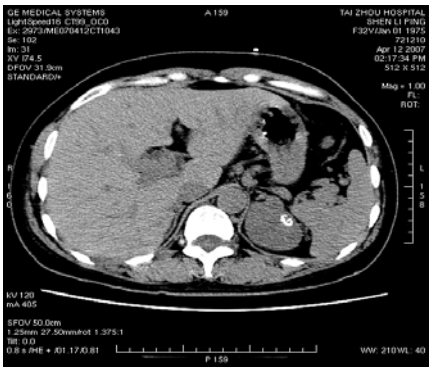

Fig.1 CT scan shows a rounded low-density mass in the left adrenal gland, with small focal areas of high attenuation, which were consistent with calcification spot about 1.2 cm×1.0 cm in size

Endocrinological results showed that plasma aldosterone was significantly increased, 386.9 pg/ml on a standing position (normal ranges: 38.1~313.3 pg/ml) and 198.3 pg/ml on a lying position (normal ranges: 29.4~161.5 pg/ml). The plasma cortisol level was 9.7 μg/dl in the morning (normal ranges: 8.7~22.4 μg/dl) and 3.4 μg/dl in the evening (normal ranges: ≤10.0 μg/dl). The serum noradrenaline and adrenaline levels were within normal limits, 6.22 ng/L and 4.50 ng/L, respectively. Other clinical laboratory findings including hemoglobin, white blood cell count, neutrophils, lymphocytes and eosinophils were 12.3 g/dl, 3800 mm^{-3}, 38%, 47.0% and 0.0%, respectively. Serum kalium was 3.3 mmol/L, a little lower than normal.

Based on medical history, physical examination, and laboratory results, sufficient evidence suggested that this patient had an adrenal tumor associated with Conn's syndrome.

The patient was then treated with retroperitoneal laparoscopic adrenalectomy of the left adrenal tumor on May 9, 2007. Following the surgery, she recovered quickly. Her BP readings were improved to the range of 120~130 mmHg in systolic phase and 72~83 mmHg in diastolic phase. She was discharge on May 15, 2007 when her BP was 118/80 mmHg.

She had been followed up for five months after tumor resection; her BP was within normal limits (mean systolic BP 120 mmHg and mean diastolic BP 76 mmHg) and there was no evidence to suggest any other discomforts.

PATHOLOGICAL FINDINGS

Macroscopic findings

Grossly, the adrenal mass was 5.0 cm×4.5 cm×2.0 cm and weighed 56.3 g. The surface was smooth without adhesion, shrinking with fibrous capsule formation. No normal adrenal tissue was identified. On the cut surface appeared yellow-greyish regions with gelatinous myxoid areas admixed with areas of firm and fibrous consistency. There was a darker red encapsulated tumor-like lesion (1.0 cm in diameter) centrally located within the tumor.

At light microscopy, the tumor was almost completely demarcated by a fibrous capsule, at the periphery of which atrophic adrenal gland parenchyma was partially found. The tumor was mostly characterized by a myxoid background containing cords and pseudoglandulars of medium-sized polygonal cells (Fig.2). The large amounts of extracellular mucous material were faintly stained by either Alcian blue (Fig.3) or periodic acid-Schiff (PAS). In limited areas (less than 25%), cell clusters having an amphophilic or clear cytoplasm were observed, which recalled the classical adrenocortical adenoma cells, but the myxoid background was still recognizable in these cytologically classical areas. The nuclei were usually centrally located and were round or oval. They had fine chromatin and generally lacked atypias, with the exception of an occasional single enlarged pleomorphic nucleus. No mitotic figures, necrosis or signs of invasive growth were observed.

The adrenal cortical tumor centrally included well-demarcated adipose tissue admixed with scattered islands of myelopoietic elements: erythroblasts, myeloid cell series and lymphocytic cells, and was eventually recognized as myelolipoma (Fig.4).

Immunohistochemical findings

Immunohistochemical studies were done on paraffin-embedded sections with antibodies against epithelial membrane antigen (EMA) (clone E29 1/75; DakoCytomation, USA), cytokeratin (CK) (clone

AE1/AE3 1/100; DakoCytomation), vimentin (clone Vim384 1/100; DakoCytomation), synaptophysin (clone SVP38 1/100; Maixin-Bio, Fuzhou, China), chromogranin A (clone A3 1/100; Maixin-Bio), S-100 protein (polyclonal 1/1000; Maixin-Bio) and alpha-inhibin (clone R1 1/50; DakoCytomation). The antibodies against vimentin, synaptophysin and alpha-inhibin were characteristic markers of adrenocortical adenoma. The results showed positive detection for vimentin, synaptophysin (Fig.5), and alpha-inhibin (Fig.6), and negative detection for S-100 protein, CK, EMA and chromogranin A.

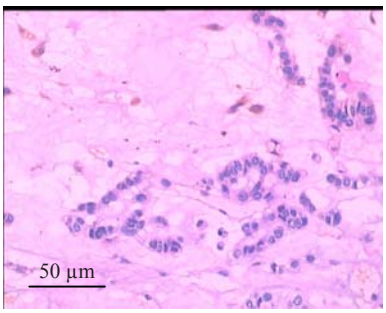

Fig.2 The tumor characterized by an abundant myxoid background containing cords and pseudoglandulars of polygonal regular cells (H & E)

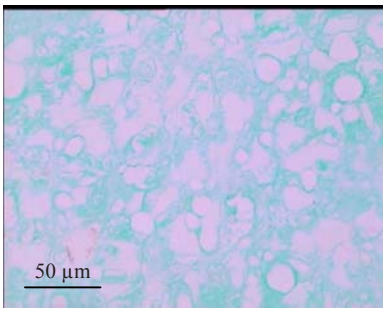

Fig.3 The tumor contained large amounts of extracellular mucous material that was positive when stained by Alcian blue

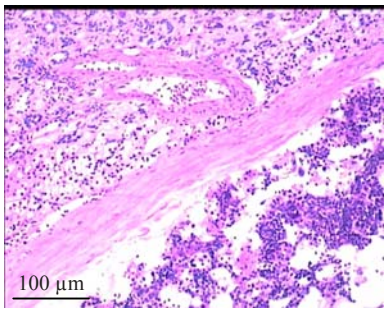

Fig.4 Photomicrograph of the intermediate of myelolipoma within the adrenal cortical adenoma. The myelolipoma is composed of mature adipose tissue and normal hematopoietic tissue

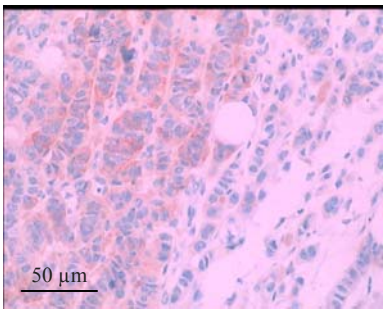

Fig.5 Immunoreactivity for synaptophysin. Positive cells were fine granular stained cytoplasm, which showed expression of neuroendocrine substance (immunostaining)

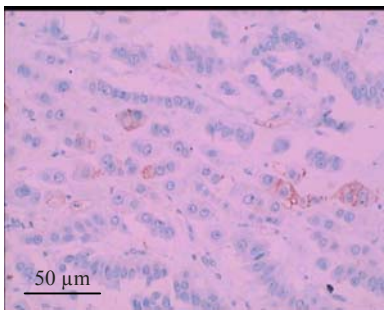

Fig.6 Immunoreactivity for alpha-inhibin. Positive cells were stained cytoplasm. The result showed that the tumor originated from the adrenal cortical source not medullary one (immunostaining)

DISCUSSION

Adrenal myelolipomas are relatively uncommon, benign and biochemically non-functioning tumor, composed of variable admixture of mature adipose tissue and hematopoietic elements. Fewer than 200 cases have been described in the literature. The pathogenesis of adrenal myelolipoma remains unclear. Myxoid changes in adrenocortical tumors are extremely rare, only 17 cases reported. The coexistence of myelolipoma within adrenal cortical adenoma is extremely rare. Usually, both tumors present as sepa-

rate entities. There are only 16 cases reported in the English, Japanese and Chinese literatures (Table 1). To the best of our knowledge, this is the first reported case of myelolipoma within a myxoid adrenal cortical adenoma.

On the mechanism for myxoid adrenal cortical adenoma and myelolipoma, Forsthoefel (1994) proposed that the formation of myxoid material might be due to a degenerative process, or production by stromal fibroblasts or tumor cells. On the other hand, the adrenal cortex has a mesodermal origin, as does connective tissue. These neoplasms can produce acidic mucopolysaccharides, which also arise from tissues of mesodermal origin. Similarly, adrenal cortical tumors might have the ability to produce connective tissue type mucins (Honda *et al*., 2001). Various theories of the etiology of adrenal myelolipoma had been presented. Olsson *et al*.(1973) suggested that the formation of necrotic tissue was the main stimulus in the pathogenesis of adrenal myelolipoma, because this neoplasm occurred in patients with severe burns, cancer and other kinds of chronic diseases in which there was a great release of necrotic tissue products. Ide *et al*.(2007) reported a case of myelolipoma associated with hyperthyroidism. They thought that thyroid hormones have important effects on development, growth, metabolism, and tumorigenesis of myelolipoma. At present views, probably involved are multiple factors including adrenal cortical metaplasia, embolism of bone marrow cells and development from embryonic rests.

We summarized the cases of myelolipoma within adrenal cortical adenoma ever reported (Table 1). There were 4 males and 13 females, with a ratio of approximately 1:3. The age at diagnosis ranged from 16 to 69 years (means 45.5 years). Thirteen out of the 17 patients had hormonal disturbances, namely, 11 Cushing's syndrome cases and 2 Conn's syndrome. Our case was the second one reported to be associated with Conn's syndrome. The tumor in 10 cases originated from the left adrenal gland. Most of the myelolipomas were smaller than 2.5 cm in diameter and the one in our patient presented 1.2 cm×1.0 cm×1.0 cm in size. Table 1 also shows that adrenal myelolipoma within cortical adenoma, or within myxoid cortical adenoma, was more common in women than in men and developed most likely in the left adrenal gland. Most such patients had hormonal disturbances such as Cushing's syndrome and Conn's syndrome.

Table 1 The clinical characteristics of myelolipoma within adrenal cortical adenoma ever reported

Case No.	Literatures	Age (year)	Sex	Myclolipoma size (cm)	Side	Endocrine dysfunction
1	Murayama *et al*., 1979	69	M	ND	R	ND
2	Cho *et al*., 1984	50	F	ND	L	Cushing's syndrome
3	Fujita *et al*., 1985	30	F	ND	L	Cushing's syndrome
4	Vyberg and Sestoft, 1986	31	F	ND	L	Cushing's syndrome
5	Saito *et al*., 1988	34	F	ND	L	Cushing's syndrome
6	Miyake *et al*., 1992	42	F	0.6×0.5×0.5	R	Cushing's syndrome
7	Cormio *et al*., 1992	62	F	0.15	L	Conn's syndrome
8	Han *et al*., 1997	26	F	2.3	L	Cushing's syndrome
9	Matsuda *et al*., 2004	29	F	0.1	R	Cushing's syndrome
10	Jiang and Huang, 2002	38	F	0.3	R	Non-functioning
11	Vrezas *et al*., 2003	60	M	2.5	R	Cushing's syndrome
12	Manassero *et al*., 2004	64	F	ND	L	Non-functioning
13	Hisamatsu *et al*., 2004	67	F	ND	L	Cushing's syndrome
14	Armand *et al*., 2004	58	F	Small foci	R	Cushing's syndrome
15	Ammoury *et al*., 2006	16	M	Peripheral foci	R	Cushing's syndrome
16	Ong *et al*., 2007	66	M	1.5×1.0×1.0	L	Non-functioning
17	Present case	32	F	1.2×1.0×1.0	L	Conn's syndrome

ND: Not detected

The diagnosis of adrenal myelolipoma within myxoid cortical adenoma relies mainly on the pathological examination, and its characteristic features include the ample extracellular myxoid material and the formation of the pseudoglanders, which are composed of variable admixture of mature adipose tissue and hematopoietic elements. In our case, the tumor contained large amounts of extracellular mucous material that was positive for staining with Alcian blue. Immunostaining was positive for vimentin, synaptophysin and alpha-inhibin. CT scan showed focal fatty density and calcification spot within the adrenal mass, making the preoperative diagnosis of this tumor possible. However, considering the diagnosis of myxoid adrenal cortical adenoma, we should first exclude the diagnosis of myxoid adrenal cortical adenocarcinoma. In the case, there were no malignant indicators such as the vascular invasion, capsular invasion, and the mitotic figures or necrosis, thus ruling out myxoid adrenal cortical adrenacarcinoma.

The differential diagnosis also included retroperitoneal neoplasms that develop myxoid changes, such as myxoma, leiomyoma, leiomyosarcoma, liposarcoma, benign and malignant nerve sheath tumor, malignant fibrous histiocytoma and chordoma. Extraskeletal myxoid chondrosarcoma must be also considered although it was most common in the musculature of the extremities. Chordoma and extraskeletal myxoid chondrosarcoma were important with respect to histological differentiation because of their epithelioid appearance. However, it seemed relatively straightforward to distinguish myxoid adrenal cortical tumor from other myxoid neoplasms at the light-microscopic level, because most myxoid adrenal cortical tumors had a region that resembles a conventional adrenal cortical adenoma or carcinoma. Nevertheless, even in the case of a tumor without a region that resembles a conventional adrenal cortical tumor, immunohistochemical examination should lead us to the correct diagnosis when the possibility of a myxoid adrenal cortical adenoma was taken into account (Honda *et al*., 2001). When pseudoglandular areas were prominent, a well-differentiated metastatic adenocarcinoma was to be taken into account first, since pulmonary, breast and, more rarely, other glandular carcinomas may spread to the adrenal gland. Strong cytokeratin expression was usually helpful to identify a metastatic carcinoma. In addition, the appearance of myelolipoma within a myxoid cortical adenoma was different from fat-containing adrenal adenomas. An adrenal tumor containing fat foci was not always the myelolipoma. It is important to observe the other components rather than fat when fat was recognized in an adrenal tumor (Yamada *et al*., 2002).

In conclusion, myelolipoma within a myxoid cortical adenoma is an incidentaloma. The mechanism of concurrence remains unclear and multiple factors are probably involved. Although the tumor is benign, it can present with complications such as Cushing's syndrome and Conn's syndrome, so it requires immediate attention and management. The diagnosis and differential diagnosis rely mainly on the pathological examination and immunohistochemistry.

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