Original Article

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Rare Atypical Adrenal Pathologies: Single-center Experience

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Abstract

Objective: To share the clinical, radiological and biochemical features of rare atypical pathologies in our adrenalectomy series.
Materials and Methods: Patients with atypical adrenal pathology among patients who underwent open or laparoscopic adrenalectomy for various indications were retrospectively reviewed. the hormonal behavior, radiological and pathological features of rare atypical adrenal pathologies in our series are demonstrated. Information about the postoperative follow-up and surveillance of the patients is given.
Results: Rare adrenal pathologies were detected in 17 (11.6%) of 146 patients who underwent adrenalectomy. Adrenal cysts (6), cavernous hemangioma (3), ganglioneuroblastoma (1), ganglioneuroma (2), ectopic thyroid tissue (1), schwannoma (1), arteriovenous malformation (1), sarcomatoid carcinoma (1), and primary adrenal lenfoma (1) were the rare atypical adrenal pathologies in our series.
Conclusion: Although there are no specific laboratory or radiological findings for most atypical adrenal pathologies, it should be kept in mind that such pathologies with a benign course can also be encountered by the clinician.
Keywords: Adrenalectomy, atypical pathologies, adrenal gland

Introduction

The prevalence of adrenal mass is quite common in the general population, and it is 3-5% in autopsy series, while the detection rate in contrasted abdominal computed tomography (CT) examinations ranges from 0.5-10% (1,2). The prevalence of adrenal adenomas increases with increasing age (3).

Adrenal masses can be presented to the clinician in four different scenarios. The first is patients admitted with adrenal-induced endocrinological complaints, as in some adrenocortical adenomas and carcinomas. These symptoms may include virilization, central obesity in Cushing's syndrome or hypertension, flushing, and headache in pheochromocytoma, or symptoms due to adenomas producing aldosterone. Secondly, they can be detected because of non-specific symptoms such as pain, weakness, weight loss, or intra-abdominal mass sensation caused by the adrenal mass. Thirdly, they may appear as adrenal metastasis in the staging screening of another malignancy. Finally, they can be detected incidentally in examinations with unrelated complaints; this condition is called adrenal incidentaloma (4).

In this study, we presented the rare pathological diagnoses found in pathological examinations performed after adrenalectomies which were performed by a single surgeon with different indications.

Materials and Methods

The data of 146 open and laparoscopic adrenalectomy cases that we performed between January 2005 and February 2020 in our urooncology clinic were retrospectively analyzed. Although our standard approach is laparoscopic, the open method has been preferred in large masses, in patients who are not suitable for laparoscopy and who are suspected of invasive carcinoma. Hormone tests in blood and urine were performed for each patient in whom adrenal mass was detected by CT or

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magnetic resonance imaging (MRI). Patients with suspected malignancy or metastasis were also evaluated with additional scans. After the completion of the evaluation of adrenal masses, patients were divided into two groups: those with non-functional adrenal mass and those with functional adrenal mass. Adrenalectomy was performed in patients who were hormonally active or suspected of malignancy, or who were symptomatic due to the size of the mass. Adrenalectomy pathologies were analyzed retrospectively. Because of the analysis, rare adrenal pathologies were evaluated considering the current literature. The study protocol was approved by the Clinical Research Ethics Committee of Gazi University Faculty of Medicine (decision no: 804, date: 26.11.2020).

Statistical Analysis

The SPSS 15.0 (SPSS Inc., Chicago, IL, USA) program was used to calculate median and percentage values.

Results

Of the 146 patients, 97 (66.4%) were female and 49 (33.6%) were male. The median age was 47 (18-73) years. Open transperitoneal adrenalectomy was performed in 24 (16.3%) patients, and laparoscopic transperitoneal adrenalectomy was performed in 122 (83.7%). In the preoperative period, 54 (36.6%) patients were evaluated by abdominal MRI, 36 (24.6%) patients by abdominal CT, and 56 (38.3%) patients by both methods. An 18-fluorodeoxyglucose Positron emission tomography/CT scan was performed on 14 (9.5%) patients with suspected malignancy or metastasis. Pathology types, numbers, and ratios are shown in Table 1. Benign epithelial cysts, endothelial cyst, pseudocyst, cavernous hemangioma, ganglioneuroblastoma (GNB), ganglioneuroma (GN), ectopic thyroid, schwannoma, arteriovenous malformation (AVM), sarcomatoid carcinoma and primary adrenal lymphoma (PAL) cases were evaluated as atypical adrenal pathologies. The various characteristics of these patients are placed in Table 2.

In our study, a total of six patients had adrenal cysts. According to their histological specifications, they were divided. Three were endothelial cysts with surrounding flat endothelial cells adjacent to the adrenal parenchyma (Figure 1b), two were pseudocysts with endothelium like epithelium on the wall of the cyst (Figure 1c), and the last was a benign epithelial cyst with mesothelial cells surrounding the multiple cystic cavities of the lesion filled with a serous fluid (Figure 1d). All six cases were metabolically inactive, three cases were asymptomatic, and one case of endothelial cyst (weakness) and two cases of pseudocyst (abdominal pain) were symptomatic. CT and MRI scans revealed cystic lesions with no contrast enhancement. In one case of endothelial cyst, MRI showed mural nodular hyperintensity on T1 weighted images due to hemorrhage. Also one case pseudocyst, CT revealed a large cystic mass with thin wall calcification. All six patients operated with the indication that the mass dimensions were larger than 40 mm (40, 45, 45, 45, 55, and 65 mm).

Another atypical adrenal pathology is the cavernous hemangioma. Three patients in our series were metabolically inactive, which was detected incidentally and operated on with the indication that the mass dimensions were larger than 40 mm (60, 75, and 90 mm). The CT and MRI scans showed large heterogeneous masses with intralesional hemorrhage and thin capsular enhancement after contrast material administration. A histological image is shown in Figure 1a.

The GNB case in our series was a 56-year-old male patient with a 65 mm solid mass detected in the right adrenal gland on CT scan performed due to abdominal pain. Hormonal examination revealed that it was not metabolically active; thus, open right adrenalectomy was performed because of suspected malignancy. A pathological examination showed GNB-intermixed (Schwannian stroma-rich). The background component of the tumor was mostly composed of ganglion cells and areas of naked neuropil, but intermixed with small round blue cell tumor cells (neuroblasts) in clusters (Figure 1e). The patient had no metastasis at the time of diagnosis. During his six-year follow-up, there was no local recurrence or distant metastasis.

There were two GN cases in our series. While one of the two patients was hormonally inactive, the other was shown to secrete catecholamine in a preoperative metabolic examination. While the hormonally inactive mass was operated on suspicion of malignancy, the mass synthesizing catecholamine was operated with a preliminary diagnosis of pheochromocytoma. Their morphologies were similar and both were mature GN. There were no naked neuropils, and the stroma was filled with mature ganglion cells (Figure 1f). Both patients were followed up without local or systemic recurrence.

Table 1. Numerical distribution of pathological subtypes

Pathology type	Frequency	Percent (%)
Adrenocortical adenoma	78	53.4
Adrenocortical hyperplasia	6	4.1
Adrenocortical carsinoma	9	6.1
Benign pheochromocytoma	22	15.1
Malignant pheochromocytoma	3	2.05
Renal cell carcinoma metastasis	1	0.68
Paraganglioma	2	1.36
Myelolipoma	6	4.1
Normal adrenocortical tissue	2	1.36
Benign epithelial cyst	1	0.68
Endothelial cyst	3	2.1
Pseudocyst	2	1.36
Cavernous hemangioma	3	2.05
Ganglioneuroblastoma	1	0.68
Ganglioneuroma	2	1.36
Ectopic thyroid	1	0.68
Schwannoma	1	0.68
AVM	1	0.68
Sarcomatoid carcinoma	1	0.68
Lymphoma	1	0.68
Total	146	100.0

AVM: Arteriovenous malformation

Table 2. Various characteristics of the patients							
Diagnosis	**Age**	**Gender**	**Symptom**	**Side**	**Maximum size (cm)**	**Hormonal hypersecretion**	**Operation type**
Endothelial cyst	24	female	weakness	right	4.5 cm	no	laparoscopic
Endothelial cyst	27	female	asymptomatic	right	4.5 cm	no	laparoscopic
Endothelial cyst	23	female	asymptomatic	right	6.5 cm	no	laparoscopic
Pseudocyst	55	female	abdominal pain	right	4 cm	no	laparoscopic
Pseudocyst	66	female	abdominal pain	left	4.5 cm	no	laparoscopic
Benign epithelial cyst	56	male	asymptomatic	left	5.5 cm	no	open
Cavernous hemangioma	32	male	asymptomatic	left	6 cm	no	laparoscopic
Cavernous hemangioma	49	female	asymptomatic	left	9 cm	no	laparoscopic
Cavernous hemangioma	70	female	abdominal pain	left	7.5 cm	no	laparoscopic
Ganglioneuroblastoma	56	male	abdominal pain	right	6.5 cm	no	open
Ganglioneuroma	55	male	asymptomatic	right	7 cm	no	open
Ganglioneuroma	42	male	tachycardia	right	6.5 cm	yes (catecholamine)	laparoscopic
Ectopic thyroid tissue	57	female	hyperhidrosis	right	2 cm	yes (catecholamine)	open
Schwannoma	42	female	asymptomatic	left	5 cm	no	laparoscopic
AVM	64	female	abdominal pain	right	7 cm	no	open
Sarcomatoid carcinoma	52	female	abdominal pain	bilateral	10.5/6.5 cm	no	open
Lymphoma	56	female	asymptomatic	right	7 cm	no	open
AVM: Arteriovenous malformation							

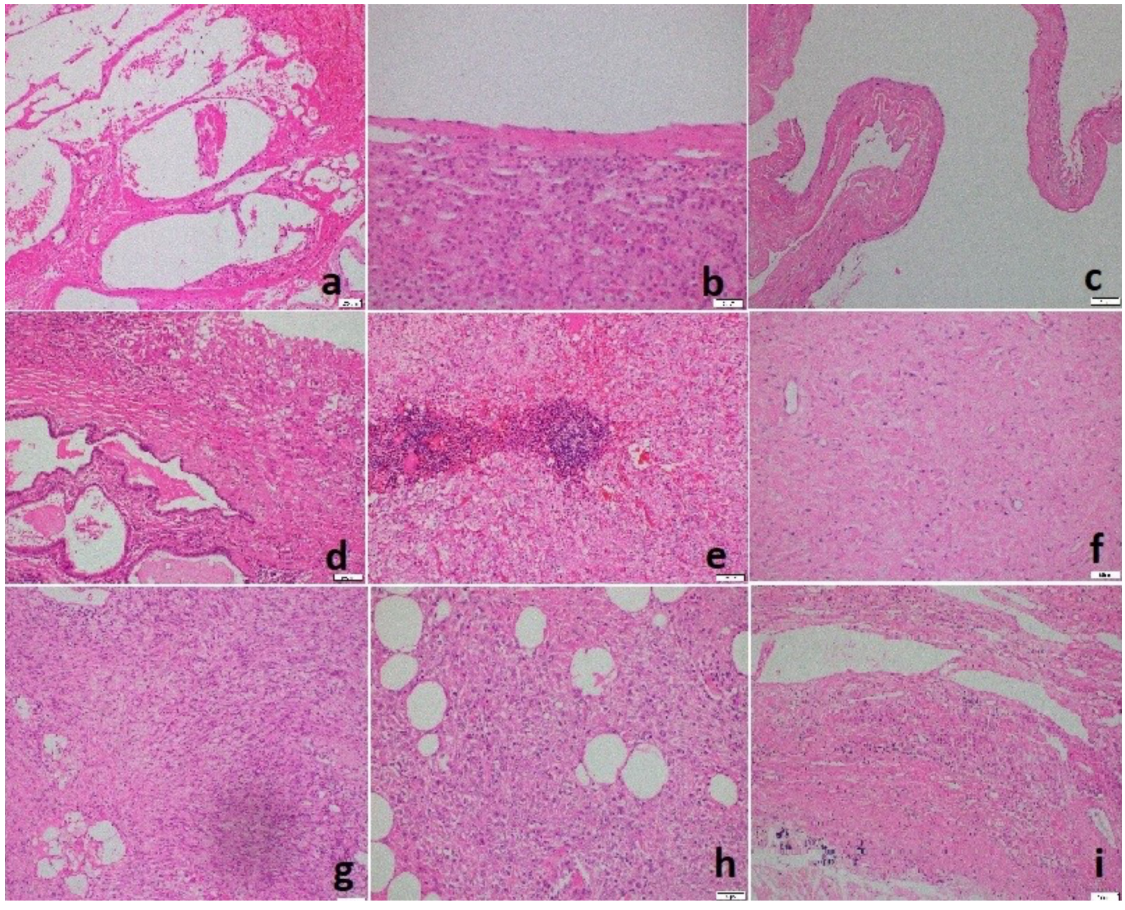

Figure 1. Histological features. (a) cavernous hemangioma, (b) endothelial cyst, (c) pseudocyst, (d) benign epithelial cyst, (e) ganglioneuroblastoma, (f) ganglioneuroma, (g) schwannoma, (h) sarcomatoid carcinoma, (i) arteriovenous malformation

The ectopic thyroid case was 57 years old woman who had undergone subtotal thyroidectomy because of hyperthyroidism 30 years ago. A 20 mm minimally enhancing mass with calcifications was found in the right adrenal gland incidentally on CT scan. The patient was considered pheochromocytoma in the metabolic evaluation. Right adrenalectomy was performed, and ectopic thyroid tissue (ETT) was detected on pathological examination.

The Schwannoma case in our series was a female with a 50 mm mass in the left adrenal gland that was detected incidentally and is non-functional in metabolic evaluation. Pathological examination revealed spindled cells arranged in hyper (Antoni A) and hypocellular (Antoni B) areas and mild lymphocytic infiltration with peculiar vascular spaces here and there (Figure 1g). No recurrence was observed in the five-year follow-up.

The AVM case was a 64-year-old woman who presented with complaint of abdominal pain. CT and MRI examinations revealed an 80 mm peripherally enhancing cystic mass originating from the right adrenal gland. Metabolic examination showed that the mass did not release hormones. Adrenalectomy was performed given that a mass size was larger than 40 mm and a suspected malignancy. The pathological feature of the lesion are large numbers of vessels of different sizes, including veins and arteries, with a dominant vein counterpart (Figure 1i). As it can be frequently accompanied, an organized hematoma was detected also. No recurrence was observed during the patient's 10-year follow-up.

A sarcomatoid carcinoma case was of a 52-year-old woman who CT and MRI scans revealed bilateral heterogeneous contrast-enhanced cystic masses with areas of hemorrhage, fluid-fluid levels and irregular borders. Also, our patient had liver invasion at the time of diagnosis, and bilateral adrenalectomy, liver lobectomy, left nephrectomy, and distal pancreatectomy surgeries were performed. The mass of infiltrative sheets of neoplastic cells with frequent mitoses, areas of necrosis and hemorrhage. Two components could be observed in the tumor. The first component showed the epithelioid cells in a syncytial pattern with large vesicular nuclei, reddish nucleoli and an eosinophilic cytoplasm with distinct borders. The second component mostly contains spindle cells and multinuclear giant cells. Both compounds were stained with vimentin and pankeratin. EMA, S-100, chromogranin, PGP 9.5, Factor-VIII, CD31 and desmin were focally stained in different areas (Figure 1h). One month after surgery, the patient died because of multiorgan failure.

The PAL case in our series, a 56-year-old woman, was investigated for a rash, while a 70 mm mass originating from the right adrenal gland was detected incidentally. This mass was metabolically inactive. After open right adrenalectomy, diffuse large B-cell lymphoma was diagnosed. It had a germinal center B subtype phenotype. The patient is on postoperative 3rd month follow-up and continues adjuvant chemotherapy treatment.

Discussion

Regardless of the indication for adrenalectomy, atypical pathologies can be encountered. In our 146-patient adrenalectomy series, atypical pathology was detected in 17 (11.6%) patients. A total of 11 different types of adrenal pathology were observed in these 17 patients.

Adrenal cysts are rare pathologies, and the incidence in autopsy series is 0.064-0.18% (5,6). Adrenal cysts are generally asymptomatic and metabolically inactive (7). More than 600 patients have been reported in the literature (4). Adrenal cysts form a subcategory that can be divided into endothelial cysts, epithelial cysts, pseudocysts, and parasitic cysts (8). The dispersion in the 220 case series published in 1966 is as follows: endothelial cysts (45%), pseudocysts (39%), epithelial cysts (9%), and parasitic cysts (7%) (9). Both endothelial cysts and pseudocysts are considered variants of adrenal vascular cysts based on immunohistochemical and ultrastructural evidence. The non-vascular adrenal cysts include epithelial cysts and parasitic cysts (10). Usually, they present as thin-walled cystic lesions with internal low-density and no contrast enhancement on CT and MRI scans (10). In a series of 41 cases, 66% of patients were reported to be symptomatic (typically, abdominal pain or gastrointestinal complaints), and 44% were asymptomatic (11). A review of more than 600 cases showed that the malignancy rate of adrenal cysts was 7% (12). The probability of malignancy is typically high in pseudocysts (5,13). Although there is no generally accepted protocol for follow-up, we believe that especially benign cysts can be followed up with ultrasound.

Adrenal cavernous hemangiomas are unusual tumors that originate in the endothelial layer of blood vessels (14). They are a rare, non-functional mass of the adrenal gland that are often diagnosed postoperatively (15). A literature review published in 2019 on adrenal cavernous hemangioma cases found 66 cases reported in the literature. Pre-operative metabolic evaluation was performed in 51 of these 66 patients, and 45 (88.2%) of them were found to be metabolically inactive (16). Although CT and MRI scans are helpful in the diagnosis, imaging findings are usually non-specific. These tumors mostly present as large complex heterogeneous masses with variable amounts of bleeding and calcification. On contrast-enhanced CT, characteristic peripheral patchy and centripetal enhancement may be found (8). On MRI, adrenal cavernous hemangiomas tend to be marked hyperintense on T2-weighted images and have focal hyperintensity on T1-weighted images due to hemorrhage and calcification (8,9). However, the preoperative diagnosis of adrenal cavernous hemangiomas is difficult, and definitive diagnosis is usually made by pathological examination of a surgical specimen. The histological of cavernous hemangioma is common all around the body and is characterized by proliferation of blood vessels with cystic dilatations in their lumens. It is generally benign, and there is no reported recurrence after excision. Large masses can cause life-threatening spontaneous retroperitoneal bleeding (17). Surgical resection is generally required to exclude malignant disease, resolve pressure-related symptoms, and prevent retroperitoneal hemorrhage. Although the prognosis of cavernous hemangiomas is excellent after excision, patients should be followed up with CT and endocrinological tests.

Peripheral neuroblastic tumors (PNTs) are a group of tumors that originate from sympathetic ganglion cells. In two-thirds of the cases, PNTs arise in the adrenal gland or the retroperitoneal paravertebral ganglia. They represent one of the most common

solid tumors in children, while the occurrence in adults is very rare (18). The International Neuroblastoma Pathology Classification separates four pathological groups with respect to the different proportions of ganglion and Schwann cells: neuroblastoma (Schwannian stroma-poor, undifferentiated/poorly, and differentiated/differentiating), GNB intermixed (Schwannian stroma-rich), GN (Schwannian stroma-dominant), and GNB nodular (composite Schwannian stroma-rich/stroma-dominant/stroma-poor) (19). GNB is a rare cause of adrenal tumors in adults. The preoperative suspicion is difficult, and the definitive diagnosis is often made by the pathologist after surgical excision (18). Thus far, 19 adrenal GNBs have been reported in the literature in the adult age group (20), and this number will be 20 in our case. There is no specific presentation; there may be symptoms such as pain due to abdominal mass compression. While only four of the cases in the literature were detected with catecholamine secretion, others were metabolically inactive. Nearly half of the patients had metastases at the time of diagnosis. Cases with metastases to the liver, lymph node, and bones have been reported (18). Most of the patients were treated only with surgery and showed no recurrence during follow-up. Adjuvant chemo-radiotherapy can be administered to patients with metastasis. In one patient who had bone metastasis and did not accept adjuvant chemo-radiotherapy, recurrence was observed 2.5 years after the operation. In only one patient, recurrence developed in the adrenalectomy field two years after the operation, and metastasis occurred in the lumbar vertebrae (21). The patient in our series had no recurrence or metastasis during six years follow-up. Due to the potential for metastasis and the possibility of being hormonally active, patients should be followed up with contrast-enhanced CT and endocrinological tests.

GNs are benign masses that originate from the neural crest and are composed of ganglion cells, mature Schwann cells, and nerve fibers. They are most commonly seen in the adrenal gland (29.7%), followed by the mediastinal sympathetic ganglia (21.8%), retroperitoneum (20.8%), and neck (10.9%), respectively (22). Most GNs are sporadic, but they can also be hereditary and associated with neurofibromatosis type II and multiple endocrinologic neoplasia type II (23). Adrenal ganglioneuromas are rare pathologies representing less than 6% of adrenal masses (24). Imaging findings are usually not distinctive. Most frequently, it appears as a homogeneously minimally enhanced solid mass with smooth borders (25). In our cases, the CT scan showed a heterogeneous solid mass containing central cystic areas and calcification. Usually, GN are metabolically inactive. In some rare cases, a GN can secrete hormones, primarily catecholamines, androgens, and vasoactive intestinal peptide (26). While one of the two masses in our series was releasing catecholamine, the other was hormonally inactive. We believe that patients should be followed up with ultrasound and endocrinological tests because of the possibility of NBs being hormonally active.

The frequency of ETT is approximately 1 in 100,000-300,000. ETT usually occurs in the base of the tongue, but it may also develop in the mediastinum or in the subdiaphragmatic organs. Additionally, the ETT in the adrenal gland (ETTAG) is an extremely rare condition (27). In our literature review, we found that 15 ETTAGs have been reported so far. This number will be increased to 16 with one patient in our series. The subdiaphragmatic ectopic thyroid mechanism was not fully revealed. The most important differential diagnosis of this entity is the metastasis of a cystic papillary thyroid carcinoma. Some researchers also considered that thyroid carcinoma could be a metastasis to the adrenal gland or ETT malignant transformation (28,29). No malignancy of the thyroid gland was detected in the post-operative examinations in the patient we reported.

Schwannomas are very rare, benign tumors that originate from the myelin sheaths of peripheral autonomic or cranial nerves. The head and neck or flexor surface of the extremities are the most related anatomic locations (30). Schwannomas originating from the retroperitoneum are much rarer and constitutes 3-5% of all schwannoma cases (31). Additionally, adrenal schwannomas account for 0.7% of all adrenal masses (32). These masses do not release hormones and are clinically asymptomatic. Thus, preoperatively, they are often misdiagnosed as non-functioning adrenal adenoma. The imaging features of schwannomas are not specific. Schwannomas appear as a well-defined solid mass with cystic degenerative changes. Our case showed a heterogeneous solid mass with central cystic necrotic areas with contrast enhancement. Almost all schwannomas display benign behavior, except for melanotic schwannoma, a rare subtype that has not been clearly identified (33). No cases in the literature have reported recurrence after resection. We think that ultrasound is sufficient in the postoperative follow-up of the patients.

In our literature review, we found that two cases of adrenal AVM have been reported to date (34,35). There are now three with one patient in our series. The pathological feature of the lesion is a large numbers of vessels of different sizes, including veins and arteries, with a dominant vein counterpart. As it can be frequently accompanied, an organized hematoma was detected also.

Adrenal sarcomatoid carcinoma is an extremely rare malignancy mass, and 21 cases have been reported in the literature to date. Only two of these cases are bilateral; one is from our adrenalectomy series and was previously published as a case report (36). Typical symptoms are mass pressure-related abdominal pain, lumbago, and weight loss. The primary treatment modality is surgery. These tumors are aggressive, and their prognosis is very poor. Primary adrenal sarcomatoid carcinomas tend to produce distant metastases, and patients usually die within two years (37). In the literature, at the time of diagnosis, two patients had liver, one patient had lung, and one patient had vena cava metastasis (36,38-40). They are generally metabolically inactive; but hormone-releasing adrenal sarcomatoid carcinoma cases have been reported (39).

PAL is extremely rare and there are fewer than 200 cases reported in the literature. It generally tends to occur in older male patients, and 70% of all cases are bilateral (41,42). Patients usually present with local pain or systemic symptoms such as weakness, weight loss, fever (41). The diagnosis is usually established using imaging-guided biopsy, surgical excision, or on autopsy (43). Immunodeficiency, Epstein-Barr virus, and mutations in the p53 and c-kit genes play a role in pathogenesis

(44,45). The most commonly reported subtype is Diffuse B-cell lymphoma, anaplastic large cell and T-cell types are rarely reported (46-49). PAL shows a poor prognosis, responds well to treatment early, but long-term complete remission is rarely observed after chemotherapy (46). The patient in our series is at postoperative 3rd month follow-up and continues adjuvant chemotherapy treatment.

Study Limitations

The small number of patients in most pathological subtypes and the short follow-up period of some of them are limitations of the study.

Conclusion

Adrenal originated masses can be encountered with different clinical findings. It is quite difficult to establish the differential diagnosis of particularly hormonally inactive masses with preoperative laboratory and radiological examinations. Surgical resection is indicated in patients with potential for malignancy, risk of spontaneous hemorrhage, increase in size over time, or symptoms of mass compression. While a surprise is not expected in pathological diagnosis after resection in hormonally active masses, it should be remembered that rare atypical pathologies can be encountered in hormonally inactive masses.

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Ethics

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Authorship Contributions

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