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Cystic lymphangiomatous lesions of the adrenal gland: A clinicopathological study of 37 cases including previously unreported cysts with papillary endothelial proliferation

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ABSTRACT

Published data regarding lymphangiomatous cysts of the adrenal glands (also known as adrenal cystic lymphangiomas) are limited to case reports and a few small case series. We analyzed the clinicopathologic features and histomorphologic spectrum of 37 cases of adrenal cystic lymphangiomatous lesions. There were 26 females and 11 males ranging from 12 to 67 years old (median, 34 years). Twenty two lesions (59.5%) were diagnosed incidentally on imaging studies for unrelated causes, while 15 cases (40.5%) were symptomatic: 8 patients presented with abdominal or flank pain and 7 patients presented with arterial hypertension. Clinically, 4 lesions (10.8%) were reported to have concurrent hormonal hypersecretion. Follow-up data were available for 23 patients (62.2%), ranging from 6 to 156 months (median, 52 mo). One of the 22 patients showed local recurrence at 12 months after partial adrenalectomy. The median size of the adrenal lymphangiomatous cysts was 4.5 cm (range, 1.5 to 10 cm). Based on the histopathologic findings these lesions were grouped into three, morphologically distinct types: typical multicystic lymphatic malformation (n = 16), typical unilocular lymphangiomatous cyst (n = 14) and lymphangiomatous cyst with papillary endothelial proliferation (n = 7). The median patient age of the first group was significantly higher than that of the other groups and calcifications in these cysts were more common than in the other two groups. The unilocular lymphangiomatous cysts were more frequently associated with a history of previous intra-abdominal surgical procedures and/or inflammatory processes than the other two groups. Cysts with papillary endothelial proliferation were significantly larger than other cysts and shared some microscopic features with a vascular neoplasm known as papillary intralymphatic angioendothelioma (PILA). In conclusion, adrenal lymphangiomatous cysts are usually asymptomatic, incidentally diagnosed lesions with a female predominance. They may imitate other adrenal tumors, both radiologically and clinically. Despite being non-functioning lesions, they should be considered as a possible cause of pseudopheochromocytoma. Although most adrenal lymphangiomatous cysts seem to be non-neoplastic, vascular abnormalities (malformations or lymphangiectasias), those with papillary endothelial proliferations may represent true neoplastic lesions.

1. Introduction

Although adrenal cysts are uncommon lesions, their importance as a clinical problem appears to be increasing due to the development and widespread availability of diagnostic imaging methods and the increasing number of incidentally detected lesions of this type [1–3]. Adrenal cysts are a heterogenous group of lesions and are traditionally divided into pseudocysts, endothelial, epithelial and parasitic cysts [4–6]. Endothelial cysts include angiomatous cysts and the much more frequent (constituting 75–90% of this group) lymphangiomatous cysts, also known as cystic lymphangiomas. The incidence of lymphangiomatous cysts reported in autopsy series of adrenal cysts reaches even 48% [6], while in surgical series it is estimated at 15–28% [7,8]. It should be noted, however, that numerous studies have postulated a close association between adrenal endothelial cysts and pseudocysts and these lesions are considered two variants of adrenal vascular cysts [9–12]. We recently showed that even 36% of adrenal pseudocysts may form on a background of lymphangiomatous lesions [13] and therefore the percentage of lymphatic changes in the general structure of adrenal cystic lesions may be larger than previously thought. A small group

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(less than 10 cases) of adrenal lymphangiomatous cysts (cystic lymphangiomas) have been analyzed in the literature [14–16]. In this study, we describe the largest series to date on cystic lymphangiomatous lesions of the adrenal gland including a previously unreported group of cysts with papillary endothelial proliferation that share some morphologic features with neoplasms of lymphatic endothelial lineage termed hobnail haemangioendotheliomas (papillary intralymphatic angioendothelioma and retiform haemangioendothelioma) [17–19]. In this study we present the clinicopathologic characteristics of 37 cases of adrenal lymphangiomatous lesions, study their histomorphologic spectrum and investigate the differences among the groups

2. Materials and methods

This study was approved by the Bioethics Committee at the Medical University of Warsaw (No. 104/17). A retrospective search of all electronic records of pathology reports since 2001 in Medical University of Warsaw Department of Pathology was performed. A total of 37 cases of adrenal cystic lymphangiomatous lesions were identified. These cases were originally diagnosed as multilocular/unilocular cystic lymphangioma (n = 19) and multilocular/unilocular endothelial cyst of lymphangiomatous type (n = 18). Each resected specimen was fixed in 10% neutral-buffered formalin for 12–24 hours and then macroscopically examined. The entire specimen was serially sectioned at 2–3 mm intervals; the adrenal cystic lesion was designated as "unilocular" only if a single cystic space was grossly identified and "multilocular" if multiple cystic spaces were grossly recognised. Tissue samples from an entire cross-section of the cystic lesion and adjacent adrenal tissue were submitted and routinely processed. For all cases formalin-fixed, paraffin-embedded, hematoxylin and eosin stained sections were retrieved from the archives and reviewed by two pathologists (LK and BG).

Immunohistochemical studies were performed using formalin-fixed, paraffin-embedded (FFPE) 4 µm tissue sections and the following antibodies from Dako (Denmark) were used: D2-40 (clone D2-40), CD31 (clone JC70 A), CD34 (clone QBEnd10), pan-cytokeratin (clone AE1/AE3), smooth muscle actin, SMA (clone 1 A4) and collagen IV (clone CIV22). Deparaffinization, rehydration and epitope retrieval of FFPE sections was performed in the PT Link (Dako); using a pH 6 retrieval buffer for collagen IV and pH 9 retrieval buffer for other antibodies. Slides were then processed with an Autostainer (Link 48 Dako) using automated staining protocols validated for each antibody. All primary antibodies were ready-to-use (RTU) with the exception of collagen IV, which was diluted 1:50. Detection was performed with the dual anti-rabbit and anti-mouse EnVision FLEX High pH Detection System (DakoCytomation, Denmark) and the chromogen 3, 3′-diaminobenzidine (DakoCytomation, Denmark). Cell nuclei were counterstained with hematoxylin. Stained slides were dehydrated and automatically mounted. Positive tissue controls were used for all antibodies (according to the manufacturer's recommendations). Negative controls were performed by omitting the primary antibodies. The result of immunostaining was characterized as: positive (P) if more than 50% of the cells of lining stained positive (with at least moderate intensity), focally positive (fP) if 10–50% of the cells stained positive (with at least moderate intensity), and negative (N) if less than 10% of cells stained positive (regardless of intensity). Clinical information, radiologic features and follow-up data were obtained from the medical records.

For descriptive purposes, continuous data were summarized using mean and median and categorical data were summarized using percentage. Comparisons between groups were performed using the Pearson's chi-squared test for categorical data and nonparametric Kruskal-Wallis test and Mann-Whitney U test for continuous data-where the Kruskal-Wallis test produced significant results, the Mann-Whitney U test was used for pairwise group comparisons. A p-value of < 0.05 was considered to be statistically significant. All analyses were performed using STATISTICA (data analysis software system), version 12, StatSoft, Inc.

Table 1
Clinicopathological characteristics of 37 adrenal cystic lymphangiomatous lesions.

Characteristics	n = 37
Age, years, mean; median; (range)	35.7; 34; (12-67)
Gender, n (%)	
Female	26 (70.3)
Male	11 (29.7)
F : M	2.4 : 1
Side, n (%)	
Right	21 (56.8)
Left	16 (43.2)
Clinical presentation, n (%)	
Incidental	22 (59.5)
Abdominal pain	7 (18.9)
Labile arterial hypertension	7 (18.9)
Flank pain	1 (2.7)
Concurrent hormonal hypersecretion, n (%)	
Yes	4 (10.8)
No	33 (89.2)
PIS/I, n (%)	
Yes	13 (35.1)
No	24 (64.9)
Location (on radiology), n (%)	
Adrenal	35 (94.6)
Extra-adrenal	2 (5.4)
Radiologic impression, n (%)	
ACL	21 (56.8)
AM-unspecified	7 (18.9)
AM-ACA?	4 (10.8)
AM-Pheo?	3 (8.1)
Kidney Cyst	1 (2.7)
Liver Cyst	1 (2.7)
Surgical procedure, n (%)	
Total adrenalectomy	33 (89.2)
Partial adrenalectomy	4 (10.8)
Follow-up (months), n (%); mean; median; (range)	23 (62.2); 55; 48; (6-156)
Size (cm), mean; median; (range)	4.7; 4.5; (1.5-10)
Gross structure, n (%)	
Unilocular	20 (54)
Multilocular	17 (46)
Calcifications, n (%)	
Yes	15 (40.5)
No	22 (59.5)
Adrenal tissue, n (%)	
Normal	33 (89.2)
ACH	4 (10.8)

F, female; M, male; PIS/I, previous intra-abdominal surgery/inflammation; ACL, adrenal cystic lesion; AM, adrenal mass; ACA, adrenal cortical adenoma; Pheo, pheochromocytoma; ACH, adrenal cortical hyperplasia.

3. Results

3.1. Clinical characteristics and general pathologic features

The clinicopathological findings are summarized in Table 1 and Supplementary Tables S1 and S2. The mean/median age of the 37 patients was 35.7/34 years (range: 12–67 years). The patients were predominantly women (70.3%; 26 females, 11 men; F:M ratio was 2.4). All adrenal cystic lymphangiomatous lesions were unilateral and more frequently located on the right side (n = 21, 56.8%), 16 lesions (43.2%) were left-sided. In 22 of 37 patients (59.5%) lesions were diagnosed incidentally on radiologic imaging, while 15 patients (40.5%) were symptomatic: 7 patients presented with abdominal pain, 1 patient presented with flank pain and 7 patients presented with arterial hypertension. History of intra-abdominal surgical procedures (e.g. Cesarean section, cholecystectomy, appendectomy) and/or inflammatory processes (e.g. acute pancreatitis) was noted in 13 patients (35.1%). All patients underwent preoperative radiologic studies (ultrasound, computed tomography or magnetic resonance imaging). An adrenal origin

Table 2
The detailed clinical features and laboratory data of 4 patients with hormonal abnormalities.

Case no	Age (y)/ Sex	Preoperative symptoms and signs	Preoperative laboratory data	Postoperative symptoms and signs	Postoperative laboratory data
6	12/F	Abdominal pain, headaches, 15-kg weight gain over a 2.5 year period; BMI 27.1 kg/m^2 (> 97th percentile)	Serum cortisol 8:00 am: 22.2 μg/dl; Serum cortisol 6:00 pm: 19.7 μg/dl; Overnight 1-mg DST: 3.7 μg/dl ACTH: 13 pg/ml 24-h UFC: 42.2 μg/24 h DHEA-S: 907 ng/ml	Resolution of abdominal pain, BMI 28.2 kg/m^2 (> 97th percentile)	Serum cortisol 8:00 am: 15.1 μg/dl 24-h UFC: 20.5 μg/24 h
14	29/M	HT (150/90 mmHg), headaches	24-h urinary metoxycatecholamines: 1278 μg/24 h Serum potassium: 4.7 mmol/l Serum cortisol 11 pm: 1.28 μg/dl	Normalization of HT (120/80 mmHg)	NA
16	38/M	HT (180/100 mmHg), headaches	Serum aldosterone: 420 pg/ml Serum potassium: 3.2 mmol/l 24-h urinary metoxycatecholamines: 270.8 μg/24 h	Normalization of HT (110/70 mmHg)	Serum potassium: 4.2 mmol/l
36	50/M	HT (150/100 mmHg), hyperhidrosis, headaches, palpitations	24-h urinary normetanephrine: 735.4 μg/24 h 24-h metanephrine: 446.6 μg/24 h Serum aldosterone: 185 pg/ml Serum potassium: 4.46 mmol/l Serum cortisol 8:00 am: 13.8 μg/dl	Resolution of hyperhidrosis, Normalization of HT, but 5-years after surgery BP was mildly elevated (140/85 mmHg)	NA

F, female; M, male; y, years; BMI, body mass index; HT, arterial hypertension; UFC, urinary free cortisol; DST, dexamethasone suppression test; ACTH, adrenocorticotropic hormone; BP, blood pressure; NA, not available.
Reference ranges: Serum cortisol 8:00 am: 5–25 μg/dl; Serum cortisol 6 pm: 2–9 μg/dl; Serum cortisol 11 pm: < 1.8 μg/dl; Overnight 1 mg DST (1 mg): < 1.8 μg/dl; ACTH: 10–60 pg/ml; 24 h UFC: < 100 μg/24 h; DHEA-S: 378–2645 ng/ml (for age-specific group); Urinary 24-h metoxycatecholamines: 100–1000 μg/24 h; 24-h urinary normetanephrine: 88–440 μg/24 h; 24-h urinary metanephrine: 52–341 μg/24 h; Serum aldosterone: 35–300 pg/ml; Serum potassium: 3.6–5 mmol/l.

of the lesions was suspected in 35 of 37 (94.6%) radiological findings; in the remaining 2 cases a kidney cyst and a hepatic cyst were suspected. Imaging studies suggested that 23 (62.2%) of these lesions were simple cysts (adrenal in 21 cases or extra-adrenal in 2 cases), 7 (18.9%) were diagnosed as unspecified adrenal masses, 4 (10.8%) as adrenocortical adenomas and 3 (8.1%) as pheochromocytomas. In 4 cases (10.8%) concurrent hormonal abnormalities were present – a 12-year-old girl was reported to have subclinical Cushing's syndrome, a 38-year-old male had aldosterone hypersecretion and 2 patients (a 29-year-old and 50-year-old male) had catecholamine excess. The detailed clinical features of these 4 patients are shown in Table 2. Surgical removal was achieved by total adrenalectomy in 32 of 37 patients (86.5%) and by partial adrenalectomy in 5 patients (13.5%). Clinical follow-up information was available for 23 of the 37 patients (62.2%), ranging from 6 to 156 months (mean/median follow-up, 55/48 mo). 21 of 23 cases showed no evidence of recurrences and metastasis. One patient, a 34-year-old woman with a 6 cm typical multicystic lymphatic malformation (TMLM), treated with partial adrenalectomy showed local recurrence at 12 months after surgery with a 5 cm cystic lesion discovered in imaging studies. The patient was followed over a period of 96 months, due to enlargement of the lesion to 10 cm in following imaging studies, the cyst was excised with total adrenalectomy. The histological examination of the specimen confirmed recurrence of TMLM. No evidence of recurrence was found at 36 months after the second operation. Of the 37 adrenal cystic lymphangiomatous lesions studied, the mean/median size was 4.7/4.5 cm (range, 1.5 to 10 cm). Most of the cysts were unilocular (n = 20, 54.1%), 17 (45.9%) cysts were multilocular. 15 lesions (40.5%) contained calcifications. Adrenal tissue showed normal architecture in 33 cases (89.2%), whereas features of nodular adrenocortical hyperplasia were recognized in 4 cases (10.8%).

3.2. Histomorphologic types of adrenal cystic lymphangiomatous lesions

The histopathological and immunohistochemical analysis of the adrenal cystic lymphangiomatous lesions allowed for classification of these lesions into three, morphologically distinct groups: (1) typical multicystic lymphatic malformations; (2) unilocular lymphangiomatous cysts and (3) lymphangiomatous cysts with papillary endothelial proliferation

3.2.1. Typical multicystic lymphatic malformation,

TMLM (syn. multiloculated cystic lymphangioma; multiloculated endothelial cyst of lymphangiomatous type). There were 16 cases in this group. The mean/median size was 4.4/4.3 cm (range, 1.5–8 cm). Upon gross examination, all lesions were multiloculated cysts composed of variably-sized, irregular dilated cystic spaces with smooth, glistening lining without any papillary excrescences filled with clear to yellow fluid (Fig. 1A). Histologically, the cystic spaces were lined by a single layer of flattened or focally hobnailed cells without atypia resembling that of normal lymphatics (Fig. 1**B-C**). In the wall of several larger cystic spaces fascicles of smooth muscle were visible. Calcifications were found in 11 cases (68.8%) (Fig. 1B) and 5 lesions (31.3%) contained lymphoid aggregates. Immunohistochemical staining results showed that the endothelial lining cells were positive for D2-40 (Fig. 1D) and CD31 (Fig. 1E) and were negative for CKAE1/AE3 (Fig. 1F) in all cases. The lining cells were negative for CD34 in 12 cases, however they were focally positive in 4 of 16 cases (25%).

3.2.2. Unilocular lymphangiomatous cyst,

ULC (syn. unilocular lymphangioma, unilocular endothelial cysts of lymphangiomatous type). This group was composed of 14 cases. The mean/median size was 3.5/3 cm (range, 2–6 cm). All of these lesions were unilocular, thin-walled cysts, lined by a single layer of flattened endothelial cells (Fig. 2A). Immunohistochemical staining results showed that the endothelial lining cells were positive for D2-40 (Fig. 2B) and CD31 (Fig. 2C) and negative for CD34 (Fig. 2D), CKAE1/AE3 (Fig. 2E) in all cases. In the cyst wall fascicles of smooth muscle were visible, which were immunohistochemically positive for SMA (Fig. 2F). Calcifications were found only in 2 cases (14.3%) and there were no lymphoid aggregates within these cysts.

3.2.3. Lymphangiomatous cyst with papillary endothelial proliferation,

LC with PEP. This group was composed of 7 cases. The mean/median size was 7.9/8 cm (range, 5–10 cm). The great majority were unilocular (n = 6), one cyst was multilocular. Histologically, the cysts were lined by endothelial cells forming diffuse (in 4 cysts) (Fig. 3A) or focal (in 3

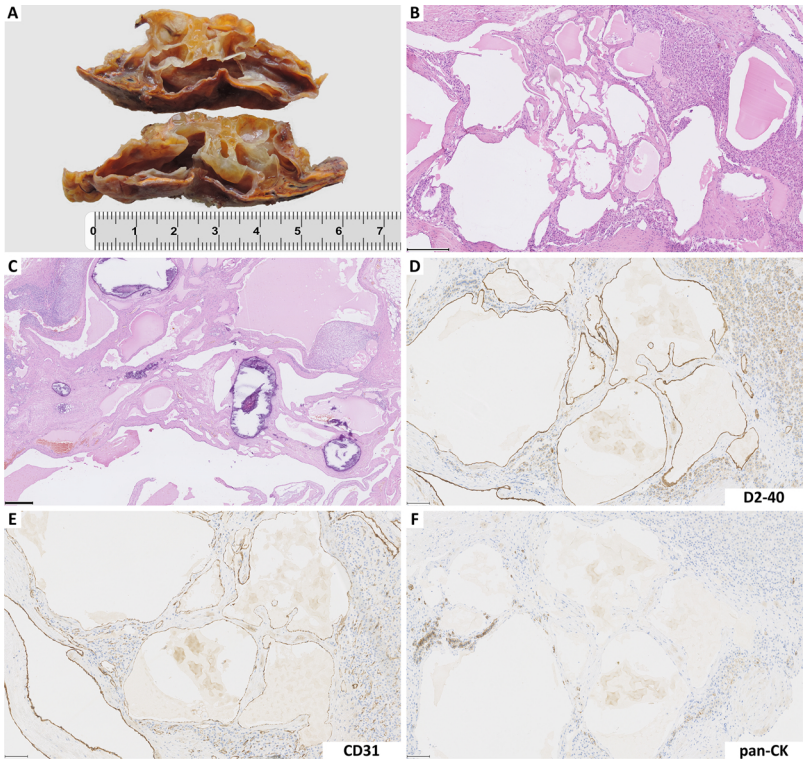

Fig. 1. Typical, multicystic lymphatic malformation. **A.** Gross examination demonstrated a thin-walled, multilocular cystic lesion. **B–C.** Microscopic examination revealed a multicystic architecture composed of multiple vascular spaces lined by flattened endothelial cells; occasionally calcifications were seen. Immunohistochemically the cyst lining was diffusely positive for D2-40 (**D**) and CD31 (*E*), but was negative for pan-cytokeratin. Scale bars: B, 250 μm; C, 500 μm; D–F, 100 μm.

cysts) papillary or pseudopapillary projections. At the base of the papillary formations there were multiple small lymphatic channels lined by a single layer of attenuated, flat endothelial cells containing nuclei that were 3–4 times smaller than the cells of the papillary structures (Fig. 3B). Occasionally solid areas composed of groups and nests of „epithelioid" endothelial cells with abundant, „clear" cytoplasm were observed (Fig. 3C). The endothelial cells of the papillary structures were columnar, they were characterized by a high nuclear/cytoplasm ratio and apically located nuclei with a matchstick-like or hobnail appearance. Although the endothelial cells of the papillary structures and solid areas showed little cytologic atypia, fairly numerous nucleoli were seen, occasionally nuclei were grooved or had intranuclear pseudoinclusions, whereas the endothelial cells of lymphatic channels contained much smaller, pyknotic nuclei. Mitotic figures were absent. In the cyst wall thick bundles of smooth muscle were found. Immunohistochemical staining results showed that the papillary endothelial lining cells were positive for D2-40 (Fig. 4**A-C**) and CD31 (Fig. 4D) and negative for CD34 (Fig. 4E) and CKAE1/AE3 (Fig. 4F) in all cases. The papillary proliferations had acellular hyaline cores and spherical accumulations of amorphous, eosinophilic material, that were positive for collagen

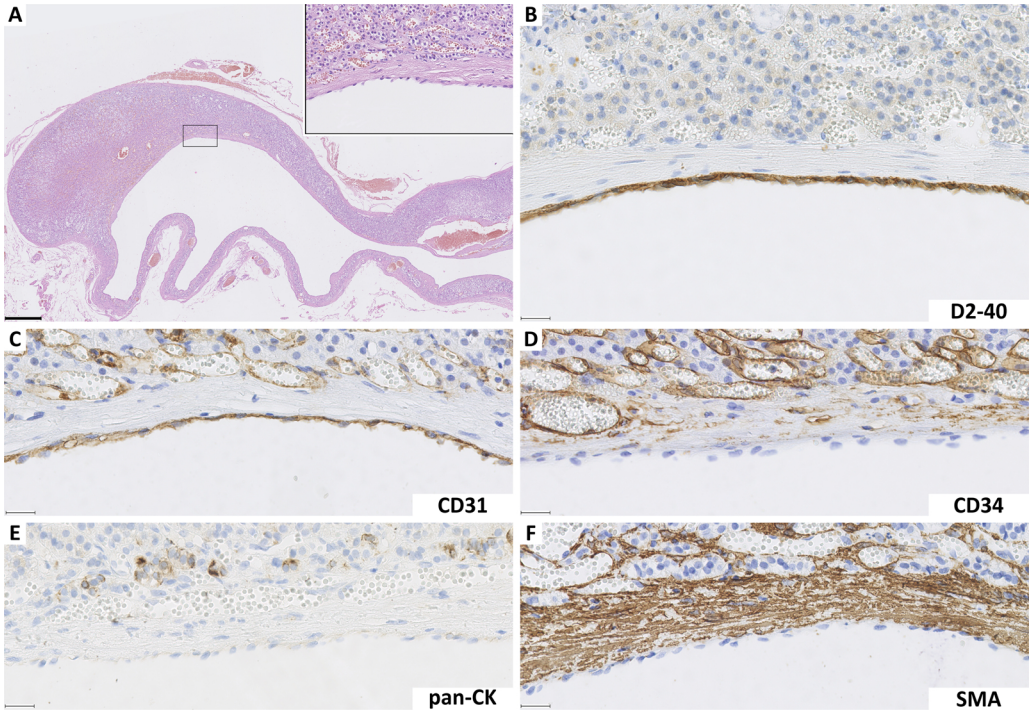

Fig. 2. Unilocular lymphangiomatous cyst. **A.** Microscopic low-power view of a thin-walled unilocular cyst lined by a single layer of endothelial cells (insert). Immunohistochemically the cyst lining was positive for D2-40 (**B**) and CD31 (**C**), but negative for CD34 (**D**) pan-cytokeratin (*E*). Immunohistochemical stain for SMA, although negative in endothelial cells was positive in smooth muscle bundles in the wall of the cyst (**F**). Scale bars: A, 500 μm; B–F, 25 μm.

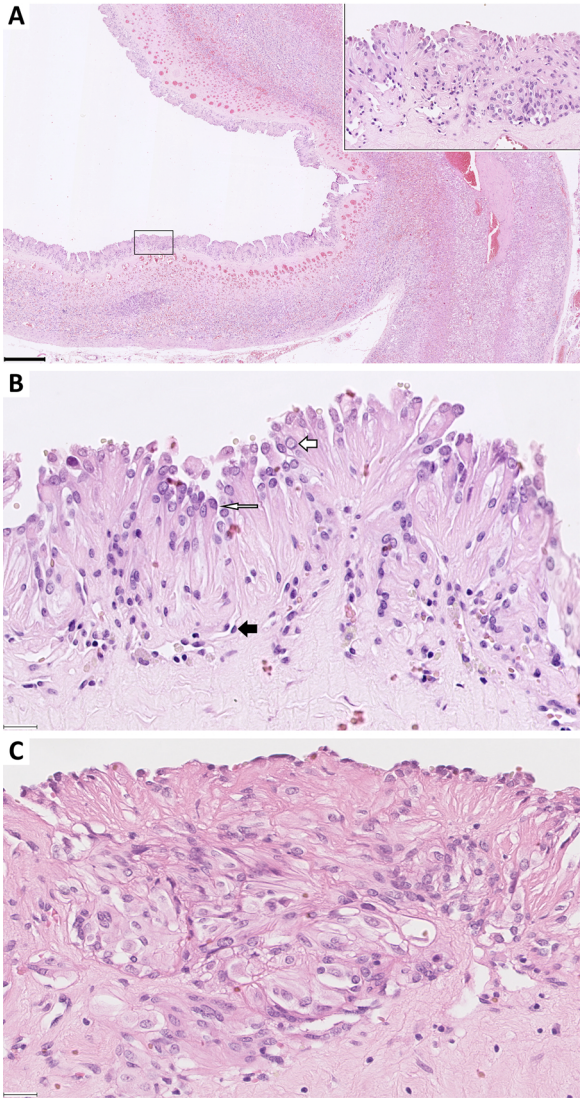

Fig. 3. Lymphangiomatous cyst with papillary endothelial proliferation. **A.** Microscopic low-power view of a unilocular cyst lined by endothelial cells forming papillary projections (insert). **B.** Papillary structures composed of endothelial cells that were characterized by a high nuclear/cytoplasm ratio and apically located nuclei, occasionally grooved (*white, thin arrow*) with a matchstick-like or hobnail appearance (*white, thick arrow*). At the base of the papillary formations there were multiple small lymphatic channels lined by a single layer of attenuated, flat endothelial cells containing nuclei that were 3–4 times smaller than the cells of the papillary structures (*black arrow*). **C.** Occasionally solid areas composed of groups and nests of „epithelioid" endothelial cells with abundant, „clear" cytoplasm were observed. Scale bars: A, 500 µm; B–C, 25 µm.

type IV. Similar perivascular hyalinisation positive for collagen IV was also seen around vessels at the bases of the papillary structures (Fig. 5).

3.3. Comparison of the clinicopathological features between histomorphologic types of adrenal cystic lymphangiomatous lesions

As shown in Table 3, the median age of patients with TMLMs was higher than those with ULCs and those LCs with PEP (39 years vs 29.5 and 33 years, respectively; $P = 0.02$). There were no significant differences in gender, laterality, clinical presentation (incidental versus symptomatic), symptoms and preoperative radiologic impression between the subtypes of adrenal cystic lymphangiomatous lesions. However, ULCs were significantly more frequently associated with a history of previous intra-abdominal surgical procedures and/or inflammatory processes than TCLMs and LCs with PEP (57.1% versus 12.5% and 42.9%, respectively; $P = 0.034$). LCs with PEP were significantly larger than TCLMs and ULCs (median size 8 cm versus 4.3 cm and 3 cm, respectively; $P = 0.0005$). Calcifications were significantly more common in TCLMs than in ULCs and (68.7% versus 14.3% and 28.6%, respectively; $P = 0.008$).

4. Discussion

In regards to lymphangiomatous lesions, inconsistent terminology is used in the medical literature. The WHO classification of soft tissue tumors, which is generally considered as the reference classification for tumors and tumor-like diseases uses the word „lymphangioma" to describe benign cavernous/cystic vascular lesions composed of dilated lymphatic channels [20]. Since these lesions are regarded as abnormalities rather than neoplasms, according to the current classification of the International Society for the Study of Vascular Anomalies (ISSVA) they should now be labeled as „lymphatic malformations" [21]. Lymphatic malformations show a predilection for the head, neck and axillary region accounting for 50–75% of all cases but intra-abdominal locations (including in the adrenal gland) of these lesions are uncommon [17]. The literature on adrenal cystic lymphangiomatous lesions includes only a few small (containing no more than 10 cases) case series [14–16].

This study represents the largest series to date on adrenal cystic lymphangiomatous lesions (lymphangiomatous cysts) in which we present clinicopathologic features, histomorphologic subtypes and follow-up. It has been reported that these lesions occur at all ages with a peak incidence between the third and sixth decades of life with a female predominance [14,16]. In this series, the mean age of the 37 cases was 35.7 years and 26 (70.3%) patients were female, however some demographical differences (discussed below) between histomorphological types of adrenal lymphangiomatous cysts were observed. These lesions tend to have a right-sided predominance (21 of 37 cases), which has been previously recognised [14,16]. They are frequently asymptomatic lesions, discovered incidentally during work-up for unrelated complaints [14,15]. In our series, incidental discovery of lesion was noted in 22 (59.5%) of 37 patients, when symptomatic, abdominal/flank pain was the most common symptom, which has also been previously reported [14].

The correct preoperative diagnosis of adrenal lymphangiomatous cysts is sometimes difficult to obtain on radiologic imaging. There are reports of these lesions being misdiagnosed as arising from an adjacent organ, such as the kidney or pancreas [22,23]. In this study, preoperative radiologic studies identified 35 of 37 cases (94.6%) as adrenal lesions, whereas two (5.4%) large cysts were suspected to be extra-adrenal lesions (in the kidney and in the liver). In our series, imaging studies were accurate in characterizing 23 of 37 cases as having a cystic structure, while an unspecified adrenal mass was favored in 7 cases, adrenocortical adenoma in 4 cases and pheochromocytoma in 3 cases.

Although adrenal lymphangiomatous cysts are not hormonally active lesions, they can sometimes be accompanied by clinical and laboratory features of hormonal hypersecretion. In our series, in 4 cases (10.8%) concurrent hormonal abnormalities were present- 1 patient had associated aldosterone hypersecretion, 1 patient was reported to have subclinical Cushing's syndrome and 2 patients had associated catecholamine excess. These lesions may occur simultaneously with other hormonally active adrenal tumors or tumor-like conditions. For example 1 of 8 lymphangiomatous cysts studied by Zheng et al [16] presented concurrently with an adrenal cortical tumor and this patient was reported to have subclinical Cushing syndrome. In our study, the increased aldosterone secretion in one of 4 patients was probably due to adrenal cortical hyperplasia (accompanied by a lymphangiomatous cyst) in the same adrenal gland. Although no laboratory test results are available to confirm the decrease in aldosterone levels after adrenalectomy, normalization of blood pressure and normal blood potassium

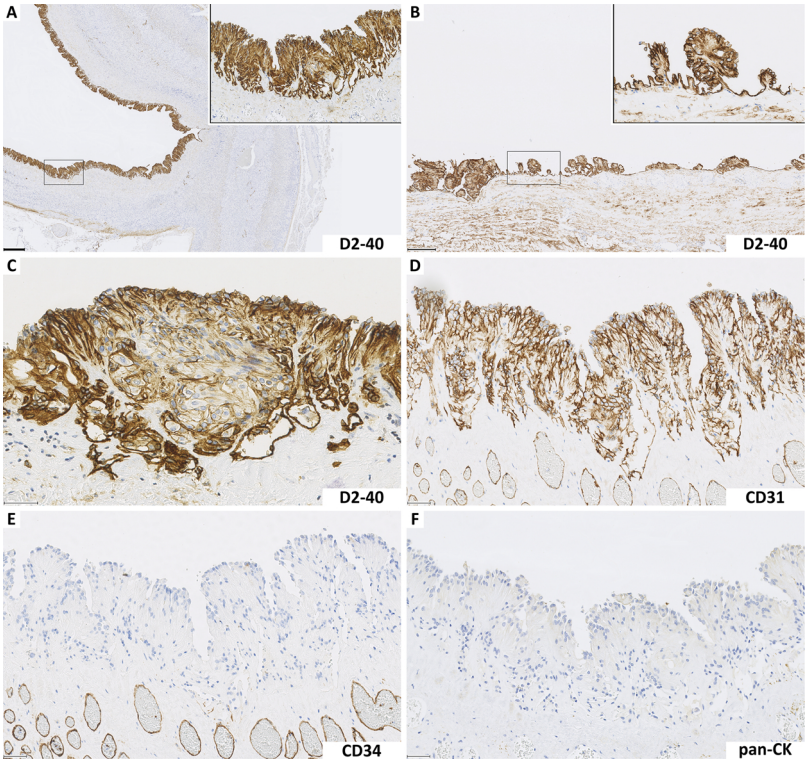

Fig. 4. Lymphangiomatous cyst with papillary endothelial proliferation. **A–C.** Immunohistochemically the cyst lining was positive for D2-40 and CD 31 (**D**), but was negative for CD34 (*E*) and pan-cytokeratin (**F**). Scale bars: A, 500 μm; B, 250 μm; C–F, 50 μm.

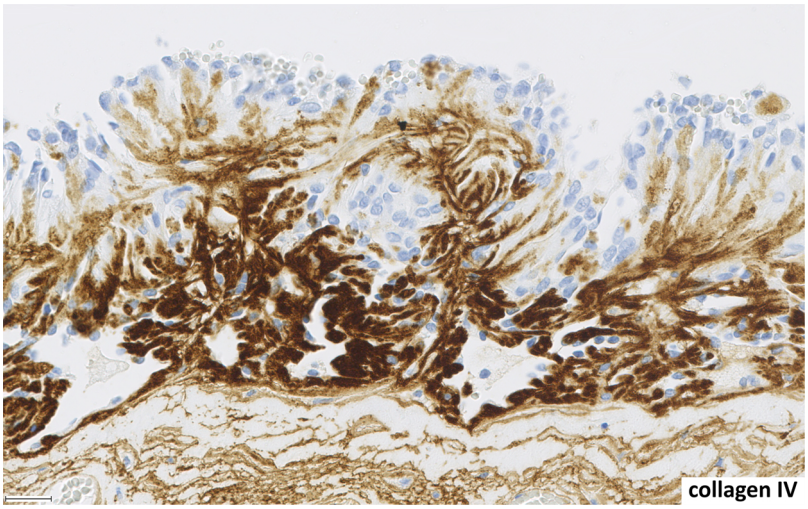

Fig. 5. Immunohistochemical stain for collagen IV in LC with PEP showed a strongly positive reaction in acellular cores and spherical accumulations of amorphous, eosinophilic material of papillary proliferations and around vessels at the bases of the papillary structures. Scale bar: 25 μm.

levels were observed in the postoperative period. Another patient, a 12-year-old, obese (BMI > 97th percentile) girl was reported to have subclinical Cushing's syndrome based on a disturbed diurnal cortisol rhythm, incomplete suppression of cortisol in the overnight 1 mg dexamethasone supression test (3.1 μg / dL) and a low normal ACTH level. Despite normal 24-h urinary free cortisol secretion and imaging studies indicating an adrenal cyst, the patient was qualified for surgical treatment. Histopathological examination of the resected specimen only revealed a 3-cm unilocular lymphangiomatous cyst without any additional, potentially hormonally active lesion within the adrenal gland (such as adrenal cortical adenoma, diffuse or nodular hyperplasia) it seems that, preoperative changes in the laboratory tests were not caused by the adrenal cyst and could have been associated with some other factors, e.g. obesity or stress. In addition, during the postoperative period, besides resolution of abdominal pain no clinical improvement was observed, e.g. weight loss. In this study, two patients were reported to have elevated urinary catecholamine metabolites and pheochromocytoma-like symptoms. The specimens were thoroughly examined and the possibility of the cystic pheochromocytoma in both these cases was ruled out. Although no laboratory results are available to confirm a normalization of catecholamine level after adrenalectomy, in both patients blood pressure returned to normal and one patient reported resolution of hyperhidrosis after surgery, which can suggest a link between the cystic lesions and preoperative biochemical changes and clinical symptoms. Although in 2008 Chien et al [8] reported an elevated urine catecholamine level in a 43-year-old patient with an

Table 3
Comparison of the clinicopathological features between histomorphologic types of adrenal cystic lymphangiomatous lesions.

	Typical multicystic LM (n = 16)	Unilocular LC (n = 14)	LC with PEP (n = 7)	*P*-value
Age (years), mean; median; (range)	41.4; 39 (18-67)	30.5; 29.5 (12-50)	33.1; 33 (25-48)	**0.02***
Gender, n (%)				
Female	13 (812)	10 (71.4)	3 (42.9)	0.178
Male	3 (188)	4 (28.6)	4 (57.1)	
F:M ratio	4.3:1	2.5:1	0.8:1	
Side, n (%)				
Right	10 (62.5)	7 (50)	4 (57.1)	0.788
Left	6 (37.5)	7 (50)	3 (42.9)	
Clinical presentation, n (%)				
Incidental	10 (62.5)	8 (57.1)	4 (57.1)	0.135
Abdominal pain	4 (25)	1 (7.15)	2 (28.6)	
Flank pain	0 (0)	0 (0)	1 (14.3)	
labile HT	2 (12.5)	5 (35.75)	0 (0)	
PIS/I, n (%)				
Yes	2 (12.5)	8 (57.1)	3 (42.9)	**0.034**
No	14 (87.5)	6 (42.9)	4 (57.1)	
Radiology-topography, n (%)				
adrenal lesion	16 (100)	14 (100)	5 (71.4)	**0.01**
extra-adrenal lesion	0 (0)	0 (0)	2 (28.6)	
Radiologic impression, n (%)				
ACL	11 (68.7)	6 (42.9)	4 (57.1)	0.287
AM-unspecified	3 (18.7)	3 (21.4)	1 (14.3)	
AM-ACA?	1 (6.3)	3 (21.4)	0 (0)	
AM-Pheo?	1 (6.3)	2 (14.3)	0 (0)	
Kidney Cyst	0 (0)	0 (0)	1 (14.3)	
Liver Cyst	0 (0)	0 (0)	1 (14.3)	
Surgical procedure, n (%)				
total adrenalectomy	13 (81.2)	12 (85.7)	7 (100)	0.487
partial adrenalectomy	3 (18.8)	2 (14.3)	0 (0)	
Size (cm), mean; median (range)	4.4; 4.3 (1.5-8)	3.5; 3.0 (2-6)	7.9; 8 (5-10)	**0.0005****
Type of cyst				
unilocular	0 (0)	14 (100)	6/7 (85.7)	< **0.0001**
multilocular	16 (100)	0 (0)	1/7 (14.3)	
Calcifications, n (%)				
Yes	11 (68.8)	2 (14.3)	2 (28.6)	**0.008**
No	5 (31.2)	12 (85.7)	5 (71.4)	
Adrenal tissue, n (%)				
Normal	15 (93.7)	11 (78.6)	7 (100)	0.243
ACH	1 (6.3)	3 (21.4)	0 (0)	

LM, lymphatic malformation; LC, lymphangiomatous cyst; PEP, papillary endothelial proliferation; F, female; M, male;
HT, arterial hypertension; PIS/I, previous intra-abdominal surgery/inflammatory process; ACL, adrenal cystic lesion; AM, adrenal mass;
ACA, adrenal cortical adenoma; Pheo, pheochromocytoma; ACH, adrenal cortical hyperplasia;
* Pairwise analysis: TMLM vs ULC, p = 0.01; TMLM vs LC with PEP, p = 0.039; ULC vs LC with PEP, p = 0.488.
** Pairwise analysis: TMLM vs LC with PEP, p = 0.003; ULC vs LC with PEP, p < 0.0001; TMLM vs ULC, p = 0.131.

adrenal endothelial cyst, it was Morse et al [24] who first unequivocally showed that this type of lesion can produce pheochromocytoma-like symptoms and catecholamine elevation. The authors reported a case a of 36-year-old female with a right-sided adrenal multiloculated cyst (showing a lymphangiomatous immunophenotype), who in the pre-operative period complained of headaches, palpitations, and was noted to be hypertensive, her plasma norepinephrine and dopamine levels were elevated. After adrenalectomy catecholamines returned to normal, although her post-operative blood pressure was still mildly elevated [24]. Elevated levels of plasma and urine catecholamines and their metabolites were also reported by Hodish et al [25] in a 59-year-old male patient with adrenal lymphangioma. In a series of 8 cases of adrenal lymphangiomas studied by Gao et al [15] five patients exhibited a slight increase in serum norepinephrine and two patients had increased epinephrine. Therefore physicians should be aware that these kinds of lesions may create a diagnostic dilemma in the setting of laboratory testing concerning pheochromocytoma and they should be considered as a possible cause of pseudopheochromocytoma. The mechanism by which these adrenal lesions produce elevated levels of catecholamines remains unknown, however we share the opinion of other authors that it may be mediated by a mass effect of the cystic lesion pushing against the adrenal medulla [24].

There is no widely accepted consensus in the literature regarding the optimal treatment of adrenal cysts, including cystic lymphangiomatous lesions. Treatment strategies include observation, cyst aspiration and surgical excison, which is especially indicated for cysts which are large (greater than 4–6 cm), symptomatic, suspicious for malignancy in imaging studies and those with associated hormonal abnormalities [2,26]. Although minimally invasive (laparoscopic) total adrenalectomy remains the operative method of first choice, some authors prefer adrenal-sparing surgery [3,27]. In our series, 32 patients were treated by total adrenalectomy, whereas 5 patients by partial adrenalectomy. On available follow-up, none of patients treated by total adrenalectomy showed evidence of recurrence. However, one patient who underwent partial adrenalectomy (of the four with available follow-up) showed local recurrence 1 year after surgery. To our knowledge this is the first documented case of recurrence of an adrenal lymphangiomatous cyst after surgical excision. It is very likely that the cyst recurrence was due to incomplete resection with cystic changes forming within the remaining fragment of the primary lesion. The multicystic and multifocal morphological structure of typical lymphatic malformations may hinder the separation of this lesion from normal adrenal gland tissue, and therefore complete resection with adrenal-sparing surgery may be more difficult than with a unilocular cyst. It seems, therefore, that the risk of local reccurence after an adrenal-sparing surgical procedure may be greater if a multicystic rather than unilocular lesion is diagnosed in post-operative histopathology. However, additional cases with further follow-up studies are needed to confirm this correlation.

We observed that these lesions on the basis of their histomorphologic features represent three, morphologically distinct types: typical multicystic lymphatic malformations, unilocular lymphangiomatous cysts and lymphangiomatous cysts with papillary endothelial proliferation.

Typical multicystic lymphatic malformation (TMLM) was the most common type of lesion in our study. Grossly and histologically they showed a characteristic, multicystic architecture composed of dilated spaces lined by flat, lymphatic endothelium. Previously reported cases in small series represent this histomorphologic type of lymphangiomatous cysts. As was mentioned above they mainly affect younger-aged females with a reported mean age between 40 and 46 years and an average lesion size of 4.8–4.9 cm [14–16]. In our case series TMLMs had the highest predilection for females (81%) compared with men (19%); the mean age of 16 cases was 41.4 years and was higher than in other groups (30.5 and 33.1 years). The average lesion size of the TMLMs was 4.4 cm and they were the most likely to be right-sided (62.5%) of all the groups. Unilocular lymphangiomatous cyst (ULC) was the second type of adrenal lymphangiomatous cysts in this study. In comparison to TMLMs they were recognized in younger patients (mean age 30.5 years versus 41.4 years). These cysts were single, unilocular, small lesions with an average size of 3,5 cm. ULCs were more frequently associated with a history of previous intra-abdominal surgical procedures and/or inflammatory processes than TMLMs and LCs with PEP (57.1% versus 12.5% and 42.9%) and therefore, “lymphangiectasia” as a pathogenetic mechanism in the formation of these lesions might be considered. These

factors, at least in some cases could have had an influence on lymphatic flow, caused a blockage or damaged intrabdominal lymphatic vessels and lead to their ectasia.

Our series included 7 cases of cysts with a diffusely or focally seen papillary endothelial lining. The majority (6 of 7) of these cysts were unilocular, they were significantly larger lesions than the other 2 groups and the papillary endothelial lining in all cases displayed a „lymphatic" immunoprofile. In the current literature we did not find reports of adrenal lymphangiomatous cysts with papillary endothelial lining, however in one reported case a large, unilocular cystic lymphangioma of the adrenal gland the authors noted „occasional pseudopapillae formation" within the lining of the cyst [28]. Papillary projections were previously described in individual cases of patients with splenic lymphangioma [29–31]. However, all these lesions were grossly solid masses microscopically forming numerous microcystic spaces lined by a single layer of endothelial cells with frequent papillary projections. This type of endothelial proliferation has been observed in other vascular lesions, termed hobnail hemangioendotheliomas, particularly in papillary intralymphatic angioendothelioma, PILA (originally described by Maria Dabska and also known as Dabska tumor) [17,32]. This very rare, usually pediatric, vascular neoplasm mainly affects the skin and subcutis of the extremities and presents as a slow growing asymptomatic cutaneous ill-defined induration or plaque [18]. We observed, that the cysts with papillary endothelial lining shared some microscopic features (e.g. "hobnail" or "matchstick-like" endothelial cells) and immunoprofile with papillary intralymphatic angioendothelioma [17,18,33]. Similarly to PILA, papillary proliferations in our cases had a central core composed of accumulated basement membrane material (strongly positive for collagen IV) [33]. As was noticed by Fanburg-Smith et al [33] such a basement membrane accumulation may indicate increased cell turnover of endothelial cells. Papillary intralymphatic angioendothelioma is defined as an intermediate (rarely metastasizing) vascular tumor, although follow-up in the largest series demonstrated no local recurrence nor metastasis [18,33]. Microscopic features of the endothelial lining demonstrating a papillary pattern of proliferating endothelial cells allow us to assume, that our 7 cases of LCs with PEP may represent true neoplastic lesions. Follow-up in 5 of the 7 cases showed no evidence of recurrences or metastasis during follow-up ranging from 9 to 106 months (median, 36 months). Although our cases showed benign behavior after excision by total adrenalectomy, additional cases with further follow-up studies are needed to rule out lesions with malignant course.

In conclusion, we analyzed the clinicopathologic features and histomorphologic spectrum of the largest series of adrenal cystic lymphangiomatous lesions to date. As has been previously reported, they mainly affect younger-aged females and have a right-sided predominance. In our study, adrenal lymphangiomatous cysts were mostly asymptomatic, incidentally diagnosed on imaging studies, and when symptomatic abdominal or flank pain was the dominant symptom. These lesions may sometimes imitate (clinically and radiologically) other adrenal cortical or medullary tumors. Although they are non-functioning lesions, they should be considered as a possible cause of pseudopheochromocytoma. Follow-up information available for 19 out of 32 patients who underwent total adrenalectomy showed no evidence of disease in all these patents at the time of this study, however 1 of 4 patients with available follow-up treated by partial adrenalectomy had a histologically confirmed local reccurence of a lymphangiomatous cyst 1 year after surgery. Although most adrenal lymphangiomatous cysts seem to be non-neoplastic, vascular abnormalities (malformations or lymphangiectasias), those with papillary endothelial proliferations may represent true neoplastic lesions.

Disclosure

The authors have no conflicts of interest and no funding disclosures

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prp.2019.03.014.

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