Original Article
Cystic lymphangioma of adrenal gland: a clinicopathological study of 3 cases and review of literature

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Abstract: Cystic lymphangioma of the adrenal gland is a rare and benign lesion, most often found incidentally during abdominal imaging studies, abdominal surgery or at autopsy. We aimed to retrospectively review all adrenal lymphangioma cases at our hospital, further document their lymphatic origin by immunohistochemical staining and discuss the differential diagnosis with other cystic adrenal gland lesions. A total of 3 adrenal lymphangioma cases were identified. All three patients were men and adults at time of diagnosis aged 41 years, 43 years, and 66 years, respectively. All were incidentally identified during investigating for unrelated reasons, two of which were discovered by routine radiologic check-up while the last one was found during imaging detection of ureteral cancer. The average size of an adrenal lymphangioma lesion was 3.2 cm (range, 2.5-4.6 cm). Histologically, all three cases showed a typical multicystic architecture with dilated spaces lined by flattened, bland, simple lining. The cystic spaces occasionally contained proteinaceous material but lacked red blood cell content. On immunohistochemical stains, D2-40 cytoplasmic staining was positive in all three lesions, whereas AE1/AE3 was negative, thus, confirming their lymphatic nature.

Keywords: Adrenal gland, lymphangioma, adrenal cyst, cystic neoplasm, D2-40, differential diagnosis

Introduction
Adrenal cystic lesions are uncommon with an incidence of approximately 0.06% in the general population and may be discovered incidentally or may be symptomatic [1]. Traditionally, adrenal gland cysts have been classified as pseudocysts, endothelial cysts, epithelial cysts, and parasitic cysts [2]. Endothelial cysts, accounting for 20% to 32% of all adrenal cysts, are further subdivided into lymphangiomatous and angiomatous cysts according to the lining of the cystic wall [2]. Adrenal cystic lymphangioma (ACL) is a very rare benign vascular lesion and subject to only small series and case reports in the literature [3-7]. Until recently, the largest serials, Ellis et al [8] had found only 9 cases of adrenal lymphangioma during a 24-year period from the file of John Hopkins Hospital. Most of the previously reported ACLs are asymptomatic and often incidentally found during imaging investigation or surgery for other unrelated causes, or at autopsy. Although current advancements in radiographic techniques have provided the possibility of clinical characterization of adrenal cystic lesions, a range of adrenal neoplasms including both adrenal cortical tumors and pheochromocytomas remain in their clinical differential diagnosis, and thus necessitating surgical resection [8]. Herein we detail the clinicopathologic features of 3 further cases of cystic lymphangioma originating in the adrenal gland treated in our institution, as well as the differential diagnosis with other cystic lesions of the adrenal gland.

Materials and methods
All three cases were retrospectively collected from the archive file in our institution (Department of Pathology, Ningbo Yinzhou Second Hospital, China) from 2006 to 2013 when electronic surgical pathology records can be available. The hematoxylin-and-eosin slides
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Postoperatively, the patient made an uneventful recovery and follow-up at 1.5 years showed no tumor recurrence.

Case 2: This patient, a 66-year-old man presented with painless gross hematuria for 2 days. CT scan showed an irregular solid mass in the pars abdominalis of the left ureter suspicious for a transitional cell carcinoma. Unexpectedly, the CT image study demonstrated an approximately 3.0-cm, well-circumscribed, non-enhancing hypo-dense mass with multiple stippled calcification located in the left adrenal bed (Figure 1). The clinical and radiologic diagnosis of the adrenal lesion was pseudocyst with calcification. Left nephrectomy and adrenalectomy were performed and the cut surface of the adrenal gland exhibited a 2.5 x 1.5 x 1.2-cm circumscribed cystic mass containing translucent, jellylike materials. The patient was alive and well at 1 year.

Case 3: A 41-year-old man with a significant medical history of hyperthyroidism for 6 years was incidentally found to have a left adrenal mass during annual health examination in an outside hospital. He had been treated with \(^{131}\text{I}\) radiotherapeutics three years ago. The laboratory examinations showed that the patient’s serumothyronine, tetraiodothyronine, cortisol, and aldosterone level all were within normal limits. With a suspect of nonfunctional adrenal cortical adenoma, he underwent left adrenalectomy shortly thereafter in our institution. The resected specimen showed a 2.5 x 1.5 x 1-cm, well-marginated multicystic mass containing yellow-to-brown fluid in the cystic spaces, with a rim of flavous normal adrenal parenchyma peripherally.

Results

Case presentation

Case 1: The patient, a 43-year-old man with a past medical history of systemic hypertensive disease for 5 years, underwent a routine abdominal ultrasound, which detected a multicystic mass in her left adrenal region. He denied gross hematuria, low back pain and abdominal distension. The preoperative laboratory examinations were unremarkable. A subsequent computer tomography (CT) scan revealed a hypo-dense, multicystic mass measuring 3.8 x 2.2 cm in the left adrenal bed, with slightly mural enhancing after administered with contrast medium. The radiologic differential diagnosis included adrenal cyst and nonfunctioning cystic adrenal tumor. Laparoscopic adrenalectomy was carried out grossly showing a 4.6 x 3.7 cm well-defined, multiloculated cystic lesion filled with aqueous clear fluid.

All the 3 cases of ACL showed similar morphologic features to those encountered in other sites exhibiting a multicystic mass composed of variable-sized, irregular dilated cystic spaces lined by flat endothelial-like cells. The lining cells were typically bland without pleomorphism and mitotic activities. The cystic channels and spaces were either empty or filled with pink, amorphous, homogeneous proteinaceous fluid without blood, mucus or necrosis debris components (Figure 2A). Case 3 was associated with intra-adrenal hemorrhage, hemosiderin deposits and cholesterol cleft were focally present.

Figure 1. Cystic lymphangioma of the adrenal gland, abdominal computed tomography scan demonstrated an approximately 3.0-cm, well-circumscribed, non-enhancing hypo-dense mass with multiple stippled calcification located in the left adrenal bed.

Histologic findings

of all cases were reviewed and immunohistochemical studies using the avidin-biotin-complex immunoperoxidase technique were performed. The following commercially available antibodies were used in all 3 cases: cytokeratin AE1/AE3, D2-40, CD31, CD34, and calretinin. Clinical information was retrieved from the electronic medical records and follow-up information was obtained by clinical interviews.
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Figure 2. Cystic lymphangioma of the adrenal gland, (A) the cystic channels and spaces were either empty or filled with pink, amorphous, homogeneous proteinaceous fluid without blood, mucus or necrosis debris components. (B) The cystic wall was thin and contained small-scattered mature lymphoid aggregates.

Figure 3. Cystic lymphangioma of the adrenal gland, (A) the cystic lining cells showed positive immunoreaction to antibody anti-D2-40 and (B) they were negative for antibody anti-calretinin.

observed. Calcification was noted in all the three cases. The cystic wall was generally thin and contained small-scattered mature lymphoid aggregates, as well as small nests of entrapped benign adrenocortical cells (Figure 2A, 2B). There is no evidence of associated adrenal hyperplasia, adrenal cortical tumor or pheochromocytoma in any of the 3 cases. In case 2 the ureteric mass was histologically confirmed as infiltrating high-grade urothelial carcinoma (T3N0M0), no evidence of malignance was identified in the adrenal mass.

Immunohistochemistry

The cystic lining cells of all the 3 ACLs showed positive immunoreaction to antibodies anti-D2-40 (Figure 3A), anti-CD31 and anti-CD34 and they were negative for antibodies anti-cytokeratin AE1/AE3 and anti-calretinin (Figure 3B), which confirmed their endothelial and lymphatic nature. The normal adrenal cortical cells expressed calretinin but not D2-40.

Discussion

Lymphangiomas are benign malformations of lymphatic system. They typically affect children and in about half of the patients the disease is already obvious at the time of birth. Approximately 95% of all lymphangiomas are located in the head and neck, axillary region and mediastinum. The remaining 5% are discovered in the abdominal cavity including the mesentery of small intestine, omentum, mesocolon, or retroperitoneum [5, 8]. Cystic lymphangioma devel-
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Cystic lymphangioma of the adrenal gland is extremely rare, with currently less than 60 cases reported in the literature. In the present study, we retrospectively found 3 ACL lesions in our institution over a 7-year period. This higher diagnostic rate of ACL in our series comparing with that previously reported could be partially due to the fact that with the dramatic improvement of the imaging techniques that many adrenal cysts are discovered as an incidental finding on abdominal US and CT examinations. All the three cases were incidentally identified during investigating for unrelated reasons, two of which were discovered by routine radiologic check-up while the last one was found during imaging detection of ureteral cancer. Although ACL lesions can grow to a very large size remaining asymptomatic, some patients may present as symptomatic, symptoms including fever, gastrointestinal disturbance, abdominal pain or a palpable mass are usually related to the size and location of the lesion [8]. However, functional features such as hypertension has also been described to be associated with ACL and adrenal endothelial cyst, because the possibility of coexistence with a pheochromocytoma has been ruled out, the etiology of this unexpected symptom observed in these cases is remains unknown and merits further investigation [2]. ACLs can occur at any ages with the peak incidence between the third and sixth decades of life, as seen in our group of cases [8]. Although bilateral and that associated with Gorlin-Goltz syndrome have been recorded with ACL [9], they were not found in our group. In addition, all the 3 ACLs in our study affected male patients and arise in the left-sided adrenal sharply contrast with Ellis et al.'s observations that ACL had a significant female predisposition and twice more frequently involved right-sided adrenal [8]. Because many studies have dealt with only a few cases, the exact epidemiological aspects of ACL need more cases to define.

Radiologically, as 2 of the three cases of the current study indicated, imaging can characterize the cystic nature of these lesions. However, it sometimes fails to establish a specific diagnosis preoperatively. The most frequent preoperative diagnosis of ACLs is a nonfunctioning adrenal neoplasm with cystic change whereas those larger lesions may be suggested as a retroperitoneal or pancreatic cystic tumor. On ultrasound, the diagnosis of ACL is suspected by the presence of a well-marginated anechoic lesion typically located in the suprarenal areas, which can show shadows or echoes when calcifications are present. On CT scan the mass is identified as a hypodense, non-enhanced lesion [3, 4]. At magnetic resonance imaging, ACL can be visualized as a thin-walled cystic lesion with low signal intensity at T1-weighted imaging and high signal intensity at T2-weighted imaging without substantial internal enhancement [10]. Recently, aspiration of the contents of adrenal cysts is recommended for their diagnosis and management, if the aspiration samples have a fluid without any malignant cells but lymphoid cells and milk-like lymph are present, the diagnosis of ACL can be made [11].

The exact pathogenesis of ACL is not completely resolved, some believe that these lesions stem from continued growth of ectopic or malformed lymphatic tissues or represent hyperplastic reaction to inflammation or a lymphatic hamartoma. Blockage of draining lymphatics, proximal dilatation of the lymphatic system, and even traumas have also been suggested as causes of ACL [8].

Traditionally, lymphangiomas are classified according to their morphological appearance into capillary, cavernous, and cystic lymphangiomas. This classification, however, is being replaced by a classification based on morphologic aspects into macrocystic, microcystic, and combined lymphangiomas [7]. These subtypes are considered as a spectrum of the same disease. Histologically, all the three cases in our group demonstrate characteristic morphologic features of ACLs previously reported showing an intra-adrenal, well-defined multicystic mass composed of irregular dilated, thin-walled channels lined by bland, flattened endothelial cells surrounding by normal-appearing adrenal parenchyma. The cystic spaces are empty or filled with acellular, homogeneous proteinaceous material with occasional calcification. Unless being associated with a pseudocyst or experiencing intra-lesion hemorrhage, the cystic spaces generally lack blood, cholesterol clefts, or hemosiderin-laden macrophages. Mucus and necrotic debris are typically not observed. There is usually only a slight inflammatory background consisting mainly of a small amount of mature lymphocytes. Although adre-
nal cystic lesions are well-known to be concurrent with a range of neoplasms including adrenocortical adenoma, carcinoma, pheochromocytoma, myelolipoma, neuroblastoma in situ, and schwannoma, such relationships are not found in both our and Ellis et al's groups [2, 8]. Immunostains are usually not needed for the diagnosis of ACL, but coexpression of D2-40, CD31, CD34, and factor VIII-related antigen by the lining cell can be used to confirm its lymphatic origin. D2-40, serving as a specific marker of lymphatic lineage, is well-known been expressed by mesothelial cells [12]. This needs to be remembered when attempting to differentiate ACLs from multilocular mesothelial cysts or adenomatoid tumors, particularly the latter, which can rarely affect the adrenal and show significant morphologic similarities to ACLs. In fact, some previously reported as invasive lymphangiomas of the adrenal from the preimmunohistochemistry era really seem to represent misdiagnosed adrenal adenomatoid tumors [13]. In addition, recently, D2-40 has also been documented to be expressed by adrenal cortical tissues and used to distinguishing adrenocortical tumors from both metastatic renal cell carcinomas and phaeochromocytoma [14], however, this staining feature is not observed in our study and other serials and this discrepancy may be explained by different conditions in specimen fixation and immunohistochemical procedures.

Besides the aforementioned adenomatoid tumors, the differential diagnosis of ACL includes other cyst types, as well as cystic benign or malignant adrenocortical neoplasms [2, 8, 15]. Pseudocysts represent the most common clinically recognized type of adrenal cyst encountered during surgery and they have been thought to be a result of hemorrhage within a tumor or hemorrhage into adrenal parenchyma due to trauma, toxic or infectious process. Adrenal pseudocysts are typically larger than ACL with a median size of 10 cm and they are usually uniloculated but may be multiloculated. The cyst wall of adrenal pseudocyst is composed of hyalinized fibrous tissue that lacks well-defined endothelial lining cells; elastic tissue, nerves, and smooth muscle may be present in the cyst wall, these features are uncommon for ACL. In addition, the cystic contents of adrenal pseudocyst contain a variable mixture of necrotic acellular debris, fibrin thrombi, blood, and cholesterol clefts in contrast with the homogeneous proteinaceous material commonly observed in the cystic channels of ACL. Epithelial cysts include true glandular cysts and embryonal cysts. The cyst walls are lined by true epithelial cells which are keratin-positive, and this is the primary distinguishing feature from ACL. Cystic benign and malignant adrenocortical neoplasms may undergo prominent degenerative changes and thus may be radiographically or pathologically mistaken for ACLs [2]. CT findings of a nonenhancing mass may help distinguish radiologically between adrenal cyst and cystic adenoma and extensive sampling and searching for residual nests of neoplastic cortical cells may help histologically differentiate cystic adrenal cortical tumor from adrenal cyst. True hemangiomas can rarely affect the adrenal gland, they are often large and most are 10 cm in size, histologically they are usually cavernous type similar to their liver counterparts and the vascular spaces often contain red blood cells component. Ancient schwannoma is another unusual cystic tumor which may occur in the adrenal, but it shows different diagnostic clues. Finally, ACLs with atypical degenerative B lymphocyte proliferations have been described in the literature. This may lead to concern for a lymphoma, particularly on needle aspiration specimens [11].

The great majority of patients with ACL have been treated with adrenalectomy and the prognosis is excellent with no evidence of recurrence [8]. Current treatment recommendations for ACLs are that small asymptomatic lesions with clear fluid can simply be observed, whereas large symptomatic lesions should be excised [7]. Other authors recommend aspiration of the contents of adrenal cysts for their diagnosis and management instead of surgical excision if the suspicion of malignancy is low, or the lesion is non-functional and asymptomatic [5]. Because of the heterogeneous etiology and overlapping clinical findings of adrenal cystic lesions, definite diagnosis relies on extensive sampling and thorough microscopic examination in order to exclude the possibility for coexisting ominous tumor.

Disclosure of conflict of interest
None.
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