Original Article
Clinical and pathological characteristics of adrenal lymphangioma treated by laparoscopy via a retroperitoneal approach: experience and analysis of 7 cases

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Abstract: To describe the clinical and pathological characteristics of adrenal lymphangioma (AL) and share our experiences of the treatment of AL with retroperitoneal laparoscopic surgery. All patients pathologically diagnosed with AL were examined. The clinical and pathological characteristics, process of diagnosis, and preparation and treatment of all patients, especially patients treated with laparoscopic surgery, were summarized and retrospectively analyzed. From January 2008 to May 2014, 8 patients underwent adrenalectomies and were diagnosed with AL in our hospital. The median age was 45.5 years. All of these patients experienced a smooth adrenalectomy: 7 performed by laparoscopy via a retroperitoneal approach and 1 performed by open surgery. Five were female and the other 3 were male. These patients had unilateral adrenal lesions. Four were located on the right which to be same as the contralateral. In addition, 1 specimen was assayed by immunohistochemistry (IHC), which revealed positive results for CD31, CD34, Factor VIII-related antigen and D2-40, and negative results for cytokeratin AE1/AE3. During a brief follow up, all patients exhibited favorable results without discomfort. AL is a benign lesion with mild bio-behavior and patients are generally asymptomatic. The use of computerized tomography (CT) combined with enhanced CT has a superior advantage in diagnosis. Laparoscopic adrenalectomies that are performed via a retroperitoneal approach would be a very safe and efficient choice for AL treatment. D2-40 can be considered as a specific IHC marker in the pathological diagnosis of AL. However, pheochromocytoma and adrenal tuberculosis should be ruled out before and during the operation.

Keywords: Adrenal lymphangioma, laparoscopic, retroperitoneal, adrenalectomy

Introduction

A lymphangioma is a rare benign malformation of the lymphatic system that originates in embryogenesis. It is predominantly distributed in the neck, axilla and mediastinum. Retroperitoneal lymphangiomas have been reported to account for nearly 1% of all lymphangiomas [1], whereas adrenal lymphangiomas (AL) are much rarer. Sporadic cases have been presented mainly in case reports, while reports of series of cases are infrequent.

The criteria for the treatment of AL are still controversial. For operations, a laparoscopy would be the first choice for adrenal lesions because of its many advantages as compared to that of with traditional open surgery. However, extra- or trans-peritoneum approaches are still under debate.

The aim of our present study was to analyze the clinical and pathological characteristics of 8 cases with ALs in detail and discuss our experiences with the diagnosis, preparation and treatment of ALs and systematically review the available literature.

Material and methods

We retrospectively searched for and collected all records of inpatients who underwent adrenalectomies and were pathologically diagnosed with ALs from January 2008 to May 2014 in West China Hospital.

Table 1. Clinical characteristics of patients

NO./Age (Yrs)/ Gender	Side of Lesion	Symptomatology	Serum Catecho-lamine, ng/L※	US	CT	Preoperative Prescription	Surgical Templates	Affiliated Pathological Findings
1/62/F	R	HT	NE: 677 E: < 25	NA	Diameter: 1.5 cm; Separation; Calcification	Y	RLS	Calcification, Fat necrosis
2/23/F	L	Lumbar pain, Micturition	NE: 443 E: 148	NA	Size: about 12×10 cm; Hematoma	Y	Open	Organized hematoma, Hemorrhage
3/44/M	L	–	NE: 306 E: 89	Size: 2.4×1.7×1.8 cm	Size: 2.4×1.9 cm; Value: 10 HU	N	RLS	–
4/34/F	L	HT	NE: 522 E: 85	Size: 3×2 cm	Size: 1.8×2.7 cm; Value: 12 HU; Calcification	Y	RLS	Calcification
5/54/M	R	–	NE; 155 E: 72	NA	Size: 2.3×2.0 cm	N	RLS	–
6/45/F	R	–	NE: 650 E: 35	NA	Size: 2.1×1.9 cm; Separation; Value: 13 HU; Calcification	Y	RLS	Calcification
7/46/F	R	HT	NE: 246 E: 113	Diameter: 3.5 cm	Diameter: 3.7 cm; Value: 15 HU; Calcification	Y	RLS	Calcification
8/62/M	L	–	NE: 649 E: 28	Diameter: 2.8 cm	Size: 5.9×2.4 cm; Value: 9 HU; Calcification	Y	RLS	Calcification

US: Doppler Sonography; CT: Computerized Tomography; F: Female; M: Male; R: Right; L: Left; HT: Hypertension; NE: Norepinephrine; E: Epinephrine; RLS: Retroperitoneal Laparoscopic Adrenalectomy; Y: Yes; N: No; NA: Not Available. ※Reference Value: NE: 174–357 ng/L; E: 60-104 ng/L.
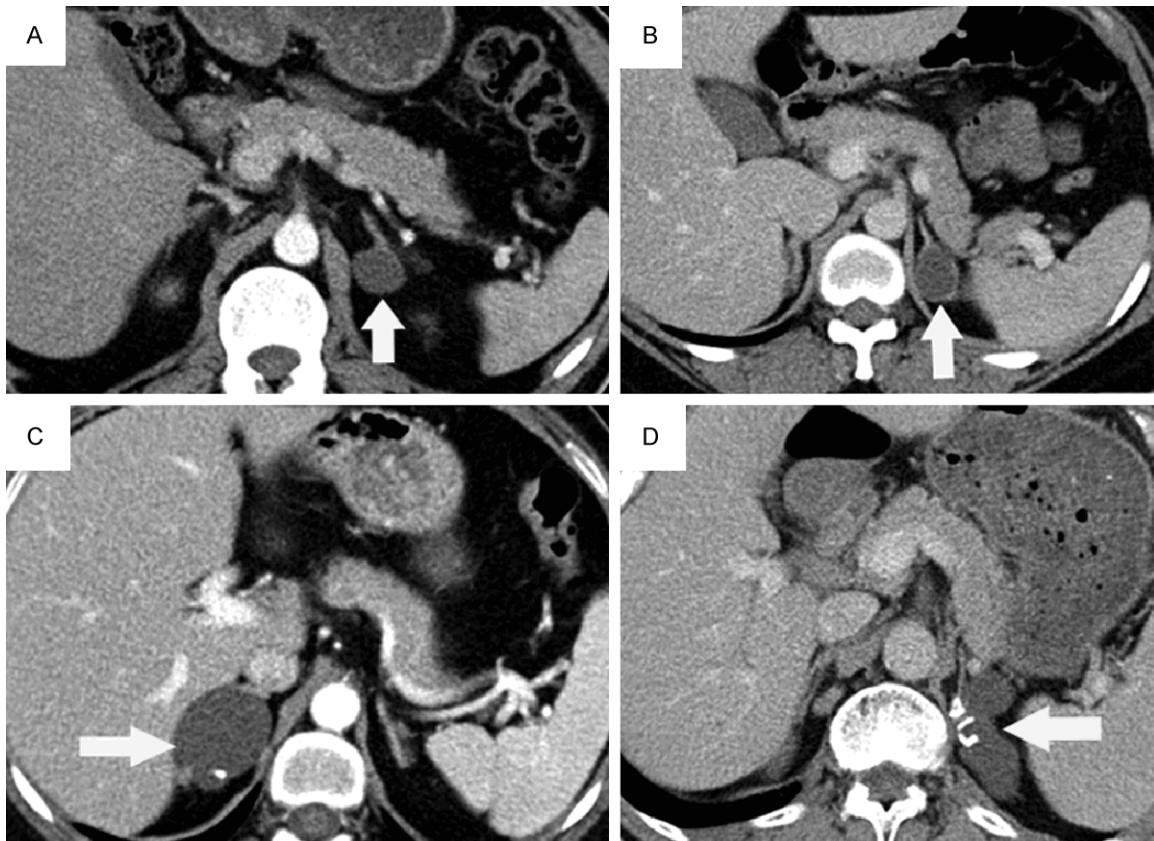
Figure 1. CT and enhanced CT of upper abdomen. Low density lesions of the 3rd (A), 4th (B), 7th (C) and 8th (D) case are demonstrated in the superior of kidney, which have been labeled by white arrows, respectively. Calcifications could be presented in the subtitle of (C and D).

Clinical characteristics

Before the operation, imaging examinations, including urinary color-Doppler ultrasonography (US) and abdominal contrast-enhanced computerized tomography (CT) were used to confirm and identify the position and details of the adrenal lesions. Because of expense, magnetic resonance imaging (MRI) was deemed second-line. When specific lesions were ascertained, adrenal hormones including serous electrolytes, cortisol, and aldosterone in erect and supine positions were routinely detected. In addition, 24-h catecholamine levels in the blood and urine were examined because of the possibility of pheochromocytoma or adrenal medullary hyperplasia, which, in our opinion, mostly affected the safety of the patient during the operation [2, 3].

For patients with hypertension, increased catecholamine levels and/or a mass diameter > 4 cm, preoperative prescriptions, including 1-4 weeks of routine oral α-adrenergic receptor blockers, phenoxybenzamine (doses usually

from 5 mg bid to a maximum of 30 mg tid) or prazosin (doses usually from 1 mg bid to a maximum of 3 mg tid), and 2-3 days of alternately transvenous doses of 1000 mL of crystalloid and colloidal solutions were applied to reduce the incidence of turbulent hemodynamics during the operation. Different doses of β2-receptor blockers were used for patients with tachycardia until the heart rate was controlled to < 90 beats per min [3].

Operative treatments

After all of the preparations were completed, the performance of laparoscopic surgery through the retroperitoneal approach was considered first for masses smaller than 6 cm. For patients with peritoneum injury during the operation, we adopted a trans-lumbar and peritoneal joint approach with balanced pressure after properly expanding the trauma in the peritoneum. Otherwise, other surgical templates, such as transperitoneal laparoscopy or even open surgery were considered. Importantly, a partial adrenalectomy should be considered for
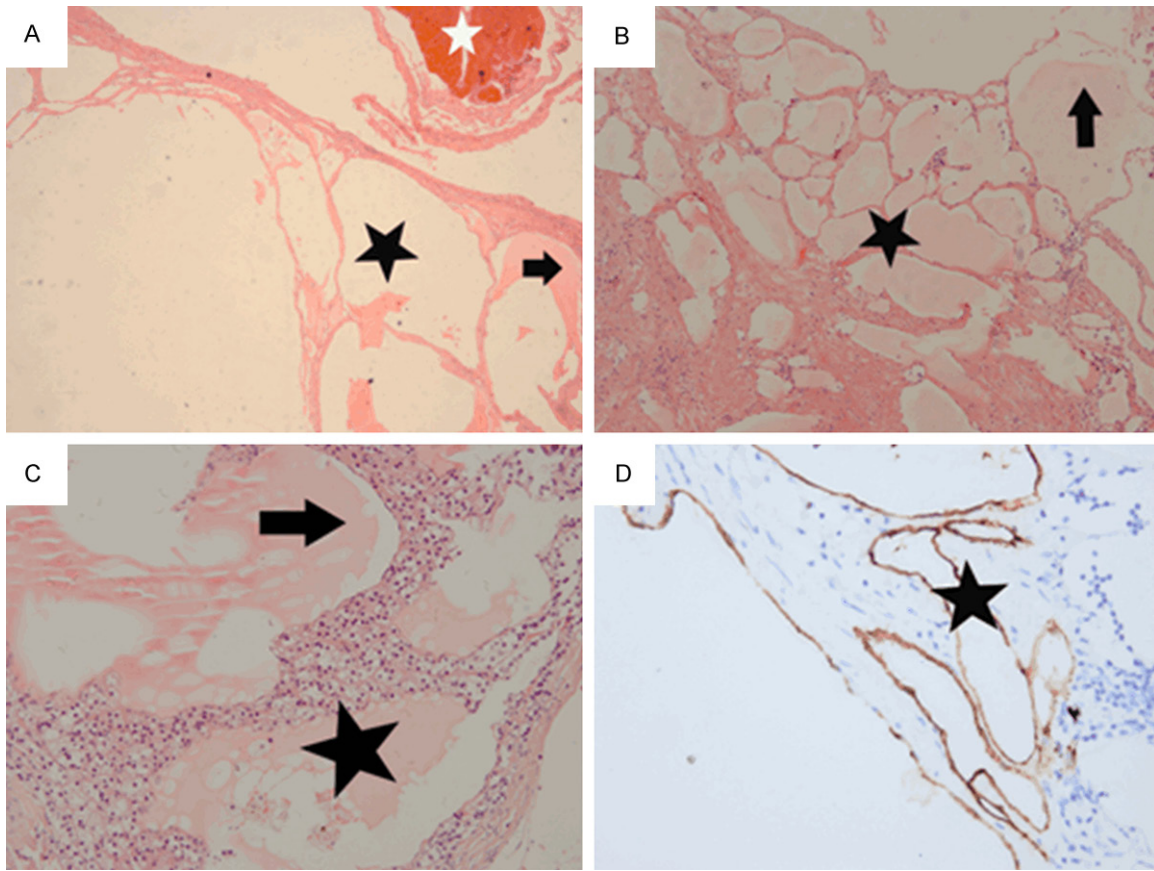
Figure 2. Hematoxylin-eosin (HE) stains of patients 2 (A, 4×10), 3 (C, 20×10) and 7 (B, 10×10), and D2-40 immuno-histochemistry (IHC) strains of the 7th patient. Dilated lymphatic ducts could be demonstrated in all patients (black stars), lymphatic fluid could be found in pictures of a, b, c (black arrows), while hematoma could be only shown in the 2nd patient (A, white star), respectively. The IHC of D2-40 presents a positive result (D).

single small lesions that are shown to be located at the extreme of the adrenal region via imaging.

Pathological analysis

All of the excised specimens were routinely examined pathologically. Furthermore, immunohistochemistry (IHC) methods that mainly focused on markers of the Factor VIII-related antigen, CD31, CD34, cytokeratin AE1/AE3 and D2-40 were conducted in the 7th patient as previously reported [6]. The pathological characteristics were further analyzed.

Because of silence of AL, follow-up of these patients was brief.

Results

In total, 8 patients who were diagnosed with AL were examined. Three of the patients complained of slight blood pressure elevations and 1 complained of a persistent dull pain in her left lumbar areas. The others were asymptomatic, for which adrenal masses were found during health examinations. No tachycardia was found in these patients during their hospitalizations. Detail characteristics of these patients were summarized in **Table 1**.

The median age of all of the patients was 45.5 years (range: 23-62 years). Five were female and the other 3 were male. All of the patients had unilateral adrenal lesions. Four were located on the left and 4 were located on the right.

In Summary, 5 patients exhibited a slight increase in norepinephrine levels, 2 had increased epinephrine levels and 6 underwent preoperative preparations of the prescriptions. Other biochemical indexes presented insignificantly anomalies.

For imaging, 4 patients were inspected by US, which showed nearly identical results as compared to that of abdominal CT scans. Fur-

thermore, to get more detailed imaging, all of the patients underwent enhanced CT, with which all of the lesions were demonstrated and the 8th patient was suspected to have adrenal tuberculosis. However, none were examined by MRI (**Figure 1**).

All of the patients experienced smooth operations with 7 being treated by retroperitoneal laparoscopic approach. The 2nd patient was treated by open surgery. No peritoneum injuries occurred. Two patients were operated on by a partial mode with normal adrenal tissue preserved. All of the cases had no replacement therapy of glucocorticoids.

Pathologically, all of the patients were diagnosed with AL with hematoxylin-eosin (HE) staining. An additional test of IHC was applied in the 7th patient. The pathological examinations revealed the following: 1) dilated lymphatic ducts and residual fluid were presented in all the specimens; 2) a hematoma could be found in the 2nd patient; and 3) positive IHC results for the Factor VIII-related antigen, CD31, CD34 and D2-40 and negative results for cytokeratin AE1/AE3 in the 7th patient could be shown (**Figure 2**).

During a brief follow-up examination, all the patients exhibited favorable results without discomfort. Two patients with hypertension were descending to normal levels, while moderate blood pressure control was required for the 7th patient.

Discussion

Adrenal cystic lesions are infrequent, with an approximately occurrence of 0.064%-0.18% in autopsy studies of the general population [4] and 5.1% of adrenal lesions [2]. According to the histological manifestations, these lesions can be divided into 4 subtypes: endothelial cyst, pseudocyst, epithelial cyst and parasitic cyst. Endothelial cysts, which account for the highest percentage (approximately 45%), can be classified as lymphangiomatous cysts (known as AL) and angiomatous cysts [5]. To date, ALs have been reported sporadically except for a maximum of 9 cases reported by Ellis et al [6].

The etiology and pathogenesis of AL are still under debate in spite of multiple possible hypotheses: including the malformation of lymphatic channels, ectasia of lymphatic channels,

obstruction of proximal lymphatic channels and cystic hamartomas [6, 7].

Patients with ALs are usually asymptomatic, and different degrees of manifestations that are triggered by mass effects have been exhibited such as abdominal pain, bowel obstruction, etc. The female gender and age in the 3rd to 6th decade are regarded as susceptible factors [4, 8]. However, these lesions are generally unilateral and no significant predilection of disease side could be found. These tendencies are similar to the observations in our report. However, bilateral lesions are not been impossible [10].

The diagnosis of an adrenal mass must rely on imaging, including Doppler US, CT and MRI. Although well-circumscribed, anechoic or centrally non-enhanced lesions with a thin wall in the superior region of the ipsilateral kidney are demonstrated by many of them, multiple factors should be taken into consideration as well.

US had been shown to have the disadvantages of lower sensitivity and limitations in distinguishing adrenal cysts from other retroperitoneal cysts or solidly adrenal masses that are accompanied by cysts [9]. In addition, US results can be easily influenced by a number of techniques. However, its advantages such as convenience and inexpensive costs should not be ignored. Although MRI has high sensitivity in detecting lipids within cystic lesions, intracystic hemorrhage, separations and complicated cysts [11-13], diagnostic dilemmas or misdiagnosis can not be completely eliminated [5]. Although worthwhile, the expensive cost of MRI limits its popularization.

In our opinion, CT combined with contrast-enhanced CT has enough sensitivity and specificity for diagnosis and antidiastole of AL, and it has the advantage of detecting calcifications. In addition, necessary details can be estimated by surgeons before and during the operation with CT pictures in contrast to US. Therefore, in our institution, US is often used for screening whereas CT is used for confirming and guiding operations. This is why none of our cases were examined by MRI.

After the adrenal lesions are confirmed, biochemical tests are very important to define the characteristics of the lesions. Generally, patients with ALs are silent. However, severe abdominal pain, hemorrhage, infection, torsion,

rupture or obstruction can occurs occasionally [14]. More importantly, cystic adenomas, glandular or retention cysts, and cystic transformation of embryonic remnants can occur in epithelial cysts [15]. In addition, small adrenal cysts can be associated with Cushing syndrome, virilization or pheochromocytoma [16]. Moreover, hemorrhage in a normal adrenal gland or an adrenal tumor can be found in pseudocysts [15]. All of these characteristics are difficult to identify in imaging examinations, which suggests additional screening with the adrenal endocrine axis.

For the hormones, catecholamines should be especially treated with caution as turbulent haemodynamics can cause severe complications during treatment. In our opinion, preoperative prescriptions are recommended in all patients with masses having diameters > 4 cm, presenting symptoms or positive catecholamine results. From our review, only 1 patient with a huge lesion was accompanied with hemorrhage, and 6 cases were prepared by prescriptions. All exhibited very stable haemodynamics during the operation.

Although adrenal cystic masses were confirmed, their treatment remains controversially. Cysts > 4 or 5 cm, functional and/or symptomatic cysts, cysts with complications (haemorrhage or calcification, etc.) or small cysts that enlarged by 1 cm each year are considered alternative criterions to surgery [2, 5, 17], while active advocators are not infrequent. However, we are more likely to agree with the latter. First, there is a possibility of 7% of malignancy in all adrenal cystic lesions [18]. However, benign or malignant cystic lesions, such as adrenocortical neoplasms and pheochromocytomas are the clinical differential diagnosis of AL despite the current improved capabilities [7]. In addition, a partial adrenalectomy with the normal adrenal tissue reserved is more possible when the lesions are small.

To remove benign lesions, laparoscopic adrenalectomies have been regarded as the gold standard by Bulus et al [19]. However a retroperitoneal approach has proven to have less interference with the gastrointestinal system and a shorter hospital stay as compared to that of a transperitoneal approach [20, 21]. In addition, the safety and efficiency of robot-assisted and laparoscopic single-site adrenalectomies

as compared to that of conventional laparoscopic surgeries have demonstrated insignificant differences [22-25].

Laparoscopic surgery has been prevalent for over a decade in our hospital. For ALs < 6 cm, we perform laparoscopic surgeries via a retroperitoneal approach because of the number of advantages with no significant differences including security, smaller trauma, less blood loss, shorter hospital stay and less interference to gastrointestinal system, etc. as compared to those of the traditional open and transperitoneal laparoscopic surgeries [3]. However, laparoscopic single-site adrenalectomies are rare and we have never performed a robot-assisted adrenalectomy.

Surgical techniques for adrenal neoplasms are varied from a total adrenalectomy to a subtotal adrenalectomy with the preservation of normal tissue [26]. Fortunately, in our study, 2 patients underwent a partial adrenalectomy with the normal adrenal tissue preserved and no recurrence was found during follow-up. In addition, aspiration of the contents of adrenal cysts instead of surgical excision has been recommended as another choice for benign, nonfunctional or asymptomatic lesions [27], and this technique has not been popularized or performed by us.

Although peritoneum injury did not occur in our study, laparoscopy adopting surgeries with trans-lumbar and peritoneal joint approaches have been considered important methods to use during retroperitoneal laparoscopic surgery with a focus on large lesions from adrenal, kidney or retroperitoneal cavities or peritoneum injury during practicing. This technique is achieved by opening the peritoneum and then expanding the crevasse to balance pressure on both sides of the peritoneum in patients undergoing laparoscopic operations with the lateral position, from which enlarged practicing spaces could be established. For large masses, especially lesions located on the left, expanded spaces could be more significant because of the effect of organic gravity after intentional peritoneal incision.

In our opinion, ALs can be brittle and rupture has appeared frequently compared to other cystic lesions in the kidney or adrenal regions, thus separation during the operation should be

carefully performed. Generally, ALs are presented as multilocular, thin-walled cystic lesions filled with nonviscous, clear, yellow-brown-colored fluid [5]. In addition, calcification has been reported as a possibility in 15%-30% patitents [4]. In our report, calcification was found in 5 of 8 patients. In the 8th patient, adrenal tuberculosis was highly suspected because of large-scaled calcification that was observed in the CT scan and observations with naked eye.

The final diagnosis of AL relies on pathology. The dominating histological feature of ALs is endothelial-lined lymphatic channels, which are separated by connective tissue [15]. In IHC, Factor VIII-related antigen, CD31 and CD34 can provide clues for diagnosis of AL [28, 29]. However, CD31 and CD34 label both blood vessels and lymphatic endothelium which makes it difficult to differentiate ALs from angiomas. A monoclonal antibody named D2-40 is expressed specifically by lymphatic endothelium, and it has been used as a more valuable marker of lymphatic lineage [15, 30]. In our study, though only 1 patient was examined by IHC, but similar results could be observed.

Hormonal replacement therapy was conducted in none of the patients. Because of the benignity and silence of ALs, all of the patients received brief follow-up examinations of blood pressure and urinary US, and exhibited satisfactory results, except for 1 patient with hypertension unremarkable blood pressure control.

Although 2 patients with hypertension had their blood pressure decrease to normal during our study, the correlation between AL and hypertension is still to be confirmed. Low adrenal reserve may be a possible mechanism. Similarly, the increased blood pressure in the 7th patient was more likely idiopathic.

In conclusion, ALs are benign and generally asymptomatic lesions with mild bio-behavior. CT combined with enhanced CT provides superior advantages for its diagnosis. However, pheochromocytoma, tuberculosis, and functional cystic lesions should still be considered with caution as occasionally confusing manifestations, which reflect the necessity of preoperative preparations. The performance of retroperitoneal laparoscopic adrenalectomies in most patients combined with the subtotal mode for selective cases are very safe and efficient choices for the treatment of AL. Furthermore,

D2-40 is more sensitive and specific than the Factor VIII-related antigen, CD31 and CD34 and can be regarded as a specific IHC marker in the pathological diagnosis of AL. Satisfactory prognoses are exhibited by most patients after the surgery.

Disclosure of conflict of interest

None.

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