Original Article

Clinical, Pathological and CT Imaging Analysis of AT-AG (Three Cases and Literature Review)

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Abstract

Background: Adenomatoid Tumor of the Adrenal Gland (AT-AG) are very rare. As the most commonly used clinical examination program, CT scan can make benign and malignant diagnosis by evaluating the characteristics of lesion shape, density and blood vessels, and provide imaging basis for treatment decisions.

Objective: To investigate the clinical, pathological and CT imaging features of AT-AG.

Methods: The clinical, pathological and CT findings of three AT-AG patients confirmed by surgery or pathology were reviewed and analyzed with reference to nine cases in literature reports.

Results: Among the 12 patients with AT-AG, 11 were male, with a median age of 40 years; 11 were diagnosed by physical examination or accident, while 1 was treated for right lumbago. Pathologically, they were characterized by microcapsule/glandular tube structures, absence of cell heteromorphosis and mitosis, positive immunohistochemical mesothelial markers, and negative endothelial markers; In addition, all of them were confirmed with single adrenal cystic or cystic solid masses on CT, including 2 with multilocular cyst and 3 with calcification. Among them, nine (75%) were oval, with the long diameter parallel to the long axis of adrenal gland, and 8 (67%) showed mild and moderate enhancement of capsule wall and solid components on enhanced scan.

Conclusion: AT-AG is more common in young and middle-aged men than other population groups, and it constitutes microcapsule/glandular structures under microscope. Its immune histo chemical mesothelial markers show positive, while endothelial markers are negative. CT findings reveal a mostly oval solitary cyst or solid mass, parallel to the long axis of adrenal gland, with mild and moderate enhancement on enhanced CT scan. Thus, being familiar with the clinical, pathological and CT features of AT-AG helps boost the understanding of the disease. [*Ethiop. J. Health Dev*: 2022: 36(1): 00-00]

Keywords: Adrenal tumors; Adenomatoid tumor; Pathology; tomography, X-ray CT

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Introduction

As the adrenal gland is an extremely rare site of occurrence for an adenomatoid tumor, Adenomatoid Tumor of the Adrenal Gland (AT-AG) has been reported in less than 50 patients [1-2], and most are pathology reports. The absence of imaging data, which the patients are exposed to, leads to understanding insufficiency of imaging doctors, and thus the disease is often misdiagnosed as other adrenal tumors before operation. Based on its benign biological behavior, accurate preoperative imaging diagnosis can avoid unnecessary surgery[2]. CT scan is the most commonly used examination scheme for qualitative diagnosis of adrenal masses, which can evaluate the characteristics of lesions such as morphology, density and blood vessels[3]. In this paper, the clinical, pathological and CT imaging data of 3 AT-AG patients were analyzed retrospectively in order to investigate the CT imaging features of AT- AG and further the understanding, in combination with a literature review.

1. Materials and Methods

1.1 Clinical Material

Clinical and preoperative CT images of 3 AT-AG patients confirmed by postoperative pathology were collected from the First People's Hospital of Xiaoshan District, Hangzhou City, Zhejiang Province; Zhongshan Hospital affiliated to Xiamen University; and Xijing Hospital of Air Force Medical University. A plain CT scan and three-phase enhanced CT scan were performed in patients 1 and 2 with Philips Brilliance 64-slice CT scanner and Philips IQon Spectral CT scanner, respectively, while patient 3 underwent only three-phase enhanced CT scan with a GE Light Speed VCT 64-slice CT scanner. Scanning conditions: tube voltage 120KV, tube current 250mAs, pitch 1.0, layer thickness 2 - 2.5 mm. Patients were treated with bolus injection of iohexol (300 mgI/ml), a nonionic contrast agent, at elbow vein with a high-pressure syringe at a dose of 1.5 ml/kg and an injection flow rate of 2.5-3.0 ml/s, and were scanned 30 s, 60 s and 120 s after injection. Imaging evaluation involved the site, size, morphology, density, composition, and enhancement features (mild, moderate and severe enhancement $<$ 20 Hu, 20-40 Hu, and $>$ 40 Hu respectively) of lesions.

Pathological specimens were fixed with 10% neutral formalin, embedded in paraffin, dehydrated routinely and sectioned continuously. Routine HE and immunohistochemical staining were performed (for assessing mesothelial markers such as CK-P, calretinin, Vimentin, AE1/AE3, D2-40, WT-1, MC and endothelial markers such as ERG, CD31, and CD34).

1.2 Literature Retrieval

Twenty-two reports were retrieved by using "adenoid tumor" and "adrenal gland" as keywords in the PubMed database (from the date of database establishment to July 2020), and 9 patients with preoperative CT image data were selected. The three patients underwent total resection of adrenal gland and mass on the affected side, and the results showed that the ill-defined boundary and significant adhesions between the masses and normal adrenal glands. The data of the three patients in this study and 9 cases in literature were shown in Table 1

2. Results

Table 1. Clinical, pathological and imaging data of 12 AT-AG patients

No.	Sex	Age (years old)	Clinical data	Location	Maximum diameter	CT features	Pathological features	Immunohistochemistry (positive marker)	Follow - up
Case 1	Male	28	Physical examination Increased uric acid and decreased cortisol	Left	3cm	Lobate cystic mass, with the largest diameter parallel to the long axis of adrenal gland, non-uniformity of image density, minimum CT value at 2 Hu, moderate enhancement	Microcapsules or glandular tubes dominate, and some cells are vacuolated, showing signet ring cells	calretinin, CK-P, Vimentin, D2-40 and Ki-67 (＜5%)	No recurrence in 1 month
Case 2	Male	37	Physical examination Elevated blood sugar and decreased serum creatinine	Left	6.5 cm	Irregular cystic mass, with the maximum diameter parallel to the long axis of adrenal gland, non-uniformity of image density, minimum CT value at 30 Hu, mild enhancement	Adenoid structure, with varying lumen sizes, and some lumens lined with flat epithelium	Calretinin, CK-P, Vimentin, MC, D2-40, WT-1, INI-1, and Ki-67 (about 5%)	No recurrence in 10 months
Case 3	Male	37	Physical examination History of hypertension	Right	2.5 cm	Elliptical cystic mass, with the largest diameter parallel to the long axis of adrenal gland, non-uniformity of image	Cystic and solid tumor cells	calretinin, AE1/AE3 and Ki-67 (＜10%)	No recurrence in 44

						density, minimum CT value at -34 Hu			months
Case 4[4]	Female	30	Physical examination	Right	8 cm	Elliptical multilocular cyst with non-uniformity of image density	Solid polylocules with smooth inner surface, yellowish transparent jelly and bleeding within the cavity, and flat epithelial cells	Vimentin and MC	No recurrence in 48 months
Case 5[5]	Male	32	Physical examination	Left	4 cm	Elliptical cystic solid mass with themaximum diameter parallel to the long axis of adrenal gland, non-uniformity of image density, and mild to moderate enhancement	It consists of cystic and sinus channels, accompanied by proliferation of lymphoid tissues and lymphoid follicles. Tumor cells are morphologically diversified, and some are signet-ring cells.	Vimentin, calretinin, MC, D2-40, CK5/6, and Ki-67 (about 1%)	No recurrence in 30 months
Case 6[6]	Male	62	Physical examination History of hypertension	Right	3cm	Elliptical cystic solid mass with the maximum diameter parallel to the long axis of adrenal gland,	Alveolar masses with thin-walled tubules and	calretinin, Vimentin, AE1/AE3 and CK5/6	No recurrence in 8

						non-uniformity of image density, and mild enhancement	capsular space with different sizes and shapes.		month s
Case 7[7]	Male	44	Physical examination	Left	17 cm	Elliptical multilocular cystic mass with non-uniformity of image density and mild to moderate enhancement	Glandular and nested structures lined with flat epithelial cells.	calretinin and EMA	No recurre nce in 3 month s
Case 8[8]	Male	39	Unexpected discovery of colon cancer history	Right	5.5 cm	Elliptical cystic mass with the maximum diameter parallel to the long axis of adrenal gland and non-uniformity of image density	It consists of reticular tubules with different sizes, channels and capsular space filled with flat endothelial cells.	CK-P, calretinin, and CK5/6	-
Case 9[9]	Male	60	Physical examination Hypertension, hyperlipemia and hyperglycemia	Right	11 cm	Lobated cystic solid mass with punctate calcification and the maximum diameter parallel to the long axis of adrenal gland	It consists of a large cystic space, a perforated channel and anastomotic tubules lined with a single layer of flat endothelial cells.	AE1/AE3, calretinin and WT-1	-
Case 10[10]	Male	26	Physical examination	Right	15 cm	Round cystic solid mass with local calcification	It consists of flat epithelial	calretinin and CK-P	-

						and mild to moderate enhancement	cells and protein-rich liquid.		
Case 11[11]	Male	54	Right lumbago Elevated uric acid	Right	3.6 cm	Elliptical cystic mass, with the maximum diameter parallel to the long axis of adrenal gland, and nodular and strip calcification	The normal adrenal cortex (center) is embedded by swirling invasive adenomatoid tumor	Calretinin	No recurrence in 12 months
Case 12[12]	Male	33	Physical examination History of hypertension	Left	1.7 cm	Elliptical cystic solid mass with the maximum diameter parallel to the long axis of adrenal gland	It consists of multiple lumens of varying sizes that locally infiltrate the adjacent adrenal glands. The intercellular space is composed of flat or cubic cells, some of which are signet ring cells.	calretinin and CK-P	-

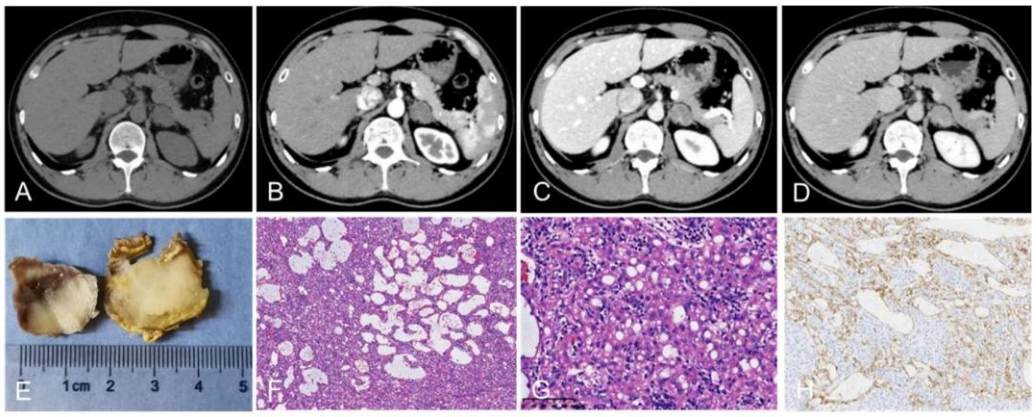

Figure 1. Male, 28 years old, adenomatoid tumor of the left adrenal gland. (A-D) illustrated plain, arterial phase, venous phase and delayed phase CT scans in turn. The left adrenal gland showed a mild low-density lobulated mass that grew along the long axis of the adrenal gland. The minimum CT value was -2Hu, the average CT value was 31Hu, and the CT values in the arterial phase, venous phase, and delayed phase after enhancement were 40Hu、 67Hu and 72Hu respectively. The tumor (E) is gray and yellow. Multiple microcapsules and glandular structures were observed microscopically (F). Some cells were signet-ring cells (G) showing cytoplasmic vacuolation and eccentrically displaced nuclei. D2-40 immunohistochemical expression (H) suggested positive.

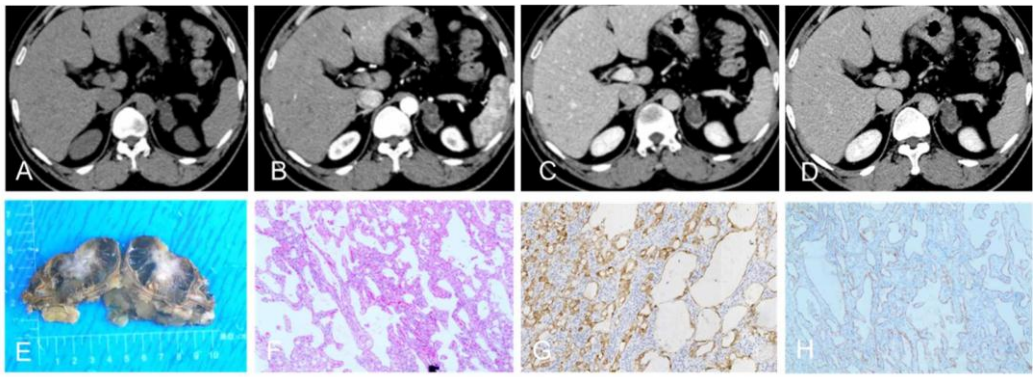

Figure 2.male, 37 years old. Adenomatoid tumor of the left adrenal gland. (A-D) illustrated plain, arterial phase, venous phase and delayed phase CT scans in turn. They showed a slightly low-density, lobulated mass of the left adrenal gland, which progressed along the long axis of adrenal gland, with mild enhancement. The tumor (E) is gray and yellow. Glandular structures with varying sizes were seen under microscope (F), and the cells presented no obvious heteromorphy. Calretinin (G) and MC (H) showed positive.

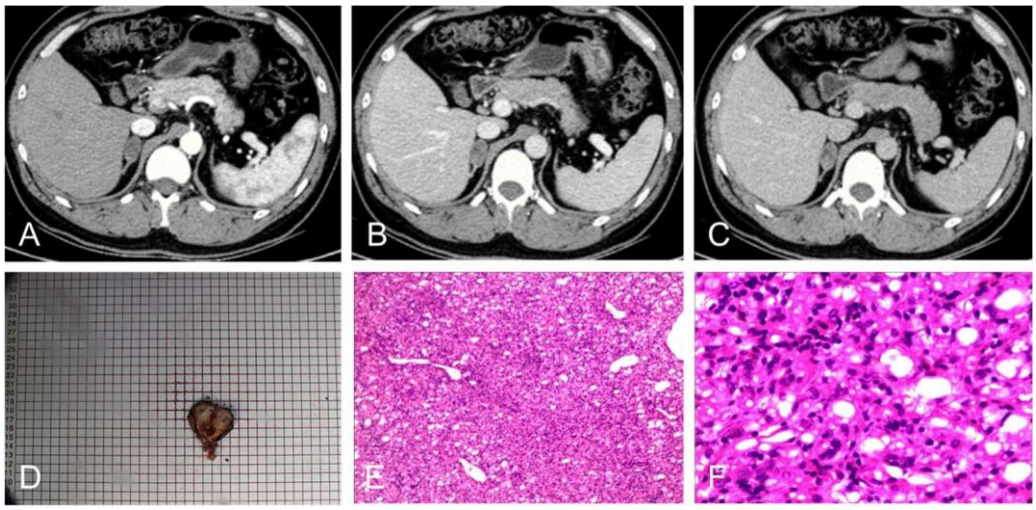

Figure 3. male, 37 years old. Adenomatoid tumor of right adrenal gland. (A-C) showed enhanced arterial phase, venous phase and delayed phase CT scans respectively. A oval cystic mass was seen in the right adrenal gland, with the maximum diameter parallel to the adrenal axis, mild enhancement, and the minimum CT value at -34 Hu. (D)The cut surface of the tumor was grayish-white and solid, with a mucus sensation on the surface. (E-F) The cells were arranged in cystic and clump-like shapes under HE staining under low and high magnification microscopes.

3. Discussion

Adenomatoid tumor (AT) is a benign neoplasm characterized by glandular structures, which arises from mesothelial cells and multipotent mesenchymal cells. It usually occurs in the genital tracts of both genders, including epididymis and spermatic cord in males, and uterus, fallopian tube and ovary in females. Besides, it is sometimes found in liver, pancreas, heart, pleura, mesentery, omentum, mediastinum, lymph nodes and adrenal glands outside the genital tracts [13]. The mechanism of AT-AG is controversial [4-6]. Most scholars associate it with the retraction of primitive mesothelial cells to adrenal gland during the development of gonad mullerian ducts, while others believe that it may be originated from pluripotent mesenchymal cells and coelomic cells [14].

AT-AGs are generally solid and a few are cystic. Under the microscope, AT-AGs were mostly microcyst, adenoid cystic, trabecular, solid and papillary structures, among which the adenoids and microcysts were the most common, and the lining cells were epithelioid cells rich in eosinophilic cytoplasm or a single layer of squamous epithelial cells. Some of the cells had obvious cytoplasmic vacuoles and eccentric nuclear displacement, forming characteristic signet ring cells, but no heteromorphosis or mitosis. In 3 patients in this study and 9 cases in the literature, Immunohistochemical mesothelial markers such as calretinin, vimentin, AE1/AE3, MC, D2-40, CK-pan and WT-1 presented positive, while endothelial markers such as CD31, CD34 and ERG showed negative.

At-AG has a much high incidence rate in males than females, with a male ratio of 91.7%. The age of onset was mostly 30-40 years old, and in this trial, it was 26-62 years old, with

the median age of 40 years old, which was consistent with the reports of Li et al[5]. Most patients have no clinical symptoms, and a few may be accompanied by hypertension, hyperglycemia and hyperhormone, such as high uric acid, high aldosterone and high plasma cortisol [15]. All 3 patients in this trial were asymptomatic, and showed different results in the laboratory examination. Patient 1 saw a doctor due to high uric acid that was speculated to be associated with tumor-induced hormone abnormalities, while decreased cortisol in preoperative examination may be related to the impaired function caused by tumor involvement in adrenal gland [5]. Both patients 2 and 3 were diagnosed by physical examination, but their blood glucose and blood pressure were increased respectively.

It is reported [15] that CT images of AT-AG are nonspecific. The author summarized the CT images of 3 cases in this trial and 9 cases in literature as follows: (1) Number and location: they were all single, with no difference between left and right sides. Tumors were found in 5 patients on the left and 7 patients on the right. (2) Morphology: Most tumors were oval, and some were lobulated. The maximum diameter was parallel to the long axis of adrenal gland in 75% (9/12) of the patients, which may be linked to the prostrate growth of mesothelial cells [16]. (3) Density and composition: Most tumors were cystic/solid, and some are multilocular, which was in line with pathological features of multiple microcapsules and glandular structures. AT-AG was occasionally subject to calcification [9-11], but no calcification was found in 3 cases. In addition, the three patients contained lipid in the lesion site, and their CT plain scan showed the minimum value ranging from -2Hu to -34Hu corresponded to the vacuolation of cell cytoplasm due to lipid content in pathology. This may be related to the normal lipid-rich residue of adrenal cortex in lesions caused by adrenal adhesion around the tumor [11]. (4) Enhancement: Predominantly mild and moderate enhancement. Three cases in this trial and 5 cases in literature presented mild to moderate enhancement, and this was speculated to the vascular structure formed due to the lack of endothelial cells in tumor tissue.

AT-AG often needs to be differentiated from cortical adenoma, ganglioneuroma, schwannoma, cyst and vascular-derived tumor on imaging, but their clinical treatment principles were compatible, and the differentiation is of little significance. However, it is of great significance to distinguish it from pheochromocytoma, metastatic tumor, cortical carcinoma, and lymphoma. (1) Pheochromocytoma: It is generally a functional disorder, and shows characteristic symptoms clinically and in laboratory examinations. Its CT manifestations present severe enhancement and cystic changes. (2) Metastatic tumor: It is common in the elderly who have a history of primary tumor, it is usually found on both sides, and it resembles primary tumor on imaging. (3) Cortical carcinoma: The tumor volume is often > 6 cm, and invasive features on imaging include necrosis, uneven enhancement, invasion of adjacent organs and blood vessels, liver and lymph node metastasis. (4) Lymphoma: It is common in middle-aged and elderly men, and mostly bilateral involved. Imaging features predominately include diffuse enlargement of adrenal volume whereas single phymatoid lymphoma is rarely seen, homogeneous CT density, seam-drilling growth, and mild to moderate progressive enhancement. It is sometimes difficult to differentiate from AT-AG, and can be

diagnosed by pathology and immunohistochemistry.

As AT-AG is often discovered by chance on imaging, its follow-up and diagnosis/treatment principles can be based on the *Management of Incidental Adrenal Masses: A White Paper of the ACR Incidental Findings Committee* [3]. No follow-up is required for masses with short diameter < 1cm. The tumor with short diameter ≥ 1 cm and < 4 cm can be confirmed as benign or malignant by regular follow-up or further examination. Retroperitoneal laparoscopic or transperitoneal laparoscopic surgery is recommended for tumors with short diameter ≥ 4 cm. At-AG patients had a good prognosis. A total of 8 patients from this trial and the literature were followed up for 1-48 months, without recurrence or distant metastasis.

To sum up, AT-AG is more common in young and middle-aged male than other population groups. Pathologically, it is characterized by microcapsule/glandular tubular structures, positive immunohistochemical markers but negative endothelial markers, mostly cystic solid mass of unilateral adrenal gland on imaging, maximum diameter parallel to the long axis of adrenal gland, and mild to moderate enhancement. Being familiar with the clinical, pathological and CT features of AT-AG helped improve the understanding of the disease and avoid over-treatment.

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