Original Article
Clinical and CT features of adrenal cystic lymphangioma: case series and literature review

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Abstract: Adrenal cystic lymphangiomas (ACLs) are rare and benign vascular tumors that are likely to imitate other adrenal cystic lesions on computed tomography (CT) images. We performed a retrospective analysis of the CT appearance and clinical data of all adrenal masses diagnosed by pathological tests at our institute and conducted a systematic review of all previous ACL reports. Although rare, ACLs should be considered when an adrenal lesion observed in a woman is asymptomatic, measures greater than 4 cm, and appears as a well-defined cystic mass with calcifications and non-enhancement patterns. Furthermore, D2-40 is a specific IHC marker for the histopathological diagnosis of ACL.

Keywords: Adrenal gland, adrenal cystic lymphangioma, pathology, computed tomography

Introduction
Lymphangiomas are benign vascular lesions that most commonly affect the neck, axilla, and mediastinum [1]. The literature on adrenal cystic lymphangiomas (ACLs) includes case reports [1-25] and small case series [26-30], and the inclusion of these lesions in broader descriptions of adrenal lesions [31, 32]. ACLs are likely to imitate other adrenal cystic lesions, and it is difficult to distinguish between the two. A correct pre-operative diagnosis of ACL is important for avoiding unnecessary extensive surgery, such as full adrenal resection and regional lymph node dissection [15].

We presented nine cases of ACL treated at our hospital over a period of 6 years as well as a summary and analysis of the clinical, histopathological, and CT details of cases reported in the English scientific literature.

Patients and methods

Patients at our hospital
Institutional review board approval was obtained for this study, and the informed consent requirement was waived due to the retrospective study design. Clinical data of patients diagnosed with ACL were collected retrospectively from January 2011 to May 2016 at the First Affiliated Hospital of Xi’an Jiaotong University. Patient’s laboratory data were collected and documented prior to treatment.

The results of pathology examinations were reviewed. Slides with a tissue section of ACL were obtained and reviewed by the study pathologist. Two radiologists with 20 and 8 years of post-training experience of adrenal imaging independently reviewed the CT characteristics of each lesion, including the location, shape, size, margins, septation, attenuation in the unenhanced and enhanced CT images, and the enhancement pattern of the lesion. Any disagreements were resolved by consensus. After discharge, the patients were followed up for at least 6 months.

Literature review
A literature search was conducted in English for case reports of ACL. We searched PubMed, MEDLINE, the Cochrane Library, and Google Scholar until May 1, 2016. The following key-
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Table 1. Clinical and imaging findings of nine patients with adrenal cystic lymphangioma

<table>
<thead>
<tr>
<th>Case No./Age (y)/Sex</th>
<th>Symptoms</th>
<th>Size (cm)</th>
<th>Side</th>
<th>Gross Morphology (Shape/Margin)</th>
<th>Septation</th>
<th>Non-enhanced (Density/Calcification)</th>
<th>Contrast-enhanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/35/M</td>
<td>None</td>
<td>9.2</td>
<td>L</td>
<td>Oval/Well-defined</td>
<td>None</td>
<td>Homogeneous/None</td>
<td>None</td>
</tr>
<tr>
<td>2/50/F</td>
<td>Flank pain</td>
<td>7.5</td>
<td>L</td>
<td>Oval/Well-defined</td>
<td>None</td>
<td>Homogeneous/None</td>
<td>None</td>
</tr>
<tr>
<td>3/40/F</td>
<td>None</td>
<td>2.0</td>
<td>R</td>
<td>Oval/Well-defined</td>
<td>None</td>
<td>Homogeneous/Peripheral punctate, nodular</td>
<td>None</td>
</tr>
<tr>
<td>4/68/F</td>
<td>None</td>
<td>8.4</td>
<td>L</td>
<td>Oval/Well-defined</td>
<td>None</td>
<td>Homogeneous/peripheral punctate</td>
<td>None</td>
</tr>
<tr>
<td>5/60/M</td>
<td>None</td>
<td>8.6</td>
<td>L</td>
<td>Oval/Well-defined</td>
<td>None</td>
<td>Homogeneous/None</td>
<td>None</td>
</tr>
<tr>
<td>6/34/F</td>
<td>None</td>
<td>12.6</td>
<td>R</td>
<td>Oval/Well-defined</td>
<td>None</td>
<td>Homogeneous/peripheral punctate</td>
<td>None</td>
</tr>
<tr>
<td>7/27/M</td>
<td>Hypertension</td>
<td>5.0</td>
<td>L</td>
<td>Oval/Well-defined</td>
<td>None</td>
<td>Homogeneous/peripheral punctate, nodular</td>
<td>None</td>
</tr>
<tr>
<td>8/43/M</td>
<td>Hypertension</td>
<td>3.0</td>
<td>R</td>
<td>Oval/Well-defined</td>
<td>None</td>
<td>Homogeneous/None</td>
<td>None</td>
</tr>
<tr>
<td>9/35/F</td>
<td>None</td>
<td>5.1</td>
<td>R</td>
<td>Lobulated</td>
<td>None</td>
<td>Homogeneous/None</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: M, Male; F, Female; L, Left; R, Right; y, years.

Pathological findings

All patients were diagnosed with ACL by hematoxylin-eosin (HE) staining. Additionally, immunohistochemistry (IHC) was performed on the samples of two patients at our hospital. IHC had been used on the samples from 35 patients in the literature as well.

The gross specimens were found to be multilocular, thin-walled cystic lesions filled with serous fluid. Cyst walls were smooth without evidence of nodularity or solid components. Microscopy demonstrated lymphatic fluid and dilated lymphatic ducts (Figure 3A-C), which were lined by flat endothelial cells (Figure 3E). Calcification was found in 33 patients (47.8%, 33/69). The calcifications noted on CT images were also apparent in the gross specimens (Figure 3D). D2-40 showed immunoreactivity in 37 patient samples (100%, 37/37) in our cases (Figure 3F) and literature case reports.

CT findings

The CT findings from the 69 cases are summarized in Tables 1 and 2. Thirty-seven patients were located in the left adrenal gland and 33 were found in the right adrenal gland. One patient had bilateral tumors. The average diameter of the tumors was 6.7 cm (range: 2.0-20.0 cm). Three quarters of the lesions in this study had maximum diameters greater than 4 cm. Though prior literatures indicated that thirteen patients had thin septations, in our series no patients had septation visible on the CT examinations. Figures 4-7 are representative examples of ACLs.
Table 2. Summary of adrenal cystic lymphangioma cases in the literature

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>PN</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Symptoms</th>
<th>Size (cm)</th>
<th>Side</th>
<th>Calcification</th>
<th>Septation</th>
<th>D2-40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoeffel et al.</td>
<td>1999</td>
<td>1</td>
<td>F</td>
<td>22</td>
<td>AP</td>
<td>L:8.7, R:7.8</td>
<td>bilateral</td>
<td>None</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Longo et al.</td>
<td>2000</td>
<td>1</td>
<td>F</td>
<td>30</td>
<td>Right FP</td>
<td>4.8×4.5</td>
<td>R</td>
<td>Peripheral punctate</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Trojan et al.</td>
<td>2001</td>
<td>1</td>
<td>M</td>
<td>40</td>
<td>None</td>
<td>5.0×4.0</td>
<td>R</td>
<td>None</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Satou et al.</td>
<td>2003</td>
<td>1</td>
<td>M</td>
<td>46</td>
<td>Palpitation</td>
<td>7.0×1.0×3.0</td>
<td>L</td>
<td>Peripheral</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Garcia et al.</td>
<td>2004</td>
<td>1</td>
<td>F</td>
<td>22</td>
<td>AP</td>
<td>4.0</td>
<td>R</td>
<td>None</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Ates et al.</td>
<td>2005</td>
<td>1</td>
<td>F</td>
<td>26</td>
<td>Lumbago</td>
<td>7.0</td>
<td>R</td>
<td>None</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Bettaieb et al.</td>
<td>2007</td>
<td>1</td>
<td>F</td>
<td>22</td>
<td>AP</td>
<td>3.5</td>
<td>L</td>
<td>None</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Chien et al.</td>
<td>2008</td>
<td>7</td>
<td>5F/2M</td>
<td>48 (31 to 59a)</td>
<td>None, 2 FP, HT, DN, mass</td>
<td>5.0 to 18.0a</td>
<td>4R/3L</td>
<td>4/7</td>
<td>None</td>
<td>7/7</td>
</tr>
<tr>
<td>Ellis et al.</td>
<td>2011</td>
<td>9</td>
<td>6F/3M</td>
<td>43 (28 to 56a)</td>
<td>3 None, 2 HT, AP, FP, BP, hematuria</td>
<td>4.9 (2.0 to 13.5a)</td>
<td>6R/3L</td>
<td>3/9</td>
<td>-</td>
<td>9/9</td>
</tr>
<tr>
<td>Cakir et al.</td>
<td>2012</td>
<td>2</td>
<td>2M</td>
<td>56/46</td>
<td>HT, Flank discomfort</td>
<td>7.0/3.0</td>
<td>R/L</td>
<td>1/2, cyst wall and septae</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Makri et al.</td>
<td>2012</td>
<td>2</td>
<td>F/M</td>
<td>40/40</td>
<td>AP</td>
<td>8.0/20.0</td>
<td>2L</td>
<td>None</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>2013</td>
<td>1</td>
<td>F</td>
<td>45</td>
<td>None</td>
<td>3.0×2.7</td>
<td>L</td>
<td>None</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Akand et al.</td>
<td>2013</td>
<td>1</td>
<td>F</td>
<td>44</td>
<td>Flank and AP</td>
<td>8.5×9.5</td>
<td>L</td>
<td>None</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Sourial et al.</td>
<td>2013</td>
<td>1</td>
<td>F</td>
<td>52</td>
<td>None</td>
<td>-</td>
<td>L</td>
<td>None</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Sallami et al.</td>
<td>2013</td>
<td>1</td>
<td>F</td>
<td>29</td>
<td>Lumbago</td>
<td>3.5×6.0×5.0</td>
<td>R</td>
<td>Punctate</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Secil et al.</td>
<td>2013</td>
<td>1</td>
<td>F</td>
<td>42</td>
<td>-</td>
<td>-</td>
<td>L</td>
<td>None</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Aoyama et al.</td>
<td>2014</td>
<td>1</td>
<td>F</td>
<td>47</td>
<td>-</td>
<td>-</td>
<td>L</td>
<td>Calcified septum</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Blanchard et al.</td>
<td>2014</td>
<td>1</td>
<td>F</td>
<td>23</td>
<td>AP and loin tenderness</td>
<td>5.2×2.5×2.7</td>
<td>R</td>
<td>None</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Jung et al.</td>
<td>2014</td>
<td>1</td>
<td>F</td>
<td>79</td>
<td>Epigastric discomfort and immovable mass</td>
<td>13.0×8.0</td>
<td>L</td>
<td>Luminal</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Zhao et al.</td>
<td>2014</td>
<td>3</td>
<td>3M</td>
<td>50 (41 to 66a)</td>
<td>HT, hematuria, hyperthyroidism</td>
<td>3.2 (2.5 to 4.6a)</td>
<td>3L</td>
<td>3, Stippled</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>2014</td>
<td>1</td>
<td>F</td>
<td>37</td>
<td>Fever</td>
<td>9.0×10.5</td>
<td>R</td>
<td>Spots</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nasir et al.</td>
<td>2015</td>
<td>1</td>
<td>M</td>
<td>-</td>
<td>Left scrotal pain</td>
<td>5.5×3.7</td>
<td>L</td>
<td>Cyst wall and luminal</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Joliat et al.</td>
<td>2015</td>
<td>1</td>
<td>F</td>
<td>38</td>
<td>Epigastric pain</td>
<td>13.4×7.2×5.2</td>
<td>L</td>
<td>None</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>2015</td>
<td>1</td>
<td>F</td>
<td>44</td>
<td>DN, headache</td>
<td>5.5×3.0</td>
<td>R</td>
<td>None</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Hodish et al.</td>
<td>2015</td>
<td>1</td>
<td>M</td>
<td>59</td>
<td>Hyperhidrosis</td>
<td>2.2×2.2</td>
<td>L</td>
<td>None</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Geramizadeh et al.</td>
<td>2015</td>
<td>1</td>
<td>F</td>
<td>43</td>
<td>HT</td>
<td>2.5×2.5×1.0</td>
<td>L</td>
<td>None</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Gao et al.</td>
<td>2015</td>
<td>8</td>
<td>5F/3M</td>
<td>45.5 (23 to 62a)</td>
<td>None, 3 HT, lumbar pain, micturition</td>
<td>1.0 to 5.9a</td>
<td>4R/4L</td>
<td>5/8</td>
<td>2</td>
<td>1st, 7th</td>
</tr>
<tr>
<td>Bosnak et al.</td>
<td>2015</td>
<td>1</td>
<td>M</td>
<td>5</td>
<td>AP</td>
<td>3.5×4.0</td>
<td>R</td>
<td>None</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Rowe et al.</td>
<td>2016</td>
<td>7</td>
<td>4F/3M</td>
<td>47 (37 to 56a)</td>
<td>None, FP, hematuria</td>
<td>4.0 (2.5 to 6.0a)</td>
<td>5R/2L</td>
<td>6/7</td>
<td>2</td>
<td>7/7</td>
</tr>
</tbody>
</table>

Notes: a, Range; Age (years); Size (cm). Abbreviations: F, female; M, male; PN, patient number; LR, laboratory test; VMA, vanillylmandelic acid; a, range; **”, not available; AP, abdominal pain; FP, flank pain; HT, hypertension; BP, back pain; DN, Dizziness.
All the tumors were well-circumscribed ovoid masses with an overall low-attenuation of its internal contents (Figure 5A). On contrast-enhanced images, the internal contents of the lymphangiomas were not quantitatively or visually enhanced (Figures 4-6). In some cases, a residual adrenal gland was visible (Figures 5B, 5C, 6B). Some adrenal lymphangiomas (47.8%; 33/69) included in this report contained punctate or nodular calcifications (Figures 4 and 7).
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Figure 3. Hematoxylin-eosin (HE) stains of patients 4 (A: ×40; B: ×100), 6 (C: ×100), and 7 (D, E: ×100), and D2-40 immunohistochemistry (IHC) stains of the seventh patient (F: ×100). Lymphatic fluid (black arrows) and dilated lymphatic ducts (black stars) were observed in (A-C), while calcification was shown only for the seventh patient (D: black arrowhead). Photomicrograph shows lymphangiomas lined by flattened endothelial cells with no significant atypia (E: black arrowhead). The IHC of D2-40 presents a positive result (F: black arrowhead).

Figure 4. CT images of a 27-year-old man with a left-sided unilocular adrenal lymphangioma. (A-C): Contrast-enhanced axial (A), coronal (B), and sagittal (C) arterial phase computed tomography (CT) images show a lymphangioma with scattered peripheral calcifications (white arrows).

Treatments and prognosis

Our entire series of patients underwent surgery. At our hospital, two patients with hypertension reported normalization of blood pressure levels after surgery. The others received routine postoperative clinical follow-ups and were determined to have no complications and no specific need for further imaging.

Discussion

Etiology and pathogenesis

Lymphangiomas arise from abnormal proliferation of the lymphatic vessels. Specifically, they are thought to result from a blockage of lymphatic flow and the development of lymphangiectasis [33]. This phenomenon could be related to abdominal trauma, surgery, radiotherapy, congenital malformations, or obstructions secondary to inflammatory processes, such as infections [33].

Clinical presentation

ACLs are usually asymptomatic and tend to be identified accidentally at autopsy [1]. However, such a finding is becoming increasingly common with the widespread use of imaging techniques [9, 13, 16, 21, 29]. This tumor occurs more frequently in women and may occur at
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Any age, with a peak in the third to sixth decades of life [1]. In this study, the patients included 26 men and 43 women, age range from 5 to 79 years, with a mean age of 40.3 years. This pattern of occurrence may be related to hormones. These lesions are generally unilateral and no significant predilection for a particular side could be found [28].

The most common symptom a patient will present with is abdominal pain. However, this is not specific to the disease and does not distinguish it from other adrenal lesions, especially when the patient has a history of other known abdominal diseases. Hypertension is the second most frequent symptom with which a patient will present. In the reported cases, there are some other nonspecific symptoms, such as hematuria, fever, and hyperhidrosis [6, 26-31, 34]. These manifestations may be caused by mass effect [28].

Pathological findings

The final diagnosis of ACL relies on pathology. Gross pathology showed that the lesions were composed of dilated lymphatic channels con-

Figure 5. CT images of a 35-year-old man (patient 1) with a left-sided adrenal lymphangioma. Non-enhanced axial (A) CT image shows an ovoid, well-circumscribed lesion with overall low-attenuation internal contents (white arrows). Contrast-enhanced coronal (B) and axial (C) multiple-phase CT images show non-enhancing contents and residual adrenal gland.

Figure 6. CT images of a 35-year-old woman with a right-sided unilocular adrenal lymphangioma. Contrast-enhanced axial (A), coronal (B), and sagittal (C) arterial phase CT images show a well-defined lesion with an oval shape, low-attenuation, and non-enhancing contents (white arrows).

Figure 7. CT images of a 40-year-old woman with right-sided adrenal lymphangioma. Non-enhanced axial CT image shows punctate and nodular peripheral calcifications (white arrow).
taining serous fluid. In addition, calcification has been reported in 15%-30% patients [28]. In this study, calcification was found in 33 patients (47.8%, 33/69).

Microscopic pathology showed that the lesions were lined by flattened, simple endothelial cells, and immunohistochemistry revealed expression of CD31 and D2-40 (a lymphatic endothelial marker) [27, 28]. CD31 is expressed on both blood vessels and lymphatic endothelium, while D2-40 immunoreactivity is restricted to lymphatic endothelium. Therefore, D2-40 is a specific marker for lymphatic origin and may be considered as a specific IHC marker for the histopathological diagnosis of ACL.

CT findings

On CT images, an ACL appears as a hypo-attenuated, well-circumscribed cystic lesion without an internal enhancement that is at or near fluid attenuation. Although previous literatures indicated that these lesions may have multiple thin septations [25-29], in our series no patients had ACLs with visible septa when examined by CT. In our cases, the mild post-contrast enhancement reported on the adrenal CT scan was primarily enhancement of the residual adrenal gland.

Multiple reports have revealed that adrenal lymphangiomas have been misidentified as originating from an adjacent organ, such as a pancreatic tail or kidney [9, 16, 27]. Fortunately, multi-planar reconstruction can partially resolve this problem, which was common in our cases.

On CT images, well-circumscribed, thin surrounding walls without solid components or nodularity may be suggestive of benign lesions. However, CT findings of ACL are difficult to distinguish from other cystic lesions of the adrenal gland, given the shared characteristics of low attenuation and its non-enhancing nature. So a diagnosis of ACL is still very difficult to make.

A variety of cystic adrenal lesions, including pseudocysts, endothelial cysts, lipid-rich adrenal adenomas, parasitic cysts, epithelial cysts, cystic cavernous hemangiomas, and cystic pheochromocytomas, should be included in the differential diagnosis. As previously noted, endothelial cysts subsume the cystic lymphangiomas [19, 20]. Lipid-rich adrenal adenomas generally show significant enhancement and a rapid wash-out [35]. Most adenomas also show a significant decrease in signal intensity on out-of-phase images [36]. Adrenal pseudocysts are considered to result from a prior hemorrhage and subsequent clot formation within a normal adrenal gland secondary to trauma, a bleeding disorder, burns, shock, or toxemia [37]. Hydatid cysts are seen in patients that live in an endemic place for echinococcosis, and are characterized by a floating membrane, or daughter cysts, and mural or septal calcifications [37].

Furthermore, septal calcification can be present in ACLs, while peripheral calcification is seen more often with pseudocysts and parasitic cysts [37]. In some patients, adrenal tuberculosis was highly suspected due to large-scale calcifications that were observed on the CT scan. Lastly, an entirely cystic cavernous hemangioma and pheochromocytoma may have an appearance mimicking adrenal lymphangioma [27, 38].

Treatments and prognosis

A study by Neri and Nance reported a 7% incidence of malignancy in their literature review of over 600 cases of adrenal cysts [23]. However, our entire series of patients underwent surgery for lesions that ultimately proved to be benign. Notably, three-quarters of the lesions in this study were larger than 4 cm in maximum diameter, and lesions of that size would likely be resected given the potential concern for malignancy [29]. Smaller lesions appear to have been resected primarily because of the uncertainty in clinical radiographic interpretations. Patients’ blood pressure returned to normal after removal of the adrenal mass. Thus, the management strategy is influenced by functional status of the cyst and the possibility of incidental malignancy.

Routine repeat imaging was not performed in most patients, perhaps because most patients had a definitive, benign pathologic diagnosis. In the literature, there was an ACL case with significant growth that was removed by transperitoneal laparoscopy [3]. The other patients had routine postoperative clinical follow-ups and were deemed to have no complications and no specific need for further imaging.
Limitations
Our study had some limitations. First, because of the retrospective nature of our study and the clinical silence of small-sized lesions, most small lesions did not require resection; hence, they were not captured in our search of the pathology database. This created a bias in our analysis by making it appear as though these small benign-appearing lesions were routinely resected. Second, the limited pathology data did not allow for a detailed radiographic-histopathological correlation, which would have helped explain the variable CT appearance of ACLs.

Conclusions
Although rare, ACLs should be included in the differential diagnosis when an adrenal lesion observed in a woman is asymptomatic, measures greater than 4 cm, and appears as a well-defined cystic mass with calcifications and non-enhancement patterns. Furthermore, D2-40 is a specific IHC marker for the histopathological diagnosis of ACL. The final diagnosis always requires the careful integration of the histology with the clinical and radiologic findings.

Acknowledgements
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Disclosure of conflict of interest
None.

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