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Case Report

Incidental adrenal hemangioma clinically suspicious for malignancy: diagnostic considerations and review of the literature

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Abstract: Adrenal hemangiomas are rare lesions often found incidentally during unrelated diagnostic work-up. We report a case of a 67-year-old man with history of hypertension, hyperlipidemia, anemia, arthralgia, joint swelling and unexplained weight loss, which prompted imaging studies. Computed tomography scan revealed a 5.4 cm adrenal mass. The patient had no clinical manifestations of adrenal medullary or cortical hyperfunction. Urine and plasma metanephrines and aldosterone/renin ratio were within normal range. The patient was taking prednisone for hand and ankle swelling, precluding assessment for Cushing syndrome. Given the size of the lesion, the possibility of malignancy was considered, and the patient elected for surgical management. The left adrenalectomy specimen weighed 54 g and revealed a 4.9 cm tan-brown mass with congested cut surface and a thin rim of residual adrenal gland parenchyma. Histologic examination showed thick and thin-walled vessels intermingled with adrenocortical elements at the periphery characteristic of a hemangioma. Surgical resection is the mainstay treatment for large, isolated adrenal masses to exclude malignancy and prevent retroperitoneal hemorrhage. Herein, we report a case of adrenal hemangioma, review a variety of other diagnostic considerations occurring in the adrenal gland, and highlight useful distinguishing features to assist in accurate diagnosis.

Keywords: Adrenal gland, hemangioma, incidentaloma

Introduction

Hemangiomas are benign tumors most frequently encountered in the head and neck region and liver and more rarely at other sites including the adrenal gland. Clinically, large adrenal lesions raise concern for malignancy. Patients are either asymptomatic or may present with non-specific abdominal symptoms. Herein, we report a case of an incidental adrenal hemangioma presenting as a large mass suspicious for malignancy. We review the literature and discuss other entities that may be considered in the differential diagnosis, with emphasis on distinguishing features.

Case report

A 67-year-old man with history of hypertension, hyperlipidemia, anemia, arthralgia and joint swelling consulted for unexplained weight loss, which prompted imaging studies. Computed tomography (CT) scan revealed a 5.4 cm mass involving the adrenal gland (**Figure 1A**). The patient had no clinical manifestations of adrenal medullary or cortical hyperfunction, and urine and plasma metanephrines and aldosterone/renin ratio were within normal range. The patient was taking prednisone for hand and ankle swelling, precluding assessment for Cushing syndrome. Given the size of the lesion, the possibility of malignancy was considered, and the patient elected for surgical management. The left adrenalectomy specimen weighed 54 g and revealed a 4.9 cm tan-brown mass with congested cut surface and a thin rim of residual adrenal gland parenchyma (**Figure 1B**). Histologic examination of the surgical specimen showed thick and thin-walled vessels with areas of intermingled adrenocortical elements at the periphery in a hemorrhagic background (**Figure 1C**, **1D**). A diagnosis of adrenal hemangioma was made.

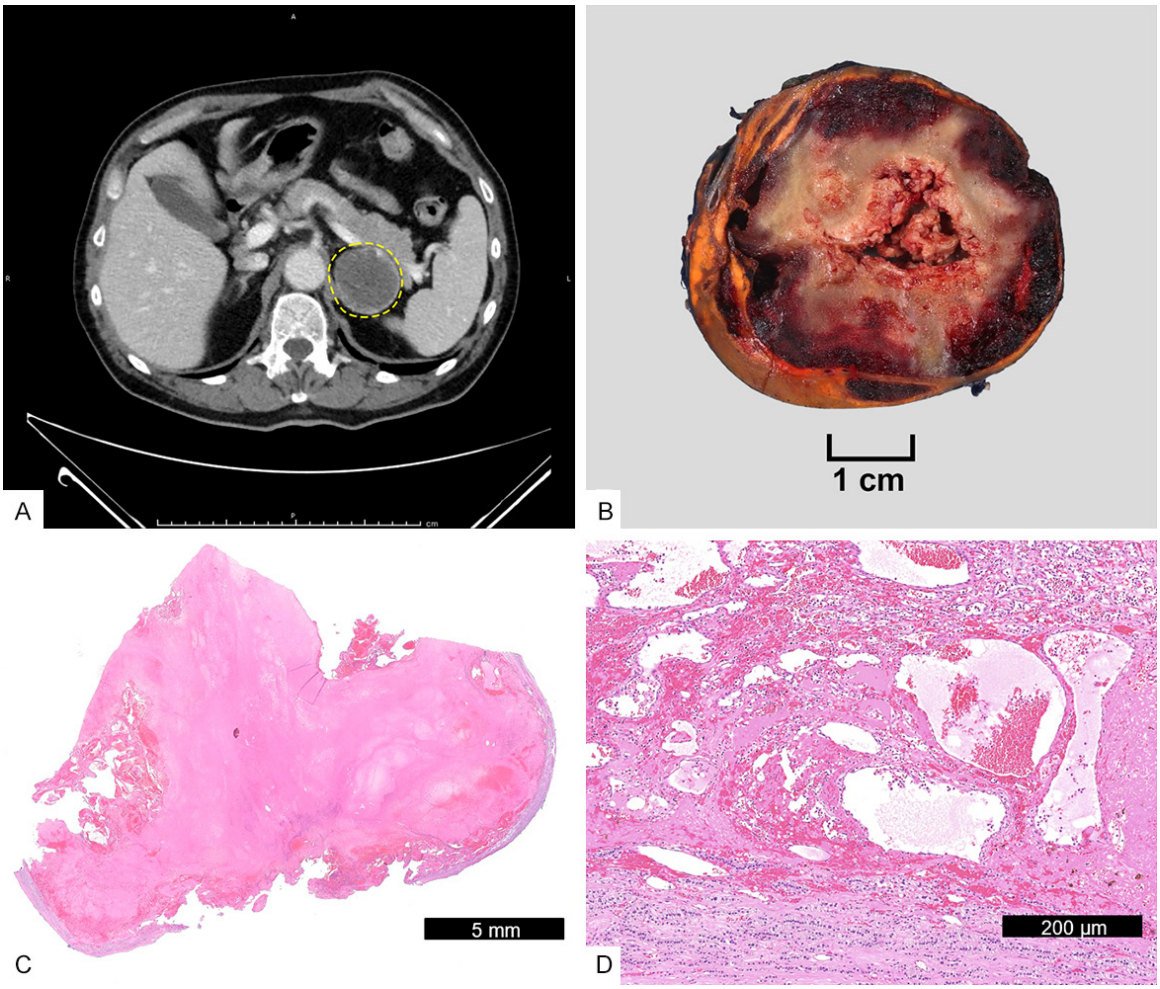

Figure 1. Hemangioma. (A) Computed tomography (CT) scan revealed a 5.4 cm mass involving the adrenal gland. (B) Gross photograph of adrenal hemangioma with a tan-brown and congested cut surface and a thin rim of adjacent residual normal appearing adrenal gland parenchyma. (C and D) Microscopy showing enlarged adrenal gland predominantly replaced by hemorrhage with variably sized, dilated vascular channels lined by a single layer of vascular endothelium and filled with red blood cells with areas of intermingled adrenocortical elements at the periphery. (C. Hematoxylin and eosin, × 2, original magnification, scale bar 5 mm; D. Hematoxylin and eosin, × 40, original magnification, scale bar 200 µm).

Discussion with differential diagnostic considerations

General features of hemangioma

Hemangiomas are exceedingly rare in the adrenal gland, first described by Johnson and Jeppsen in 1955 in a case found while searching for cause of severe hypertension [1]. Since that time 138 cases have been published in the English literature, the majority of which are individual case reports and a few case series [1-96]. It is also worth mentioning that some reports (approximately 35) have been published in non-English languages [97-130]. A few cases were associated with other pathology, including adenoma and hemangioendothelioma [12, 49, 85]. Other pathologies morphologically similar to adrenal hemangioma include pseudocysts, endothelial cysts, and arteriovenous malformations and are considered separately below.

Clinical findings

Of the cases previously reported, there was a slight female predominance. Our patient presented at a slightly older age than the mean age reported in the literature (67 years vs 60 years, range 19-84 years). Most cases were unilateral (right, 66; left, 56; bilateral, 1; laterality not specified, 15). Generally, adrenal hem-

Table 1. Summary of characteristics of previously reported cases of adrenal hemangioma in the English literature (*n=138*) [1-96]

Characteristics	n (%)*
Mean age (year) (*n=106*)	60 (range, 19-84)
Sex *(n=134)*	
Female	76 (55%)
Male	58 (42%)
Mean size (cm) (*n=108)*	10.1 (range, 1-42)
Laterality (*n=123)*	
Right	66 (53.7%)
Left	56 (45.5%)
Bilateral	1 (0.8%)
Mean weight (g) *(n=48)*	969 (range, 54-5000)
Presenting symptoms (*n=108)*	
Pain (epigastric, abdominal, flank, back, groin)	38 (35%)
Mass (abdomen, retroperitoneal, flank)	18 (17%)
Follow-up care for cancer	12 (11%)
Medical screening, surveillance	12 (11%)
Hypertension	8 (7%)
Urinary symptoms	7 (6%)
Gastrointestinal symptoms, nonspecific	6 (6%)
Endocrine pathology, nodular adrenal hyperplasia	2 (2%)
Syncope	2 (2%)
Anemia	2 (2%)
Night sweats, generalized fatigue	1 (1%)
Calcifications (*n=101)*	
Present	43 (43%)
Absent	58 (57%)

*Percentage calculated based on total number of cases in which clinical data was reported.

angiomas are asymptomatic or present with nonspecific abdominal symptoms. The majority of patients were incidentally detected (108) and clinical presentation was as follows: pain (38), mass lesion (18), follow-up care for cancer diagnosis (12, two with subclinical Cushing disease), medical screening and surveillance (12), hypertension (8, two associated with abnormal endocrine hyperfunction), urinary symptoms (7), nonspecific gastrointestinal symptoms (6), nodular adrenal hyperplasia (2), syncope (2), anemia (2), night sweats and generalized fatigue (1). Seven patients had suspected hemangioma by imaging (performed for pre-operative staging, abdominal/back pain, retroperitoneal mass or follow-up evaluation for malignancy at another site) [28, 37, 47, 69, 79, 82, 85]. A prior or presenting history of malignancy at other sites including bile duct, vulva, lung, breast, colorectal, gastric, and prostate has been described [13, 63, 69, 74, 86, 111, 112]. Preoperative hormone levels were normal with a few exceptions. Payne in 1869 [131] and Muller-Stuhler in 1933 [132] reported cases of bilateral hemangiomas at autopsy, the latter showing signs of adrenal insufficiency and later Lorenzon in 2013 [63] reported a case associated with subclinical hypercortisolism. Other adrenal hemangiomas associated with hyperfunction [29, 46, 56] or adrenal hyperplasia [34, 67] have been reported. Three cases of adrenal hemangiomas coexisted with hemangiomas from other sites, two in the liver and one in peripelvic fat of the ipsilateral kidney [21, 37, 52]. Summary of clinicopathologic characteristics from previously reported cases of adrenal hemangioma in the English literature are summarized in **Table 1**.

Gross features

Most adrenal hemangiomas are well-circumscribed and encapsulated masses, most measuring greater than 10 cm; however, sizes up to

42 cm have been reported [70]. They typically have a tan-brown, hemorrhagic cut surface with a soft consistency and may show cystic areas with presence of calcifications. In our review of the literature, the mass size and weight in our case was smaller than the mean mass size (4.9 cm vs 10.1 cm, range 1-42 cm) and mean adrenal gland weight (54 g vs 969 g, range 54-5000 g). Calcifications were present in 43 cases and absent in 58 cases.

Histopathology and immunohistochemistry

Hemangiomas are usually well-demarcated and characterized by dilated vascular channels lined by a single layer of vascular endothelium. Immunohistochemical findings include positivity for CD31, C34, and ERG.

Management

There is little consensus on management strategy of an incidental adrenal lesion. Size and functional status are two important factors that should be taken into consideration prior to initiating treatment. Many institutions recommend surgery for masses 3 to 4 cm in size [133, 134]. Most recommend removal of lesions greater than 4 cm [133, 135]. Observation and surveillance with serial CT scans and biochemical testing is recommended for lesions less than 4 cm in patients older than 50 years and in patients with hormonally inactive lesions less than 3 cm [136].

In the published literature to date, most cases were completely resected, except in four cases, three of which had prior or presenting history of malignancy at other sites. In one case, a partial resection revealed an 8 cm mass with plasma and urinary steroid abnormalities with uneventful follow-up of 4 weeks after surgery [29]. In another case, CT scan showed a heterogeneous mass measuring 3 cm; biochemical testing was not reported. In view of the small size and radiologically benign appearance, the patient was maintained on regular follow-up with ultrasound examination for increase in size [69]. One other case reported by Wilson et al [82] showed definite characterization by CT, PET, and MRI of a right adrenal adenoma (1.6 cm) and a left adrenal hemangioma (4.2 cm). Two additional cases reported by Foresti et al [85] presumed a diagnosis of an adrenal hemangioma-adenoma collision tumor. Both patients declined surgery and no change in size was noted after follow-up of 24 and 12 months, respectively. Follow-up of 72 cases showed no clinical evidence of recurrence (range 2 days-11 years).

Differential diagnosis

The development of adrenal hemangioma raises additional differential diagnostic considerations based on anatomic and pathologic similarities, ranging from nonneoplastic entities to malignant tumors, listed in **Table 2**.

Pseudocysts: Adrenal pseudocysts are cystic lesions within the cortex or the medulla of the adrenal gland, surrounded by a fibrous wall with no true epithelial lining. Pseudocysts account for 40% of reported adrenal cysts. Pseudocysts can occur from birth to 80 years, with peak prevalence between the third to sixth decade and a female to male ratio of 2:1. The majority of cases are asymptomatic; however, larger cysts may cause a compressive effect on adjacent organs, or cause abdominal symptoms as well as nausea and vomiting and can mimic an acute abdomen if rupture or bleeding occurs [137]. Overall, pseudocysts have a wide spectrum of appearances showing a solid, cystic, or mixed appearance in different imaging modalities. Calcification may be seen. Histologically, pseudocysts are typically unilateral, of varying sizes demonstrating a well-defined walled off cystic cavity lacking an epithelial lining. The cyst contains fluid or semi-solid amorphous material composed of clotted blood and fibrin (**Figure 2**). A thin rim of residual adrenal tissue may be found at the periphery. The distinction between a hemorrhagic pseudocyst from a cystic or degenerative adrenal cortical neoplasm (benign or malignant) may be challenging. The presence of fibrinoid thrombotic material versus necrotic tumor cells in the absence of autonomous hormone production can aid in the diagnosis [138]. In cases with rupture, an organizing process may be present with associated cholesterol clefts, admixed with pigment-laden macrophages.

Endothelial cysts: Endothelial cysts can be subcategorized into lymphangiomatous and angiomatous cysts, depending on histologic origin of endothelium. Lymphoangiomatous cysts are more commonly encountered (discussed below) [139].

Table 2. Differential diagnosis of adrenal hemangioma including histopathology and immunohistochemical features

	Histopathologic features	Summary of ancillary techniques
Hemangioma	Dilated vascular channels lined by a single layer of vascular endothelium	CD31, CD34, and ERG positive
Pseudocyst	Cyst devoid of inner wall lining Cystic wall, hyalinized fibrous capsule, may contain entrapped bland adrenal cortical cells Amorphous cyst contents composed of organizing serum, blood clot, and fibrin Abundant cholesterol clefts, pigment-laden macrophages	None
Endothelial cyst, Lymphangiomatous type	Lymphatic spaces lined by attenuated endothelium	D2-40 positive
Arteriovenous malformation	Presence of both arteries and veins, nerve bundles may be present	Histochemical stains: Movat pentachrome and elastin Immunohistochemistry: S100 for nerve and nerve fibers
Hemangioblastoma	Prominent capillary vasculature surrounded by stromal cells with vacuolated or lightly eosinophilic cytoplasm, stromal cell nuclei may be pleomorphic	Inhibin, aquaporin-1 positive, NSE (33%) in stromal cells PAX2, PAX8 negative
Angiosarcoma	Solid sheets or nests of epithelioid cells with cellular pleomorphism, increased mitotic activity, abundant amphophilic or eosinophilic cytoplasm, round to irregular vesicular nuclei, and accentuated nucleoli	CD31, CD34, FLI-1, and Factor VIII antigen positive

Lymphangiomatous cysts: Lymphangiomatous cysts can occur at all ages with a peak incidence between the third and sixth decades of life [140, 141]. These lesions primarily affect the neck, axillary and mediastinal region, and occasionally the abdomen. It is worth mentioning, that a discrepancy in radiologic appearance may result in these lesions being misinterpreted as arising from adjacent organs, including reports of a suspected pancreatic tail cyst [142] or a cystic lesion of the kidney [143]. The pathogenesis of these lesions is unclear. One possibility is these lesions arise because of abnormal development and/or ectasia of lymphatic vessels [144, 145]. Another possibility is that the lesions result from obstruction or after injury to the lymphatic system [145]. Histologically, lymphangiomatous cysts are characterized by the presence of cysts lined by attenuated endothelial cells (**Figure 3**). D2-40 as a marker for lymphatic endothelium may be used in combination with vascular markers such as CD31 and CD34 and may increase the diagnostic accuracy in differentiating lymphangiomatous cysts from hemangioma [146].

Arteriovenous malformation: Arteriovenous malformations (AVM) are commonly seen in the central nervous system as well as the lung, liver, and intestines and less frequently on the trunk or limbs [147, 148]. The clinical presentation varies according to location and size. The cause of AVMs is unknown. It is typically present at birth and develops by abnormal expression of angiogenic growth factors [149] and may result as a consequence of arterial or venous damage of a thrombotic event [150]. Individuals with conditions like hereditary hemorrhagic telangiectasia and PTEN hamartoma tumor syndrome and those with certain genetic abnormalities may be more likely to develop AVMs [151]. AVMs are characterized by a tangle of arteries and veins (**Figure 4A**, **4B**). In contrast, hemangiomas result from an exuberant angiogenic proliferation. The use of histochemical stains such as Movat pentachrome or elastin stain helps to show the presence of arteries, arterioles, or both, which are frequently used as diagnostic criteria for differentiating AVMs from hemangiomas [152]. An immunohistochemical stain may be used to highlight nerve fibers, which favors AVM over hemangioma [153, 154].

Hemangioblastoma: Hemangioblastoma (HBL) is a rare, benign tumor with high vascularity that usually involves the cerebellum, brainstem or spinal cord [155]. Rarely, they have been

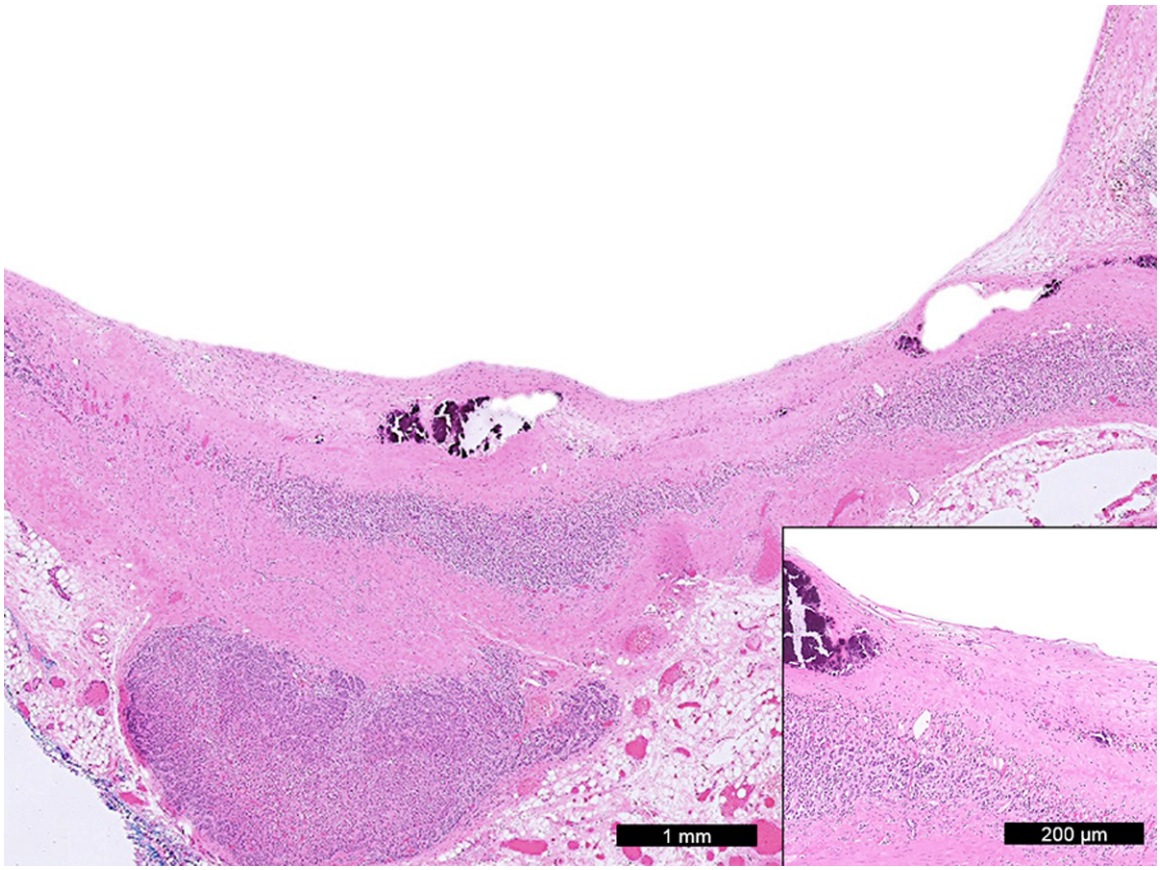

Figure 2. Pseudocyst. Cyst wall consists of dense fibrous tissue without a lining (inset). The cyst wall is composed of hyaline fibrous tissue and prominent calcifications present. (Hematoxylin and eosin, × 4, original magnification, scale bar 1 mm; inset, hematoxylin and eosin, × 40, original magnification, scale bar 200 µm).

diagnosed in extraneural tissues like liver, lungs, pancreas, retroperitoneum, soft tissue, presacral region, maxilla, and kidney [155-162]. In the adrenal gland, HBL is extremely rare with only five cases reported in the literature [156, 163-166]. Various cell lineages such as vascular, glial, neural, fibrohistiocytic, and smooth muscle/myofibroblastic have been proposed for the origin of the stromal cells, which represent the neoplastic element of these neoplasms [156, 167, 168]. Most HBLs arise sporadically, while they are also frequently associated with loss of function of *VHL*, with frequent occurrence in von Hippel-Lindau (VHL) disease [169-171].

HBL is a well-circumscribed, highly vascularized tumor, typically with a solid mural nodule associated with an adjacent surrounding cyst or solid mass along with interspersed stromal cells containing abundant foamy vacuolated cytoplasm with mild nuclear pleomorphism (**Figure 5A**, **5B**). Immunohistochemistry may be performed to exclude other clear cell lesions like metastasis from a clear cell renal cell carcinoma, vascular tumor, or melanoma [156, 167, 168]. Since proper recognition has a therapeutic and prognostic bearing, application of a targeted immunohistochemical panel may permit correct classification of tumor lineage, including inhibin [172] and aquaporin-1 [173, 174]. Immunohistochemical stains for CD34 and other vascular markers will highlight the vascular component, while stromal cells are negative.

Angiosarcoma: Angiosarcoma is a rare, high-grade tumor (less than 1% of all soft tissue sarcomas) that develops from the endothelium of blood and lymphatic vessels in the skin and superficial soft tissue [175], although other sites including the breast, lung, liver, spleen, kidney, adrenal gland, and bone have been reported [176, 177]. Primary adrenal angiosar-

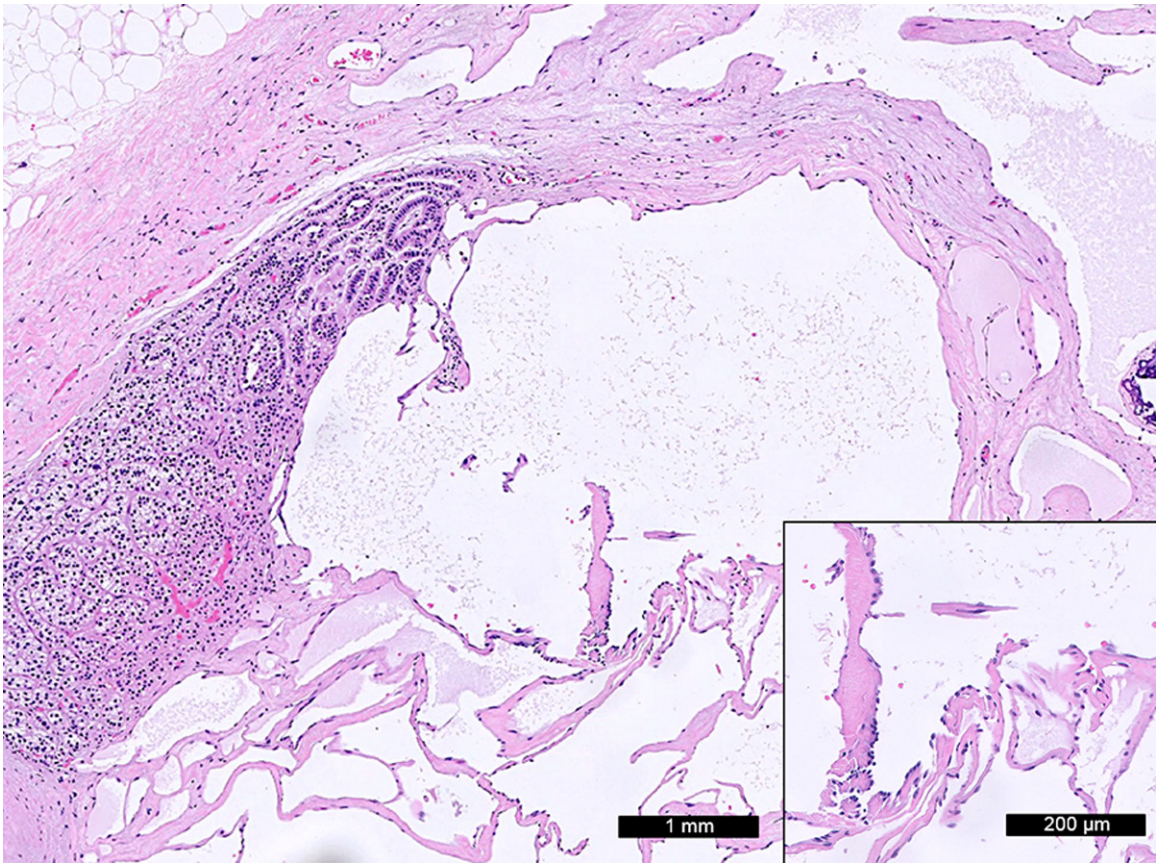

Figure 3. Lymphangiomatous cyst. Variably sized lymphatic channels lined by a single layer of lymphatic endothelial cells (inset). (Hematoxylin and eosin, × 4, original magnification, scale bar 1 mm; inset, hematoxylin and eosin, × 40, original magnification, scale bar 200 µm).

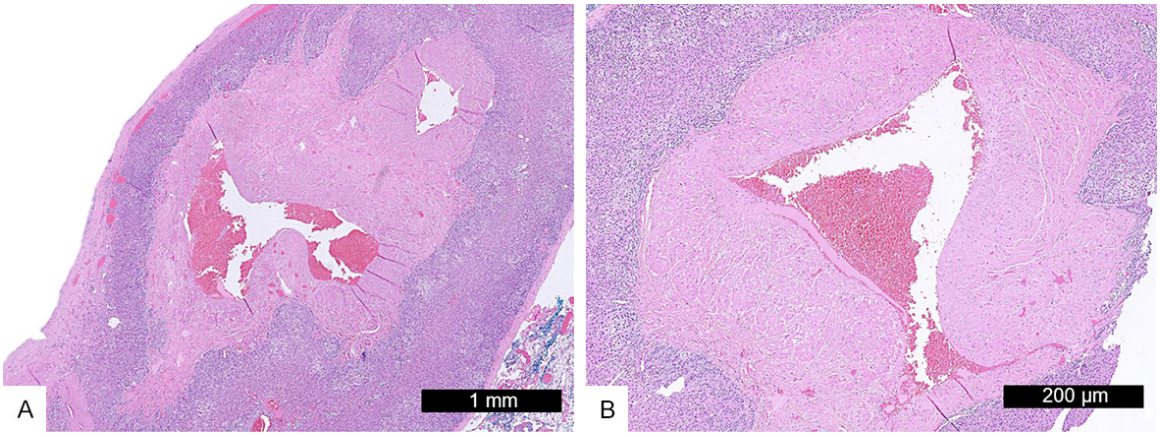

Figure 4. Arteriovenous malformation. (A and B) Thick-walled blood vessel in adrenal gland tissue. (A. Hematoxylin and eosin, × 4, original magnification, scale bar 1 mm; B. Hematoxylin and eosin, × 40, original magnification, scale bar 100 µm).

coma is exceedingly rare with only 26 cases reported in the literature [178-192]. Known predisposing factors for developing angiosarcoma include chronic lymphedema, history of radiation therapy, familial syndromes, prior anabolic steroid therapy, and exposure to chemical carcinogens such as arsenic, vinyl chloride, or thorium dioxide [177, 180]. The peak incidence is

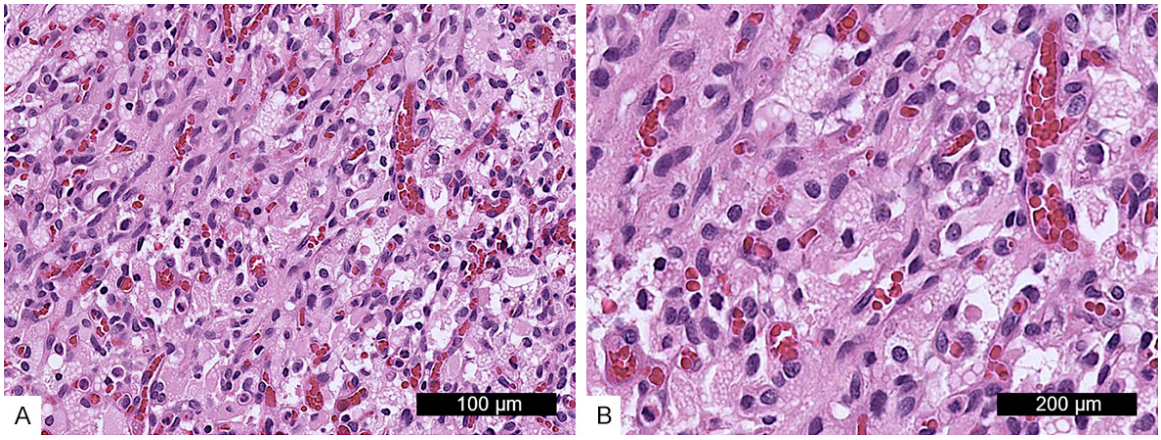

Figure 5. Hemangioblastoma. (A and B) Highly vascular tumor with numerous thin-walled vessels surrounded by nests of stromal neoplastic cells with vacuolated, lipid-like cytoplasm. (A. Hematoxylin and eosin, × 10, original magnification, scale bar 100 μm; B. Hematoxylin and eosin, × 40, original magnification, scale bar 200 μm).

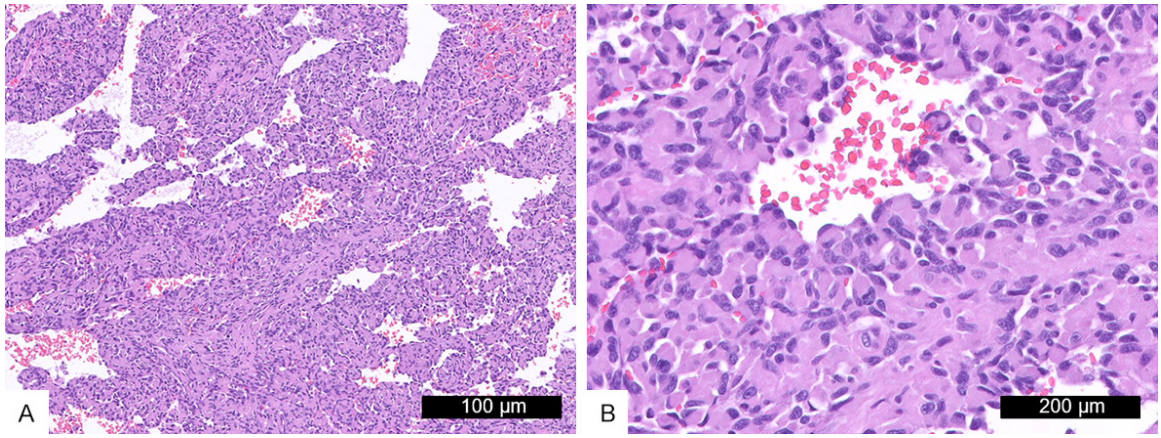

Figure 6. Angiosarcoma. (A and B) Infiltrative vascular neoplasm with anastomosing channels lined by high grade atypical epithelioid endothelial cells. (A. Hematoxylin and eosin, × 10, original magnification, scale bar 100 μm; B. Hematoxylin and eosin, × 40, original magnification, scale bar 200 μm).

in the seventh decade of life. Symptoms are nonspecific and may vary based on where the tumor occurs. Grossly, these tumors present as complex cystic or solid mass with ill-defined, infiltrative borders and can present at large size (up to 16 cm in diameter). In contrast to benign hemangiomas, angiosarcomas are characterized by a destructive anastomosing network of vascular channels lined by atypical endothelial cells with hyperchromatic nuclei, prominent nucleoli and increased mitotic activity (**Figure 6A**, **6B**). These tumors may express epithelial markers such as cytokeratin, which can lead to a misdiagnosis of metastatic carcinoma or adrenal carcinoma; however, immunohistochemical positivity for endothelial markers (CD31, CD34, FLI-1, ERG, and Factor VIII antigen) are useful in identifying endothelial differentiation and is often helpful [178, 180 183, 184, 193].

Conclusion

The evaluation and classification of benign adrenal cysts and vascular tumors continue to pose a challenge in surgical planning. Adrenal hemangiomas are among a group of uncommon entities that have similar, overlapping clinicopathologic features to other benign and malignant adrenal neoplasms. A multidisciplinary collaborative approach is essential for effective management. The majority of patients undergo partial or total adrenalectomy; however, surveillance may be an option for small, nonfunctioning adrenal incidentalomas.

Disclosure of conflict of interest

None.

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