

Primary adrenal teratoma: Clinical characteristics and retroperitoneal laparoscopic resection in five adults

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Received October 26, 2014; Accepted August 17, 2015

DOI: 10.3892/ol.2015.3701

Abstract. Primary adrenal teratoma is extremely rare. To investigate the clinical characteristics and further enrich the limited knowledge on its diagnosis and treatment, the present study retrospectively analyzed the detailed clinical data of five patients with primary adrenal teratomas treated in the Peking Union Medical College Hospital (Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China) between March 2009 and February 2014. The five patients were female, aged from 16 to 51 years (mean, 36.0 ± 16.3 years), with solitary lesions that were incidentally found on routine physical examinations. The tumor size ranged from 2.4 to 9.0 cm (mean, 6.0 ± 2.7 cm). Ultrasonography revealed a mixed echo in four patients, and computed tomography showed mixed density masses with fat components and calcification in three patients. Adrenal-related endocrine tests were normal in all five patients, and no abnormalities were found in the three patients who underwent somatostatin receptor scintigraphy examination. All patients were treated with retroperitoneal laparoscopic surgery, with no complications, and the resected tumors were identified as mature cystic teratomas pathologically. To date, the patients have been followed up for 4-60 months post-operatively, with no recurrence. In conclusion, this rare adrenal teratoma is an occult entity to which reproductive females are susceptible. The tumor exhibits no typical clinical manifestations or adrenal-related laboratory abnormalities, and the pre-operative diagnosis mainly relies on imaging characteristics of a heterogeneous lesion containing fat components with scattered and marginal calcifications. The preferred treatment is retroperitoneal laparoscopic surgery, and the prognosis is good.

Introduction

Clinically, teratoma is a germ cell tumor derived from primordial germ cells, which have the potential to differentiate into somatic cells (1). Mature teratoma usually contains two or three germ cell layers from the endoderm, mesoderm and ectoderm (2). A typical mature teratoma often contains components from each of the three germ layers, including lipid, epithelium, bone, cartilage, hair, fat, muscle and nerve tissue. Teratoma most commonly affects neonates and adolescents, and is mainly prevalent in women. The most common sites of occurrence are the gonads, namely the male testis and the female ovary, with extragonadal teratomas accounting for only 15% of all teratomas and often occurring in regions of the body axis, including the mediastinal and sacrococcygeal regions (3,4).

Primary adrenal teratoma is extremely rare, and only a few individual case studies and small series can be retrieved from the clinical literature (5-7). To the best of our knowledge, the largest reported series of patients with primary adrenal teratoma described three cases in a study by Lam and Lo (8). Between March 2009 and February 2014, 3,901 patients with adrenal disease were treated in the Peking Union Medical College Hospital (Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China), of which, five patients presented with primary adrenal teratoma, accounting for only 0.13%. Considering the limited information on primary adrenal teratoma, a detailed analysis of the clinical characteristics of the five patients was conducted in the present study, and the literature on adrenal teratoma reported in the past 10 years was also briefly reviewed.

Patients and methods

General information and clinical manifestations. Five female patients aged from 16 to 51 years (mean, 36.0 ± 16.3 years) were treated for primary adrenal teratomas in the Peking Union Medical College Hospital between March 2009 and February 2014. All the adrenal teratomas were incidentally found by ultrasonography during routine physical examinations, without typical clinical symptoms and hypertension, with the exception of abdominal discomfort in one patient and palpable masses in two. The time period from the discovery

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Key words: adrenal gland, teratoma, diagnosis, laparoscopic resection, adult

of adrenal lesions to undergoing surgery ranged from 2 weeks to 13 years. Informed consent was obtained from all patients prior to collecting the clinical data.

Imaging and laboratory tests. Imaging and laboratory tests were completed prior to surgery. All five patients underwent color Doppler ultrasonography, and four patients underwent normal and enhanced computed tomography (CT) scanning. Three patients received somatostatin receptor scintigraphy with ^{99m}Tc -hydrazinonicotinyl-Tyr³-octreotide (^{99m}Tc -HTOC), and scintigraphy was performed at 1 and 4 h post-injection. Synthesis and labeling of ^{99m}Tc -HTOC were conducted as previously described (9). ELISA kits (Bio-Rad Laboratories, Inc., Hercules, CA, USA) were used, according to the manufacturer's instructions, to assess adrenal-related endocrine levels. This included the following: Plasma adrenocorticotrophic hormone (normal range, 0-46 pg/ml), renin activity (normal range, 0.93-6.56 ng/ml/h), angiotensin II (normal range, 55.3-115.3 pg/ml), aldosterone (normal range, 6.5-29.6 ng/dl), cortisol (normal range, 4.0-22.3 $\mu\text{g/dl}$), 24-h urinary free cortisol (normal range, 12.3-103.5 $\mu\text{g/24 h}$) and 24-h urinary catecholamines [normal ranges: norepinephrine (NE), 16.69-40.65 $\mu\text{g/24 h}$; epinephrine (E), 1.74-6.42 $\mu\text{g/24 h}$; and dopamine (DA), 120.93-330.59 $\mu\text{g/24 h}$].

Treatment and follow-up. All patients were treated with retroperitoneal laparoscopic resection. Patients with left-sided adrenal teratomas were placed in the right lateral position for surgery, and patients with right-sided adrenal teratomas were placed in the left lateral position (Fig. 1A). Routinely three trocars were placed during the procedure (Fig. 1B). One 10-mm trocar was placed at 2 cm above the superior border of the iliac crest in the midaxillary line (point 1), another 10-mm trocar was placed under the lower edge of the twelfth rib in the posterior axillary line (point 2) and one 5-mm trocar was placed in the anterior axillary line at the level of point 1 (point 3). During the surgery to resect the largest tumor (diameter, 9 cm), another 5-mm trocar was placed at point iv (under the costal margin in the anterior axillary line), in order to facilitate the procedure.

With regard to the post-operative follow-up scheme, patients were followed up at 3, 6 and 12 months during the first year, and at 18 and 24 months during the second year, then followed up once a year thereafter.

Results

Each of the five patients presented with a solitary adrenal teratoma, with a mean tumor diameter of $\sim 6.0 \pm 2.7$ cm (range, 2.4-9.0 cm) (Table I). Two lesions were located in the left adrenal glands and three in the right. Ultrasonography showed clear boundaries and regular shapes in all patients. Lesions were of mixed echo in four patients and hypoechoic in one. No marked blood flow signals were observed within the masses of any patient upon color Doppler flow imaging (Fig. 2A). CT showed mixed density inside three lesions and soft tissue density inside one, including irregular fat components, cystic areas and separation, as well as nodular calcifications on the edge (Fig. 2B). The CT values of the soft tissues in the normal scan and in the arterial phase

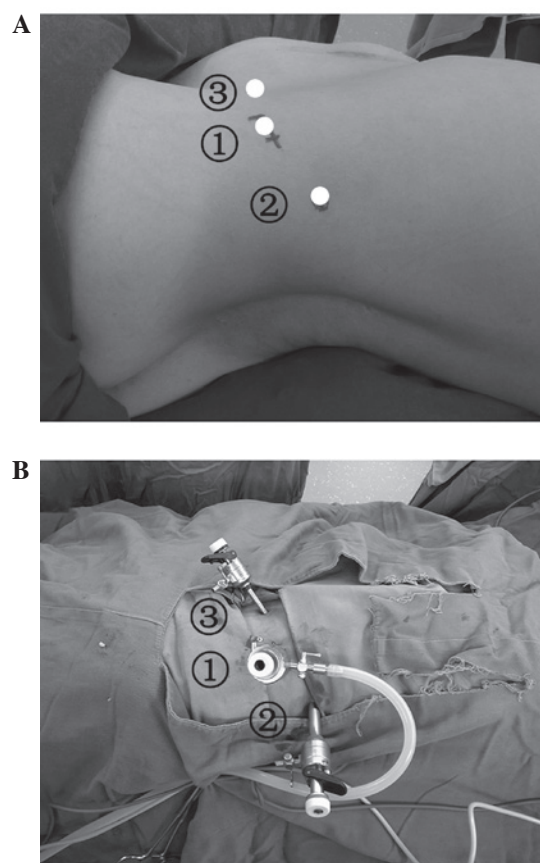


Figure 1. Surgical position and the location of trocars. (A) A patient with a left-sided adrenal teratoma placed in the right lateral position for surgery. (B) Two 10-mm trocars were placed at points 1 and 2, respectively, and one 5-mm trocar was placed at point 3.

were -92 to 43 HU and 58 to 85 HU, respectively (Fig. 2C). Negative results were found in the three patients who underwent somatostatin receptor scintigraphy examination. Adrenal-related endocrine laboratory results [range (mean \pm SD)] were within normal limits in all patients: Plasma adrenocorticotrophic hormone, 7.7-26.7 pg/ml (20.1 ± 8.5 pg/ml); renin activity, 1.06-6.27 ng/ml/h (3.90 ± 2.40 ng/ml/h); angiotensin II, 57.3-96.3 pg/ml (73.1 ± 15.4 pg/ml); aldosterone, 9.3-26.5 ng/dl (17.5 ± 7.0 ng/dl); plasma cortisol, 6.5-20.3 $\mu\text{g/dl}$ (13.5 ± 6.1 $\mu\text{g/dl}$); 24-h urinary free cortisol, 30.4-63.6 $\mu\text{g/24 h}$ (48.7 ± 12.9 $\mu\text{g/24 h}$); and 24-h urinary catecholamines [NE, 10.93-28.16 $\mu\text{g/24 h}$ (19.66 ± 6.27 $\mu\text{g/24 h}$); E, 0.87-2.20 $\mu\text{g/24 h}$ (1.43 ± 0.55 $\mu\text{g/24 h}$); and DA, 72.00-282.66 $\mu\text{g/24 h}$ (162.12 ± 77.97 $\mu\text{g/24 h}$)].

The surgical duration (from skin incision to suturing) was 70-135 min (mean = 113.0 ± 26.6 min) and the intraoperative blood loss was 30-80 ml (mean, 56.0 ± 19.5 ml). All patients underwent surgery without any complications. All the perirenal drainage tubes were removed at 2-4 days post-surgery, and all the patients were discharged at 3-7 days post-surgery.

All the five specimens were identified as mature cystic teratomas pathologically. The gross appearance showed yellow or gray nodular masses, which were covered by smooth capsules outside the surface (Fig. 3A), and the cut surfaces were multilocular with diameters ranging from 2 to 5 cm, containing hair and cheese-like sebaceous material inside (Fig. 3B). The inner

Table I. Demographic data and imaging features.

Case no.	Gender/age, years	Pre-operative diagnosis	Tumor size, cm	Side	Ultrasonography Echo/CDFI	Computed tomography		
						Density	Calcification	Fat
1	F/21	Adrenal teratoma	8.5	Right	Mixed/-	Mixed (mainly cystic)	+	+
2	F/16	Adrenal teratoma	9.0	Right	Mixed/-	Mixed (mainly cystic)	+	+
3	F/43	Adrenocortical carcinoma	4.9	Left	Hypoechoic/-	Soft tissue density	-	-
4	F/49	Adrenal myelolipoma	5.3	Left	Mixed/-	Mixed (mainly soft tissue)	+	+
5	F/51	Adrenal tumor (unspecified)	2.4	Right	Mixed/-	NA	NA	NA

F, Female; CDFI, color doppler flow imaging; NA, not available.

Table II. Review of characteristics of adrenal teratoma in the past 10 years.

First author/s, year (ref.)	Case no.	Gender/age, years	Clinical signs	Tumor size, cm	Location	Imaging		
						Texture	Calcification	Fat
Castillo <i>et al</i> , 2006 (5)	1	F/61	-	8.0	Left	Heterogeneous	+	NA
Li <i>et al</i> , 2011 (6)	2	F/38	Soreness	10.0	Right	Heterogeneous	-	+
Huang and Wang, 2013 (7)	3	F/64	-	6.3	Left	Heterogeneous	+	+
Bhatti <i>et al</i> , 2013 (10)	4	M/22	Flank pain	10.8	Left	Heterogeneous	+	+
Tang <i>et al</i> , 2014 (11)	5	F/39	-	22.5	Right	Heterogeneous	+	+
Zhao <i>et al</i> , 2014 (12)	6	F/21	Backache	6.0	Right	NA	+	+
	7	F/35	-	8.0	Right	NA	+	+

F, female; M, male; NA, not available; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Table III. Review of management of adrenal teratoma in the past 10 years.

First author/s, year (ref.)	Case no.	Surgery	Pathology	Follow-up, months
Castillo <i>et al</i> , 2006 (5)	1	Laparoscopic	MCT	12
Li <i>et al</i> , 2011 (6)	2	Open	MCT	24
Huang and Wang, 2013 (7)	3	NA	MCT	6
Bhatti <i>et al</i> , 2013 (10)	4	Open	MCT	6
Tang <i>et al</i> , 2014 (11)	5	Open	MCT	18
Zhao <i>et al</i> , 2014 (12)	6	Open	MCT	80
	7	Open	MCT	57

NA, not available; MCT, mature cystic teratoma.

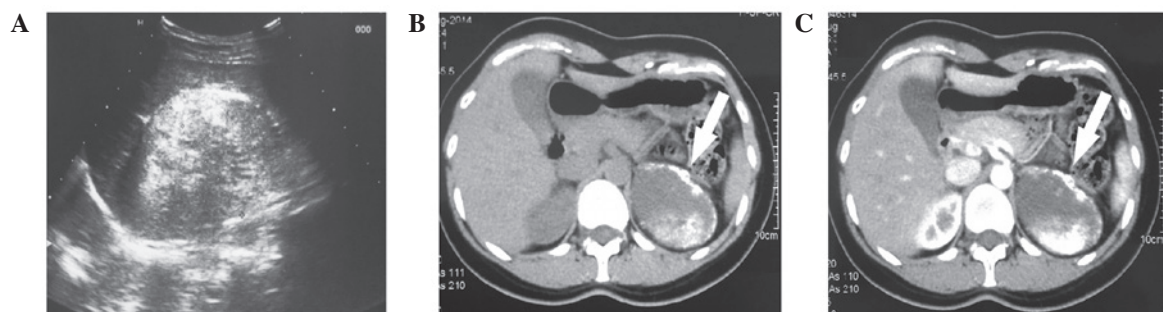


Figure 2. Imaging features of an adrenal teratoma from one case. (A) Ultrasonography showing a mixed echo. (B) Computed tomography revealing a mass with mixed density and calcifications in the left adrenal region, as indicated by the white arrow. (C) Mildly enhanced mass.

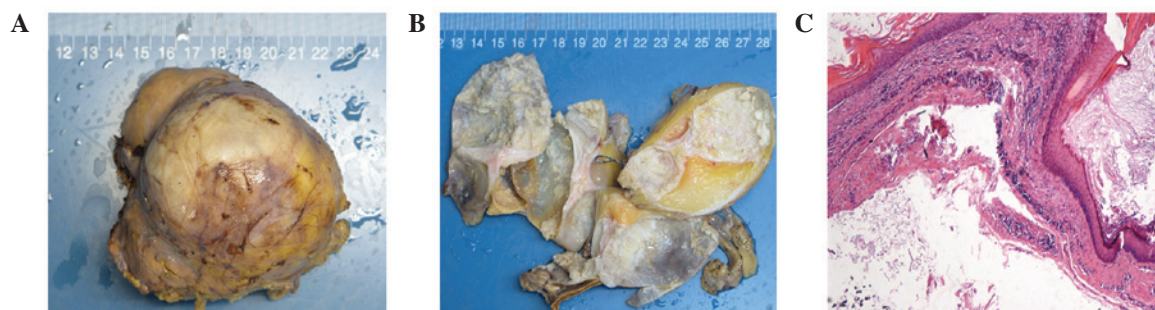


Figure 3. Pathological features of an adrenal teratoma from one case showing (A) the gross appearance of the adrenal teratoma and (B) the cut surfaces and cheese-like sebaceous material inside. (C) Hematoxylin-eosin staining under the microscope (x40 magnification).

surfaces of the cyst walls were smooth and partially calcified. The wall thickness was 0.1-0.4 cm, with certain cartilaginous components and adrenal tissues. After draining the cystic fluid substances, the largest specimen weighed ~200 g. The stratified squamous epithelium, hair shafts, fat cells, gastrointestinal epithelium and respiratory epithelium, were observed under a microscope (Fig. 3C).

The five patients have been followed up regularly for 4-60 months post-surgery and are currently alive with no signs of recurrence.

Discussion

Adrenal teratoma is so rare that a literature review only retrieved a total of 11 cases from Pubmed in the past 10 years, with seven adult cases (5-7,10-12), including one male and six

females, aged from 21 to 64 years (mean \pm SD, 40.0 \pm 17.0 years) (Table II). This is consistent with the findings that adrenal teratomas only accounted for 0.13% of adrenal lesions over the same period and that reproductive females were susceptible, as indicated by the present study.

Since patients with adrenal teratomas often have no specific clinical manifestations, lesions cannot be found until the diameters become large enough. The mean diameter (\pm SD) was 6.0 \pm 2.7 cm in the present study results and 10.2 \pm 5.7 cm in the review. Meanwhile, patients with adrenal teratomas usually have no abnormalities in adrenal-related endocrine tests and nuclear medicine examinations, resulting in difficulties in distinguishing adrenal teratoma from other lipomatous tumors (12), such as myelolipoma, angiomyolipoma, retroperitoneal lipoma and liposarcoma, as well as tumors with massive necrotic liquefied components, such as pheochromocytoma. In

the present study, adrenal myelolipoma could not be pre-operatively ruled out in four cases and pheochromocytoma could not be excluded in one.

Myelolipoma is the most common lipomatous tumor of the adrenal gland without endocrine function (12). Ultrasonography shows a hyperechoic mass, and CT reveals a well-defined mass of mixed density with mainly fat-containing components. Pheochromocytoma often has the typical clinical symptoms of hypertension, headache, palpitation and sweating, and the level of 24-h urinary catecholamines (NE, E and DA) are always above the normal limits. Somatostatin receptor scintigraphy and ¹³¹I-MIBG scintigraphy are mostly positive, and the latter has a high specificity in diagnosis. Features on CT include cystic masses or solid masses with necrosis and significant enhancement. Due to the large impact on the circulatory system, patients with a long history may suffer from catecholamine cardiomyopathy (13). Therefore, routine preparation with pre-operative oral phenoxybenzamine should be conducted if pheochromocytoma cannot be completely ruled out. Retroperitoneal liposarcoma (14), which originates from mesenchymal tissue and can be classified into five types, mainly shows expansive growth and results in a squeezing effect on the surrounding tissues and organs, without any specific clinical manifestations. The diagnosis also relies mainly on imaging. The CT characteristics of well-differentiated liposarcoma are similar to that of the fat content, while undifferentiated tumors appear dense and heterogenous, and can be markedly enhanced with intravenous contrast (15).

As for a typical mature cystic teratoma, the radiographic characteristics are usually as follows: i) Ultrasonography shows a mixed echo in the mass, hyperechoic fat-rich ingredients and hypoechoic cystic areas, with a clear boundary and regular morphology (16). ii) CT scan shows mixed density elements, such as fat, bone and other soft tissue densities with separations and calcifications. Mild enhancement can be seen in the soft-tissue components or cystic walls (17). It has been reported that 93% of lesions contain fat components and 56% contain calcifications (18). iii) Magnetic resonance imaging often reveals equal signals on T1-weighted imaging (T1WI) and slightly higher signals on T2WI, with a nodular focus and clear boundary (19). Among the 12 patients in the present study and review, 75% (9/12) presented with heterogeneous lesions, as well as fat compositions and calcifications.

Currently, laparoscopic surgery remains the primary option for adrenal tumors. Laparoscopic technology, which had been used in adrenal surgery since 1992 (20), has been developed rapidly and used increasingly in urology cases. Today, laparoscopic surgery is the gold standard for adrenal lesion removal (21). Upon consideration of our limited clinical experience, we believe that laparoscopic surgery is superior to open surgery for the following reasons: i) Anatomical factors: Adrenal glands are deeply and covertly located inside the perirenal fat medially above the kidney, which means that it is too difficult to complete surgical procedures by open surgery due to the limited vision, particularly when dealing with the central vein of the adrenal gland. However, the zoom effect of the laparoscopic camera system has just solved these problems. ii) Nature of lesion: The majority of benign adrenal tumors are regularly shaped. Although closely associated with the surrounding tissues and organs, local infiltration and a

rich blood supply are rare. Therefore, a laparoscopic resection with less bleeding and surrounding damage is more suitable. iii) Advanced laparoscopic devices and skilled surgeons: Compared with open surgery, in addition to its equal safety and effectiveness, laparoscopic surgery is less invasive so patients experience a shorter hospitalization period.

In contrast to previous studies, which conducted open surgery in 71.4% (5/7) of patients (Table III), patients in the Peking Union Medical College Hospital, for whom the maximum diameter was ~9 cm, were all treated successfully with a retroperitoneal laparoscopic resection. This proves that laparoscopic surgery is suitable for even those adrenal tumors with large diameters and can be successfully conducted by skilled surgeons.

The pathological characteristics of typical mature teratomas are mostly cystic with two or three germ layers, an intact capsule, a smooth appearance, cheese-like sebaceous material, hair, bone and fat compositions. Immature teratomas are mostly solid and contain various differentiations of immature embryonic tissues (22). In the present study and the review of the previous 10 years, a total of 12 cases were identified with mature cystic teratomas, which have been followed up for 4 to 80 months post-surgery with no recurrence (Table III). Although a prior study has stated that 1.46% of mature cystic teratomas develop malignant transformation (23), a good prognosis should be obtained as long as the lesion is removed completely. However, regardless of whether the tumor is a mature or immature teratoma, regular post-operative follow-up is necessary to detect and treat the recurrence or metastasis in a timely manner (24).

In conclusion, reproductive females are susceptible to these rare adrenal teratomas. Without typical clinical manifestations and adrenal-related laboratory abnormalities, the lesions are found relatively late when they become larger. The pre-operative diagnosis mainly relies on the imaging characteristics of a mixed echo on ultrasonography, and a heterogeneous density containing fat components with scattered and marginal calcifications on CT. The combination of a variety of screening methods may improve the accuracy of diagnosis pre-operatively to distinguish the mass from other lipomatous tumors. Retroperitoneal laparoscopic surgery is the preferred treatment for adrenal teratoma, and the prognosis is good. Patients should be closely followed up after surgery whether the tumor is a mature or immature teratoma. However, the present results are not comprehensive due to the limited number of cases. Further studies and long-term follow-up data are required in the future.

Acknowledgements

The authors would like to thank Dr Yu Xiao (Department of Pathology, Peking Union Medical College Hospital) for providing support in analyzing the pathological results.

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