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Running head: Benign vascular tumors, cysts and pseudocysts of the adrenal gland
Abstract

Benign adrenal vascular tumors, cysts and pseudocysts are a heterogeneous group of relatively uncommon entities that may pose diagnostic challenges radiologically and pathologically. However, there are only a few small cases series, systematically characterizing the clinicopathologic features of these lesions. We identified 55 cases of benign adrenal vascular tumors, cysts and pseudocysts (23 pseudocysts, 17 hemangiomas, 8 lymphangiomas, 6 angiomatous endothelial cysts and 1 arteriovenous malformation) from a multi-institutional Urologic Pathology database between 2000-2017, and retrospectively analyzed their clinicopathologic features. We found that these lesions have a female predominance and the majority are right-sided. These lesions may occur simultaneously with other adrenal tumors associated with hormonal hypersecretion. A substantial portion of pseudocysts were semi-solid or solid with no fluid collection, mimicking a solid adrenal tumor, and resulting in adrenalectomy. In addition, a small proportion of benign vascular lesions may have coexisting epithelial tumors, requiring extensive specimen sampling and thorough microscopic examination.

Keywords: Adrenal gland; vascular tumor, cyst, pseudocyst; hemangioma; lymphangioma; angiomatous endothelial cyst; vascular malformation
1. Introduction

Neoplasms such as adenomas, pheochromocytomas and adrenocortical carcinomas represent the most common tumors of the adrenal gland. Primary adrenal vascular tumors, cysts and pseudocysts are relatively rare, occasionally presenting with non-specific clinical findings, and are thus underrecognized. Benign adrenal vascular tumors, cysts and pseudocysts comprise a group of lesions characterized by significant heterogeneity. This group may include subclinical benign lesions such as pseudocysts, endothelial lined cysts (angiomatous and lymphangiomatous cysts), hemangioma and vascular malformations. However, the frequency of detection of benign adrenal vascular tumors, cysts and pseudocysts is increasing due to improved radiologic imaging techniques. It is generally accepted that both vascular and epithelial lesions may be large, and emit heterogeneous signals, causing a major diagnostic dilemma for radiologists. As a result, surgical excision of these lesions is increasing. The evaluation and classification of adrenal vascular tumors, cysts and pseudocysts remain a challenging area in adrenal pathology not only because these lesions are rare and often display overlapping morphologic features, but because the lesions are often obscured by the extensive hemorrhage.

To date, there are only a few case series and case reports on benign adrenal vascular tumors, cysts and pseudocysts [1-13]. In reported case cohorts, the emphasis had focused on differential diagnosis of benign adrenal vascular lesions versus epithelial neoplasms in a setting of cystic lesions or hemorrhagic lesions of the adrenal gland [3,5-7]. Herein we present the heterogeneity of these lesions and report 55 cases of benign
adrenal vascular tumors, cysts and pseudocysts with their major clinical and histological characteristics.

2. Materials and methods

A search was made through a multi-institutional electronic database of Urologic Pathology files and consult cases for benign vascular tumors of the adrenal gland between 2000-2017. Macroscopic pathologic features of the cases were obtained through review of the pathology reports and gross photographs. Cases with only “isolated” intra-adrenal hemorrhage were excluded from the study. Hematoxylin and eosin (H&E)–stained sections and available immunohistochemical stains of each case were reviewed and the original diagnosis was confirmed. Non-vascular lesions if simultaneously present were also documented. Patient demographics, clinical presentations, tumor radiologic features and follow-up data were obtained. This study was completed following the guidelines of and with approval from our Institutional Review Boards.

3. Results

Search of databases retrieved 1439 adrenal gland specimens and identified 55 (3.8%) cases with benign adrenal vascular tumors, cysts and pseudocysts. Forty-seven cases were from the routine surgical pathology services and 8 cases were from the expert consultation services. All cases were adrenalectomies. There were 23 (42%) cases of pseudocysts, 17 (31%) cases of hemangiomas, 14 (25%) cases of endothelial cysts including 8 (14%) cases of lymphangiomas and 6 (11%) cases of angiomatous endothelial cysts, and 1 (2%) case of arteriovenous malformation. The clinicopathologic features of all cases are summarized in Tables 1 and 2.
3.1. Adrenal pseudocyst

Pseudocyst was the most common lesion in this study. The mean age of the 23 patients was 49 years (range: 19-71 years). There were 14 (61%) female patients and 9 (39%) male patients. There were 10 Caucasian patients, 11 African American patients, and 2 Asian patients. There was a slight right-side predominance with 13 cases on the right and 10 on the left. Clinically, the most common presentation was vague abdominal/flank/back pain, particularly in patients with large lesions, presumably due to compression of surrounding viscera by the lesion. Four (17%) patients recalled a remote history of trauma. Two (8%) of 23 pseudocysts were concurrent with benign adrenal cortical adenoma and pheochromocytoma, and had associated glucocorticoid excess and elevated metanephrine, respectively. One (4%) of 23 was found during work-up for renal cell carcinoma. The remaining 18 lesions were incidentally found during imaging studies for unrelated causes.

Radiologic studies often exhibited a broad range of appearances described as a suprarenal cystic, mixed or a predominantly solid mass. Focal calcification was often seen. All cases were unilateral. There was no spontaneous or traumatic rupture in all cases. Grossly, the mean size of the pseudocysts was 6.5 cm (range: 1.6-23.2 cm). The pseudocysts had a thick, smooth or partially granular wall with no true cyst lining appreciated. The cyst contents, as demonstrated on imaging, were variable in appearance. Eight cases had partial or complete classic pseudocyst cavity and fluid collection, containing variable amount of dark green to serosanguineous fluid (up to 750 ml). Eleven cases were semisolid and heterogeneous with some areas composing of yellow tan to
green gelatinous material while other areas consisting of brown red hemorrhagic material with a sponge-like texture (Figure 1a).

Four cases showed predominantly solid appearance with extensive necrosis and hemorrhage with organization. In those cases, abundant inspissated tan-brown chalky material filled the cystic cavity. The larger pseudocysts usually displaced the adrenal gland to the periphery, forming a thin rim of golden yellow adrenal tissue. Histologically, all pseudocysts were devoid of inner wall lining. The cystic wall consisted of a hyalinized fibrous capsule containing nests of entrapped bland adrenal cortical cells. Amorphous cyst contents were composed of a mixture of organizing serum, blood clots and fibrin (Figure 1b). In cases with infarction or necrosis, abundant cholesterol clefts, pigment-laden histiocytes and organization were present.

3.2 Hemangioma

Hemangioma was the second most common lesion in this study. Demographically, all 17 patients were adults at time of diagnosis with a mean age of 65 years (range: 48-87 years). There were 8 Caucasian patients, 8 African American patients, and 1 Asian patient. There were 13 female and 4 male patients. All hemangiomas were unilateral, more frequently located on the right side (12 right-sided and 5 left-sided). Clinically, 2 of 17 hemangiomas were concurrent with adrenal cortical adenoma and had associated mineralocorticoid and glucocorticoid excess. One of 17 hemangiomas was found during work-up for renal cell carcinoma. The remaining lesions were incidentally found during imaging studies for unrelated diseases.
For non-incidental hemangiomas, the most common symptoms were pain (51%) and hypertension (22%). Pain was vague and nonspecific, localized in the back, flanks, right upper quadrant, or abdomen. Hypertension was not refractory and well controlled with medications. Radiologically, CT imaging usually showed a solid or cystic mass with peripheral nodular contrast enhancement and partial central filling isodense to blood. MRI imaging often demonstrated a heterogeneous lesion which had large hemorrhagic areas with intrinsic bright T1 and dark T2 signal intensity and non-hemorrhagic areas with hyperintense T2 and gradual enhancement. Speckled calcifications were radiologically detected in some cases. Surgical removal was achieved by total adrenalectomy in all patients.

Grossly, the mean size of the tumors was 3.5 cm (range: 1.5-8.3 cm). Four of 17 hemangiomas presented as a pure solid, well-defined, dark red to white-tan mass with a spongy cut-surface. Thirteen of 17 cases had focal cystic changes. Calcifications were observed in 10 of 17 cases. Large calcifications were usually centrally located with an irregular, stellate branching pattern, while microcalcifications were speckled throughout the lesion. Additional gross findings included variable fibrosis, thrombosis, hemorrhage, and necrosis. In small hemangiomas, cortical or subcapsular origin was easily appreciated while in large tumors, the majority of the adrenal medulla was often replaced by the lesion with a rim of residual tan yellow normal appearing adrenal parenchyma (Figure 2a).

Histologically, all cases were characterized by variably sized, dilated vascular channels lined by a single layer of endothelium, and filled with red blood cells (Figure 2b). The vascular channels were separated by variable fibrous stroma, which occasionally
had entrapped benign adrenal epithelial cells. Immunohistochemical stains showed the endothelial cells were positive for CD31, CD34, ERG and negative for D2-40 and pancytokeratin. All patients had no evidence of recurrent symptoms with a median follow-up of 4 years (range: 7 months-11 years).

3.3. Endothelial cysts

Endothelial cysts were the third most common adrenal lesion in this study. They were subclassified as lymphangiomatous cysts and angiomatous cysts.

3.3.1 Lymphangiomatous cysts

Lymphangiomatous cysts were more common in our retrospective review. Demographically, all 8 patients were adults at time of diagnosis with a mean age of 40 years (range: 25-51 years). There were 5 Caucasian patients and 3 African American patients. There was a female predominance with 6 female and 2 male patients identified. All lymphangiomatous cysts were unilateral with 5 right-sided and 3 left-sided. Clinically, 2 patients manifested flank pain or discomfort, 1 patient was reported to have subclinical Cushing’s syndrome, and the remaining 5 patients were asymptomatic and incidentally found with adrenal cystic lesions. Imaging studies revealed a think-walled unilocular or multilocular cystic adrenal mass.

Grossly, the mean size of the cysts was 4.9 cm (range: 1.2-8.0 cm). All cysts displayed a wrinkled and glistening tan-pink membranous internal lining. The cystic contents were clear to light yellow proteinaceous fluid. There was no fibrous capsule or papillary excrescences identified (Figure 3a). The remaining adrenal parenchyma was usually unremarkable. Histologically, the lesions were composed of small, capillary-sized lymphatic channels lined with flat bland endothelial cells. Walls of dilated lymphatic
channels contained lymphoid aggregates, entrapped normal-appearing adrenal cortical cells and rarely proliferation of smooth muscle cells. The cystic contents were proteinaceous fluid containing no marked red blood cells (Figure 3b). Coalescence of dilated lymphatic channels formed cystic change. Immunohistochemical staining results showed that the vessel lining was positive for D2-40, ERG, CD31 and negative for pancytokeratin (Figures 3c-3f). No evidence of recurrence was found in any of the patients.

### 3.3.2 Angiomatous cysts

There were six cases of angiomatous cysts identified. The mean patient age at diagnosis was 65 years (range: 58-69 years). There was a female predominance with 4 females and 2 males. There were 3 African American patients and 3 Caucasian patients. All angiomatous cysts were unilateral with 4 right-sided and 2 left-sided. Three patients presented with moderate flank or abdominal pain with one patient having an adrenal adenoma identified during further work-up, with associated hormone hypersecretion. One case was an incidental finding. CT or MRI imaging usually showed a heterogeneous cystic adrenal mass, which demonstrates lacy, delayed, peripheral enhancement.

Grossly, the mean size was 5.1 cm (range: 2.9-7.0 cm). A thin fibrous capsule was appreciated in 4 of 6 cases. The angiomatous cysts were heterogeneous with some cystic areas filled with blood coagulum and some areas showing marked infarction, hemorrhage and organization (Figure 4a). There were no areas or papillary excrescences identified. The cysts significantly compressed the surrounding unremarkable adrenal parenchyma. Histologic findings showed thin-walled, cystic space lined by a single layer of bland, flattened endothelial cells (Figure 4b). One case had focal papillary endothelial
hyperplasia (Figure 4c). Immunohistochemical staining results showed that the endothelial lining was positive for CD31, ERG, CD34 and negative for D2-40 and pancytokeratin. These patients had no evidence of recurrent symptoms or adrenal mass with a median follow-up of 3 years (range: 1-6 years).

### 3.4 Arteriovenous malformation

Only one case was identified in this study. The patient was a 69-year-old African American female, who presented with a large abdominal mass on the right side. The patient had an outside biopsy diagnosis of metastatic well differentiated neuroendocrine tumor of the liver. Clinically, the adrenal mass was thought to represent a metastasis from the liver primary. However, MRI imaging revealed a very large hemorrhagic adrenal mass (14.9 x 12.1 x 9.7 cm) with peripheral solid heterogeneous non-enhancing components, suspicious for nonfunctioning adrenocortical neoplasm. Right adrenalectomy was performed.

Grossly, the lesion was cystic and hemorrhagic. The capsule of the cyst was thick and smooth. The cystic cavity was filled with red-brown friable material and thick serosanguineous fluid (Figure 5a). No papillary areas were identified. The majority of the adrenal gland was replaced by the lesion with only a small portion of relatively normal appearing adrenal parenchyma left. A glistening tan well-circumscribed nodule (0.5 cm in greatest dimension) was identified in adrenal parenchyma. Histologically, the lesion was predominantly composed of a central organizing hemorrhage with admixture of malformed arteries and venules as well as associated reactive fibrosis and inflammatory changes at the periphery (Figures 5b and c). The small nodule in adrenal parenchyma was consistent with an adrenocortical adenoma. No evidence of carcinoma, hemangioma or
angiosarcoma was identified. The patient was followed up 6 months and had no evidence of adrenal recurrence or metastasis.

4. Discussion

Adrenal vascular tumors, cysts and pseudocysts consist of a heterogeneous group of uncommon entities. This study represents the largest series to date on benign adrenal vascular tumors, cysts and pseudocysts, and presents a comprehensive review of the clinicopathologic features and follow-up (Tables 1 and 2). The incidence of benign vascular lesions is approximately 4% of all adrenal masses in this case cohort. Pseudocysts and hemangiomas are found to be two most common entities, comprising 42% and 31% of all study cases, respectively. Demographically and clinically, benign adrenal vascular lesions tend to have a female predominance and right-sided. There were no significant racial differences identified in any of the vascular lesions. The patients often presented with vague symptoms of abdominal/flank/back pain and those with concurrent adrenocortical adenomas had elevated mineralocorticoid and/or glucocorticoid levels. Although adrenal vascular lesions are non-functioning and do not cause endocrinology abnormalities, vascular proliferations within the lesions may lead to enhanced entry of active endocrine metabolites into the blood flow [14].

We found that vascular lesions may appear very similar radiologically and grossly to other primary adrenal tumors due to secondary changes such as hemorrhage, thrombosis, necrosis, organization and calcifications. Therefore, a complete histopathological and immunophenotypic assessment of these lesions following adrenalectomy is essential to avoid potential diagnostic pitfalls. In addition, a small portion of benign vascular lesions and pseudocysts may have concurrent primary adrenal
tumors. Pathologists should be aware that, in the setting of vascular lesions of the adrenal gland, extensive sampling and thorough microscopic examination is necessary in order to exclude the possibility of coexisting underlying adrenal tumors.

Pseudocysts considered as a variant of adrenal vascular cysts, were the most common benign entity in this study [6]. They occur in all age groups but most frequently in the forth to fifth decades. The reported mean diagnostic age of 8 cases was 46 years with lesion size ranging from 0.9 to 17 cm; in our case series, the mean age of 23 cases was 49 years with lesion size ranging from 1.6 to 23.2 cm [15]. The pathogenesis is believed to have a vascular origin, arising from organization of a previous traumatic hematoma or a toxic, infectious or abnormal hemorrhage [6]. All pseudocysts were unilocular, encapsulated, and devoid of inner wall lining and neoplastic epithelium. A substantial number of reported pseudocysts had well-defined fibrous cystic walls with variably sized cystic cavities and fluid collection with no predominant solid component [15]. However, pseudocysts may also be associated with concurrent adrenal tumors. The reported percentage ranged from 7% to 19% [6,7], and was 9% in our study. This highlights the importance of extensive pathologic sampling of adrenalectomy specimen and a diligent search for other adrenal neoplasms in the setting of adrenal pseudocysts.

Hemangioma was the second most common benign adrenal lesion in this study. It mainly affects females in the fifty and sixty decades. The reported median age at diagnosis was 61.8 years with average lesion size of 4.8 cm; in our case series, the mean age of 17 cases was 65 years with average lesion size of 3.5 cm [7]. Clinically, 2 of 17 cases had concurrent hormonal hypersecretion. Radiologically, CT imaging usually revealed a solidary or cystic mass with peripheral nodular contrast enhancement. Usually
smaller hemangiomas were incidentally found during the evaluation of unrelated conditions or histopathologic examination of adrenal epithelial tumors. Unlike their more common counterparts in the liver and kidney, capillary and anastomosing types in adrenal gland are very rare with only limited number of case reports [13]. All 17 cases in current study were cavernous type, which is the most common histological type in adrenal hemangioma. Intratumoral heterogeneity with associated cystic features was a common finding in our case series. The cystic or mixed cystic and solid appearance of hemangioma produces overlapping features with pseudocyst and epithelial tumors and therefore should be considered in the differential diagnosis of a cystic or hemorrhagic adrenal mass.

In contrast to other vascular lesions or cysts, lymphangiomatous cysts mainly affects younger-aged adult females with a reported mean age of 42 years at diagnosis and an average lesion size of 4.9 cm [9]. In our case series, the mean age of 8 cases was 40 years with an average lesion size of 4.8 cm. Clinically, it was less commonly associated with endocrinology abnormalities. Only one case was reported to have subclinical Cushing’s syndrome. Lymphangioma-like adenomatoid tumor is the main histologic mimic of lymphangioma [16-17]. Although it is positive for D2-40, it is also positive for other mesothelial markers such as calretinin and WT-1. A complete immunophenotypic assessment of the lesion is essential to avoid misdiagnosis.

A few case series and reports of angiomatous endothelial cysts have been documented in the literature, and this entity may be associated with calcifications and other benign adrenal neoplasms, including pheochromocytoma [18-20]. We had 6 cases in this study. As other benign vascular lesions, angiomatous endothelial cyst had a slight
female predominance and a right-side preference. There were no racial preferences. Similar to hemangioma, it mainly affected females in the fifth and sixth decades. The mean age at diagnosis was 65 years in our series. The major differential diagnostic entities include pseudocysts and other cystic/vascular lesions, and cystic epithelial tumors.

The single case of adrenal arteriovenous malformation in our series was a large 14.9 cm abdominal mass in a 69-year-old African American female. Clinically, it was thought to be a metastatic liver mass given the patient’s known history of well differentiated neuroendocrine tumor. The patient did not have any history of congenital vascular malformations and also had no infections, amyloidosis or metastatic tumor growth in the adrenal gland. Interestingly, patients with adrenal arteriovenous malformations may subsequently develop adrenal hemorrhagic endothelial cysts [21].

In conclusion, benign adrenal vascular tumors, cysts and pseudocysts are a heterogeneous group of uncommon entities. They may have similar clinical, radiological and gross features with other benign and malignant adrenal neoplasms. The evaluation and classification of benign adrenal vascular tumors, cysts and pseudocysts remains a challenging area in adrenal pathology not only because these lesions are rare and often display overlapping morphologic features, but because the lesions may be obscured by extensive hemorrhage.
References


**Figure Legends**

Figure 1a: Gross photo of adrenal pseudocyst with unilocular, thick-walled capsule and filled with yellow green gelatinous material and brown red organized hemorrhage.

Figure 1b: Microscopic correlate of Figure 1a, showing absence of cystic lining (original magnification ×20).

Figure 2a: Cavernous hemangioma with a solitary, well-defined appearance and composed of white tan fibrous areas and dark red hemorrhagic areas.

Figure 2b: Microscopic correlate of Figure 2a, showing variably sized, dilated vascular channels lined by a single layer of vascular endothelium and filled with red blood cells (original magnification ×20).

Figure 3a: Lymphangiomatous cyst with unilocular, thin-walled cyst lined by a white pink inner cystic membrane.

Figure 3b: Microscopic correlate of Figure 3a, showing lymphatic channels lined with flat cells. Note entrapped bland cortical cell nests in the cyst wall (original magnification ×10).

Figure 3c: Immunohistochemical stain for D2-40 (Positive expression)

Figure 3d: Immunohistochemical stain for ERG (Positive expression)

Figure 3e: Immunohistochemical stain for CD-31 (Positive expression)

Figure 3f: Immunohistochemical stain for Pancytokeratin (Negative expression)
Figure 4a: Angiomatous cyst filled with blood coagulum, fibrin and organization;

Figures 4b and 4c: Microscopic correlate of Figure 4a, showing a single layer of vascular endothelial lining with focal area of papillary endothelial proliferation (original magnification ×20).

Figure 5a: Arteriovenous malformation with thick capsule and filled with red-brown friable material and thick serosanguineous fluid.

Figures 5b and c: Microscopic correlate of Figure 5a, showing admixture of malformed arteries and venules. (b: original magnification ×4; c: original magnification ×20)
Table 1
Clinical Features of Patients with Benign Adrenal Vascular Tumors, Cysts and Pseudocysts

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of cases</th>
<th>Mean age yrs (range)</th>
<th>Female/ male</th>
<th>Max. mean size cm (range)</th>
<th>Right/ left side</th>
<th>Concurrent hormonal hypersecretion</th>
<th>Concurrent adrenal tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocyst</td>
<td>23</td>
<td>49 (19-71)</td>
<td>14/9</td>
<td>6.5 (1.6-23.2)</td>
<td>13/10</td>
<td>2/23</td>
<td>2/23</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>17</td>
<td>65 (48-87)</td>
<td>13/4</td>
<td>3.5 (1.5-8.3)</td>
<td>12/5</td>
<td>2/17</td>
<td>2/17</td>
</tr>
<tr>
<td>Lymphangiomatous cyst</td>
<td>8</td>
<td>40 (25-51)</td>
<td>6/2</td>
<td>4.8 (1.2-8.0)</td>
<td>5/3</td>
<td>1/8</td>
<td>1/8</td>
</tr>
<tr>
<td>Angiomatous cyst</td>
<td>6</td>
<td>65 (58-69)</td>
<td>4/2</td>
<td>5.1 (2.9-7.0)</td>
<td>4/2</td>
<td>1/6</td>
<td>1/6</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>1</td>
<td>69/NA</td>
<td>1/0</td>
<td>14.9/NA</td>
<td>1/NA</td>
<td>1/1</td>
<td>1/1</td>
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Abbreviations: NA- Not applicable
Table 2
Histopathological Features of Benign Adrenal Vascular Tumors, Cysts and Pseudocysts

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cystic contents</th>
<th>Cystic wall/capsule</th>
<th>Entrapped cortical cells</th>
<th>Hemorrhage/thrombosis/necrosis/fibrosis/calcifications</th>
<th>Positive IHC</th>
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<tbody>
<tr>
<td>Pseudocyst</td>
<td>Serum, blood, fibrin, histiocytes, cholesterol clefts, fibrosis</td>
<td>Thick</td>
<td>Yes</td>
<td>Yes, common in large cyst</td>
<td>None</td>
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<tr>
<td>Hemangioma</td>
<td>RBCs</td>
<td>Thin</td>
<td>Rare</td>
<td>Yes</td>
<td>ERG CD31 CD34</td>
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<tr>
<td>Lymphangiomatous cysts</td>
<td>Proteinaceous fluid</td>
<td>Thin</td>
<td>Yes</td>
<td>Rare</td>
<td>ERG CD31 D2-40</td>
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<tr>
<td>Angiomatous cyst</td>
<td>Blood, fibrin</td>
<td>Thin</td>
<td>Yes</td>
<td>Yes, Common in large cyst</td>
<td>CD31 CD34</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>Blood, fibrin</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
</tr>
</tbody>
</table>
Highlights

- Benign adrenal vascular tumors, cysts and pseudocysts may pose diagnostic challenges radiologically and pathologically.
- We identified 55 cases of benign adrenal vascular tumors, cysts and pseudocysts.
- These lesions have a female predominance.
- The majority of benign adrenal vascular tumors, cysts and pseudocysts are right sided.
- These lesions may have coexisting tumors that may be associated with hormonal hypersecretions/endocrinologic abnormalities.
Figure 1