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Case Report

Cystic lymphangioma-like adenomatoid tumor of the adrenal gland: report of a rare case and review of the literature

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Abstract: Adenomatoid tumors (AT) are uncommon, benign tumors of mesothelial origination most frequently encountered in the genital tracts of both sexes. Their occurrences in the extragenital sites are much rarer and could elicit a variety of differential diagnosis both clinically and morphologically. With regard to the adrenal gland, to the best knowledge of us, only 31 cases of AT have been reported in the English literature. Several histologic growth patterns have been documented in AT, among which cystic type is the least common one. We herein present a further case of AT arising in the adrenal of a 62-year-old Chinese man with a medical history for systemic hypertensive disease. The tumor was incidentally identified during routine medical examination. An abdomen computed tomography scan revealed a solitary mass in the right adrenal. Grossly, the poorly-circumscribed mass measured 3.0 x 3.0 x 2.0 cm with a cut surface showing a gelatinous texture with numerous tiny cystic structures. Microscopic examination showed an infiltrated lesion with honeycomb appearance mimicking a lymphangioma, which composed predominantly of variably sized and shaped anastomosing small cystic spaces lined by flattened endothelial-like cells, without any epithelioid or signet-ring like components present. Foci of extraadrenal tumor extension, lymphoid aggregates with occasional germinal centre formation, intralesional fat tissue, stromal myoid proliferation and ossification were also observed. Immunohistochemical analyses confirmed the mesothelial differentiation of this tumor and indicated a diagnosis of cystic lymphangiomatoid AT of the adrenal.

Keywords: Adrenal gland, adenomatoid tumor, lymphangioma, benign mesothelioma, immunohistochemistry, adrenal cyst

Introduction

Adenomatoid tumors (AT) are relatively unusual benign tumors that are most commonly encountered in the genital tracts of both sexes including paratesticular structures in males and uterus, fallopian tubes, and ovary in females, respectively [1, 2]. AT are histologically characterized by anastomosing tubules lined by epithelioid and flattened cells. The mesothelial derivation of AT has been well established by immunohistochemical and ultrastructural analyses [3, 4]. These tumors much less frequently occur in extra-genital locations but have been described in various organs and anatomic sites including the pancreas, heart, liver, pleura, omentum, intestinal mesentery, mediastinum, lymph node, and adrenal gland [5, 6]. In these unexpected sites, such as the adrenal glands, which are devoid of a mesothelial layer, AT may pose a diagnostic challenge with a range of differential diagnosis. During a laboriously searching PubMed for AT originating from the adrenal, we could find only 31 such cases reported in the English language literature to date [7-29]. Herein, we report a further case of an adenomatoid tumor of the adrenal gland histologically mimicking a cystic lymphangioma, and a brief review of the previous published such lesions is also discussed.

Case presentation

In April in 2012, a 62-year-old Chinese man with a past medical history of systemic hypertensive disease for 10 years was found to have

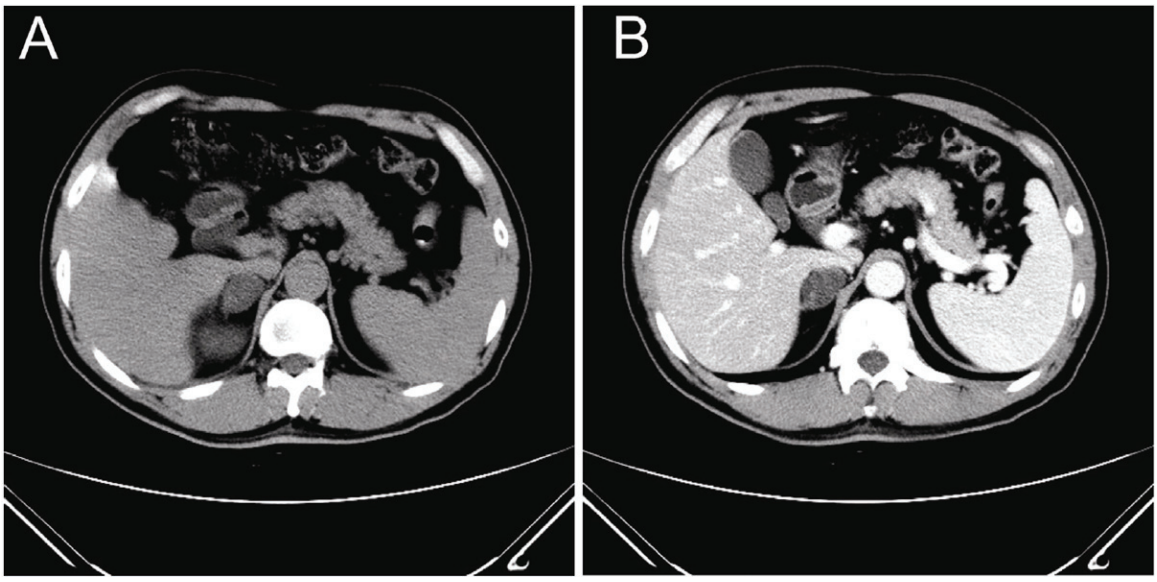

Figure 1. Abdominal computed tomography scan demonstrated (A) a well-circumscribed, expansile hypodense, right adrenal mass with (B) slight peripheral enhancement pattern with contrast.

Figure 2. Cut surface showed an ill-defined oval mass occupying most of the adrenal gland tissue, with a gelatinous texture containing multiple scattered, thin-walled translucent cysts. A small remnant of yellow adrenocortical tissues was noted at the periphery of the specimen.

an incidental right-side adrenal mass on routine medical examination at our hospital. The abdominal computed tomography (CT) scan demonstrated an expansile hypo-dense, relatively well-demarcated, oval mass measuring 3.2 cm x 2.8 x 2.0 cm in his right adrenal gland region with slight peripheral enhancement pattern with contrast (**Figure 1A**, **1B**). Imaging studies of the contralateral adrenal and all other internal organs were unremarkable. The patient's blood pressure level was 170 x 91 mmHg on admission. There was no family history concerning familial diseases of any endocrine organs of the body and he denied any symptoms of palpitations, diaphoresis, flushing. The preoperative laboratory examinations revealed that the urinary vanillylmandelic acid, catecholamine, and cortisol levels all were within normal limits. Based on the above findings, the suspected diagnosis was non-hyperfunctional cortical adenoma. Subsequently, the man underwent a right laparoscopic total adrenalectomy with no postoperative complications and he was discharged a week after the surgery with a blood pressure reading of 150/84 mmHg. Recently, at an 8-month follow-up, the man was in a good status without evidence of tumor relapse.

Immunohistochemical studies

The adrenalectomy specimen was fixed overnight in 10% neutral buffered formalin, embedded in paraffin and 4-μm sections were stained with hematoxylin and eosin. Immunohistochemical analysis was performed manually according to Envision two-step method. A large panel of commercially available primary antibodies were used including cytokeratin (AE1/AE3), cytokeratin5/6, vimentin, calretinin,

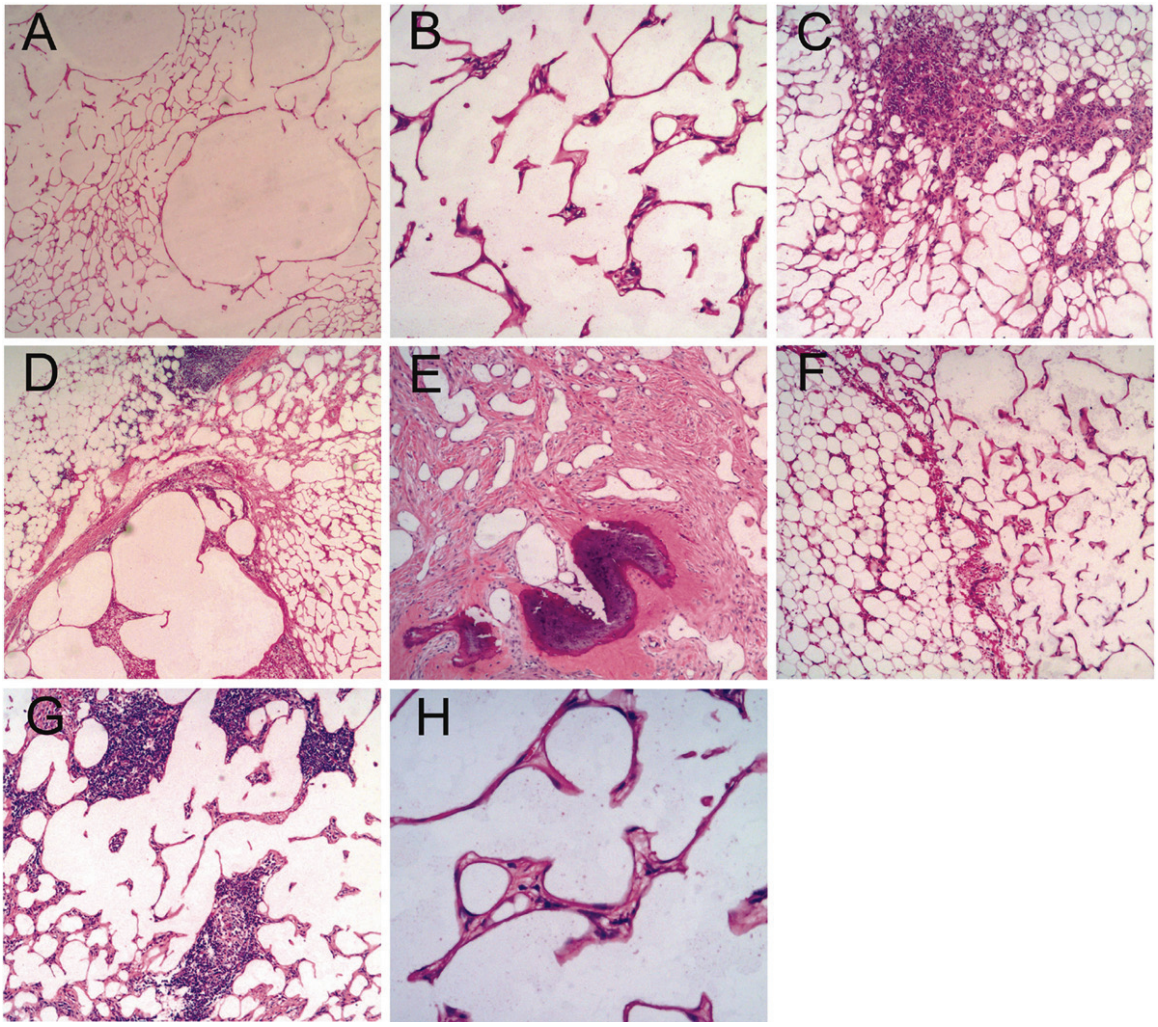

Figure 3. At low magnification, (A) the lesion showed a honeycomb appearance of anastomosing cystic canals of varying sizes and shapes without solid areas, (B) lined by endothelial-like cells, (C) infiltrating the adrenal cortical tissue peripherally. (D) Focally the tumor penetrating the capsule into periadrenal adipose tissue was depicted. (E) Foci of stromal myoid cells proliferation, metaplastic ossification, (F) intratumoral fat tissue, and (G) lymphoid aggregates with occasional germinal centers were also noted in the tumor. At higher power, (H) the endothelial-like cells lining the cystic spaces were in general inconspicuous or flattened without any malignant features.

CD31, CD34, CEA, factor VIII-related antigen (FVIII), α-smooth muscle actin (SMA), melan-A, HMB45 and S100 protein. Appropriate positive and negative controls were run concurrently for all the markers tested.

Pathological findings

Grossly, the resected specimen showed an ill-defined oval mass of 3.0 x 3.0 x 2.0 cm occupying most of the adrenal tissue, with small remnants of yellow adrenocortical tissues visible at the periphery. On cut surface, the tumor was gelatinous, gray-to-pale yellowish in color with a sponge-like appearance containing multiple tiny thin-walled, translucent cysts (**Figure 2**). No areas of hemorrhage or necrosis were identified in the mass.

Microscopically, the tumor mass manifested a honeycomb appearance as a lymphangioma-like tumor, composed predominately of variably sized and shaped, anastomosing thin-walled tubules, fenestrated channels, and small cystic spaces, lined by inconspicuous or flattened endothelial cell-like cells (**Figure 3A**, **3B**), infiltrating and compressing the normal adrenal cortical tissues peripherally (**Figure 3C**). Focal involvement of adrenal capsule and extension into periadrenal adipose tissue were also noted

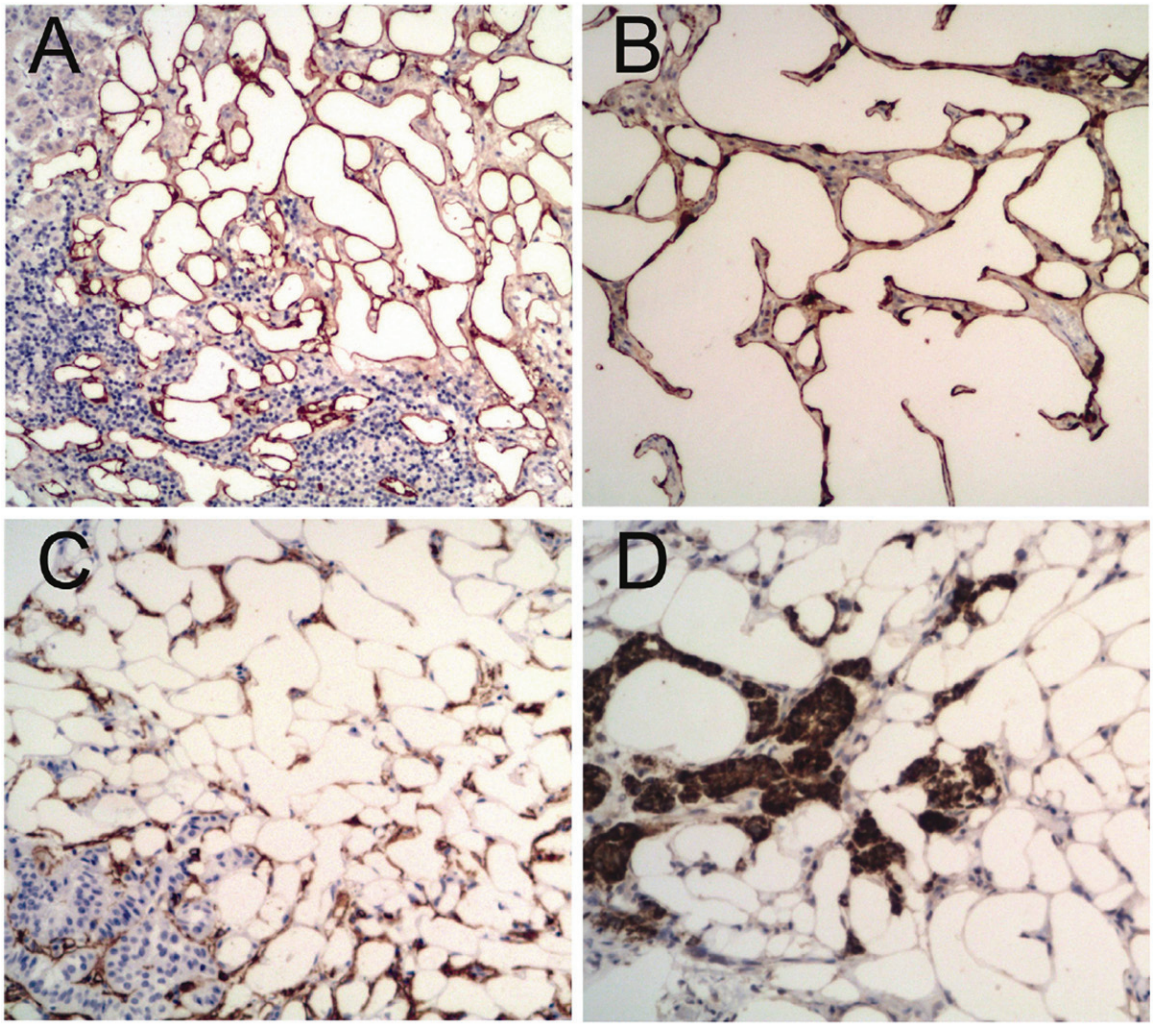

Figure 4. Immunohistochemically the flattened cells were strongly positive for (A) cytokeratin5/6 and (B) calretinin, the same cells were negative for (C) CD34 and (D) melan-A. These features supported the mesothelial nature of the tumor.

(**Figure 3D**). Some of the cysts contained slightly basophilic mucinous materials. The intervening septa between the cysts or channels were in general very thin and were fibrous, paucicellular; they focally became widen with proliferation of interlacing myoid cells (**Figure 3E**). Occasionally stromal ossification (**Figure 3E**) and intralesional adipose tissue (**Figure 3F**) were observed. A few small-scattered lymphoid aggregates with occasional germinal centre formation were also noted at the periphery of the tumor (**Figure 3G**). At higher power, these lined endothelial cell-like cells were overall bland lacking nuclear pleomorphism, tumor necrosis and any mitotic activity (**Figure 3H**).

Immunohistochemically, the flattened cells displayed evidence of mesothelial differentiation, with strong positivity for AE1/AE3, cytokeratin5/6, calretinin and vimentin (**Figure 4A**, **4B**), and were negative for endothelial markers used (CD31, CD34, FVIII) and CEA, SMA, HMB45, melan-A, and S100 protein (**Figure 4C**, **4D**).

The histological appearance together with the immunophenotypic characteristic of this tumor was indicated of a diagnosis of cystic lymphangioma-like adenomatoid tumor of the right adrenal gland.

Discussion and review

AT are very rarely located in the extragenital sites [5, 6]. With regard to the adrenal glands, as far as we known, less than 3 dozen of AT have been described so far in the English litera-

ture [7-29]. Although the mesothelial origin of AT has been well documented, the adrenal gland is devoid of a mesothelial lining, thus the occurrence of AT in the adrenal is not readily explained. It has been presumed that their histogenesis being related either to the entrapment of pluripotent mesenchymal cells associated with the müllerian tract in the adrenal or to the displacement therein of mesothelial inclusions or cysts [3, 4]. The former standpoint is currently predominant.

AT originating in the adrenal typically affect adults, almost all of whom are males with only one female case reported [10]. Because of the close embryological relationship of the adrenal glands and the gonads, it has been suggested that the difference of gonad embryogenesis between male and female systems may contribute to the male predominance of adrenal AT [20]. Most patients are within their third to fifth decades with the peak incidence in the fourth decades. These tumors are usually nonfunctioning, asymptomatic and discovered incidentally during radiological examinations, surgical procedures for other unrelated reasons, or at autopsy. Occasionally patients may present with symptoms due to the tumor, one patient suffered from gross hematuria directly attributed to compression of the upper pole of the kidney by the adrenal AT [7]. Including the current one, 7 cases of adrenal AT are found to be associated with hypertension [9, 15, 17, 19, 21, 22], however, in only two cases this symptom is confirmed to due to the tumor [9, 15], both patients manifest abnormal hormonal function either as an elevated urinary homovanillic acid or as hyperaldosteronism. One of the 2 cases is found to be concurrent with micronodular adrenal cortical hyperplasia [15] suggests that such endocrinopathies are likely caused by stimulation of the normal adrenal parenchyma by AT, however, the inherent relationship of hypertension and AT in the adrenal merits further investigation. These tumors have also been reported in association with human immunodeficiency virus (HIV) infection [11, 28] and disseminated coccidioidomycosis [11], Cushing syndrome [8], and 2 cases are coexisting with adrenal myelolipoma [22]. In addition, AT have been most recently documented in associated with hereditary condition, where a 24-yar-old young man who presented with concurrent adrenal adenomatoid tumor and bilateral carotid body tumors was confirmed to harbor germline succinate dehydrogenase complex subunit D (SDHD) gene mutation by molecular genetic studies [29]. Radiologically AT of the adrenal lack specific imaging features and are usually solid but rarely may be extensively cystic [5, 12, 19], so that they are often confused with other more common adrenal tumors such as benign nonfunctioning adenoma, lymphangioma, myelolipoma, and cysts of various types. Calcified components may occasionally be identified in AT that could lead to a diagnosis of a malignance [18, 21, 23].

Both the left and right lateral adrenals can be affected with the left side appearing to be more commonly involved than the right side. Grossly, AT of the adrenal gland are typically smooth, firm or soft, and pale or yellow-tan ranging from less than 1 cm to 17 cm in maximum diameter. Most of them are presented as solid masses, whereas some have been described as mixed solid and cystic, and occasionally as entirely or almost entirely cystic often with intramural tiny nodules [24, 25]. They may be grossly well-circumscribed or poorly-defined and frequently compress adrenal parenchyma at the periphery.

Histologically, AT of the adrenal can be manifested both as marginated with well-defined capsule and as infiltrative, occasionally extending into the adrenal capsule or periadrenal adipose tissue. Several histologic growth patterns have been described in AT as follows: adenoidal, angiomatoid, cystic, and solid, lymphangiomatoid, and papillary. Usually one pattern predominates, but an admixture of two or more patterns is more common. The cystic type of AT is the least common one and has been the subject mostly of a single case report [7, 10, 14, 18, 23-25]. The most common pattern consists of variably sized and shaped tubules and fenestrated channels arranged in a fibrous stroma of variable prominence. These tubules and channels are lined by cells from plump epithelioid to flattened, endothelial cell-like cells. Some tumor cells have prominent intracytoplasmic vacuolization imparting a signet-ring cell appearance. Similar to those observed in the genital cases, lymphoid aggregates with germinal centre formation is a common findings in AT in the adrenal gland. However, stromal smooth muscle fibers proliferation, which commonly seen in the AT of genital tract, is much less frequently encountered in the adrenal counter-

part. Other histological characteristics have been noted including: intratumoral adipose tissue [19, 22, 26], dystrophic calcifications [10, 14, 18, 20, 21, 23] and metaplastic ossification [18]. Stromal mucin production has also been demonstrated by staining with Alcian blue; however, intracellular epithelial mucin has not been seen using Diastase-periodic acid-Schiff or mucicarmine histochemical stains [24, 26]. Cytologically the tumor cells are generally bland and show only slight size variations, the nuclei are typically uniform and round to oval without pleomorphism, atypia, tumor necrosis, or mitotic activity.

Immunohistochemically, AT of the adrenal always show the usual immunoprofiles of mesothelial lineage, including positive immunoreactions for cytokeratin (pankeratin, cytokeratin5/6), and calretinin, D2-40, WT1, mesothelial cell antigen, and vimentin. Ultrastructural analysis has been used in a majority of cases, the long, bushy microvilli of coelomic type were always observed, other various findings including: basal laminal, cytoplasmic fibrillar networks, junction complexes and developed desmosomes [24, 28].

Because of the rarity of these lesions in this unusual location, lack of specific radiologic features and existence of a variety of growth architectures and cytologic features, AT arising in the adrenal may cause confused both clinically and histologically. Their differential diagnosis includes all other entities occurring in the adrenal like: primary adrenal tumors (adrenocortical adenoma or carcinoma, phaeochromocytoma), lymphangioma, metastatic adenocarcinoma, especially signet ring cell carcinoma, multicystic mesothelioma, and adrenal cysts of various origins. This distinction may be particularly difficult to make if the pathologists are confronted with a frozen section or limited fine needle aspiration samples [14].

Numerous irregular cysts spaces lined by flattened cells, as the current case indicated, may suggest a vascular neoplasm, especially lymphangioma which can rarely involves the adrenal gland [30]. In fact, some previously reported as invasive lymphangiomas of the adrenal at pre-immunohistochemistry era, which according to other authors really seem to represent misdiagnosed AT [14, 31]. However, lymphangioma is positive for endothelial markers and negative for cytokeratin and mesothelial markers and the opposite is true of adrenal AT. It should be noted that D2-40, a marker which is known to be positive in endothelia of lymphatics, could also stains the tumor cells of AT. Recently, Ellis et al [30] detail the clinicopathologic and immunohistochemical characteristics of 9 case of adrenal lymphangioma, D2-40 cytoplasmic positive staining is observed in all these cases, thus D2-40 alone is helpless to distinguish adrenal lymphangioma from AT. AT rich in vacuolated cells and pseudoglandular growth pattern with an infiltrated appearance at the periphery could lead to a misdiagnosis of signet cell carcinoma or adenocarcinoma. However, these tumors always exhibit conspicuously malignant features including nuclear pleomorphism, elevated mitotic indices, and desmoplastic reaction, all features will be absent in AT. Primary adrenocortical tumors may occasionally experience cystic degeneration giving an appearance resemble to AT, searching for the remnant nests of neoplastic cortical cells could help to distinguish these two conditions. Multicystic mesothelioma may have focal areas identical to AT, however, this lesion often arises in the pelvic peritoneum of young-to-middle aged women. Rarely, AT may morphologically present as unique papillary features [13] need to be differentiated from well-differentiated papillary mesothelioma, which commonly occurs in the peritoneum and also drives from mesothelial cells. Benign cysts of various origins in the adrenal, including pseudocysts, and parasitic cysts can be easily differentiated from AT by their absence of mesothelial lining layer [32].

Although extra-adrenal or capsule penetration of AT into periadrenal adipose tissue has been described, similarly to their genital counterpart, the benign biological behavior of these tumors originating from the adrenal has been confirmed by the lack of local recurrence and metastases reports. Surgical intervention by laparoscopic adrenalectomy without any specific post-operative surveillance protocol seems to be sufficient treatment of adrenal AT.

In conclusion, we present here a rare case of cystic lymphangiomatoid adenomatoid tumor in the adrenal gland, this very uncommon subset of AT located in this unexpected site should attract the attention of surgical pathologists and should be added in the differential diagno-

sis of adrenal cystic lesions to avoid misdiagnosis with more ominous conditions.

Conflict of interest

None.

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