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Case Report

Two Cases of Adrenal Cysts Lined by Thyroid Follicular Epithelium: Addressing Cellular Origin and Malignancy Concerns

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Abstract

Adrenal cysts lined by thyroid follicular epithelium are rare, with only 14 reported cases of "ectopic thyroid tissue" to date. While the primary consideration for differential diagnosis is thyroid carcinoma metastasis, exclusion of metastases is determined based on the absence of a primary thyroid lesion, serological euthyroidism, lack of thyroglobulin elevation, and absence of epithelial atypia. Herein, we report 2 cases of adrenal cysts lined by thyroid follicular epithelium. Case 1 was a 60-year-old woman with a right adrenal cyst. Case 2 was a 51-year-old man with a left adrenal cyst. Over time, both cysts became larger, necessitating an adrenalectomy. Cystic epithelia were lined with thyroid follicular epithelium, exhibiting moderate atypia. Human bone marrow endothelial cell marker-1 and galectin-3 were focally positive; CK19 was positive in Case 1, and all 3 markers were positive in Case 2, previously reported as an immunophenotype of thyroid carcinoma. CD56 expression was positive in both cases. Targeted next-generation sequencing revealed several low-frequency mutations; however, no major driver alterations for thyroid cancer were detected. Adrenal cysts can be lined by thyroid follicular epithelium. Challenges arise in determining the malignant or benign nature of adrenal cysts.

Key Words: adrenal cyst, thyroid follicular epithelium, ectopic thyroid gland, HBME-1, galectin-3, CK19

Abbreviations: CT, computed tomography; HBME-1, human bone marrow endothelial cell marker-1; NGS, next-generation sequencing; ODxTT, Oncomine Dx Target Test Multi-CDx system; PTC, papillary thyroid cancer.

Introduction

Adrenal cysts are rare, accounting for only up to 4% of adrenal masses [1], but they may be encountered in routine clinical practice. They are classified into 4 distinct types: (a) pseudocysts, which are most common, lacking a cellular lining; (b) endothelial (vascular) cysts; (c) epithelial or mesothelial cysts; and (d) parasitic (hydatid) cyst [2]. Adrenal cortical adenomas, pheochromocytomas, and metastatic carcinomas may also present with cystic changes. Ectopic thyroid tissue is rare in subdiaphragmatic organs and extremely rare in the adrenal glands, with only 14 cases reported to date [3–14]. Herein, we report 2 cases of adrenal cysts lined by thyroid follicular epithelium, highlight the importance of considering malignancy, and discuss the challenges associated with confirming whether they are metastatic carcinomas or malignant transformations from ectopic thyroid tissue. Our findings shed light on the rare occurrence of adrenal cysts lined by thyroid follicular epithelium, providing crucial insights for improved diagnostic accuracy and informed decision-making in the management of adrenal masses.

Case Presentation

Case 1

Case 1 involves a 60-year-old woman with a history of diabetes, hypertension, and early-stage breast cancer, who had undergone partial mastectomy 5 years previously. A right adrenal cyst was identified on computed tomography (CT) during the postoperative follow-up (Fig. 1A).

Case 2

Case 2 involves a 51-year-old man with no remarkable medical or family history. A left adrenal cyst was incidentally detected by CT (Fig. 1D).

Diagnostic Assessment

Case 1

The cyst gradually increased in size from 40 to 57 mm over 5 years. No nodular components or contrast enhancement was observed. In the thyroid gland, multiple small nodules or cysts

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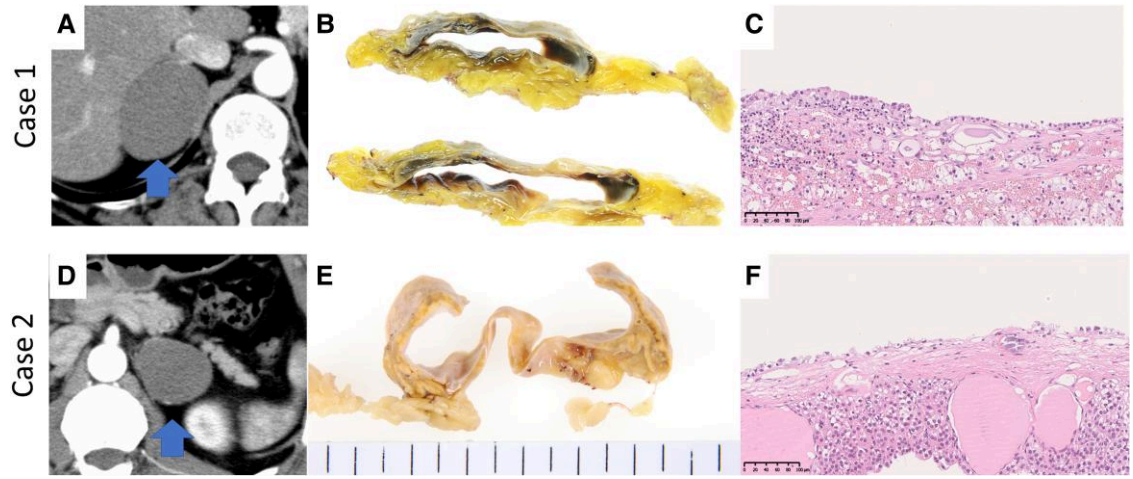

Figure 1. Case 1 (A-C) and Case 2 (D-F) findings. A, D, Unilocular cyst in the adrenal gland. B, E, Gross finding. C, F, The cyst was covered with a monolayer of a moderately atypical epithelium.

< 10 mm in size were detected in both thyroid lobes on CT. Ultrasonography was not performed. Laboratory analyses revealed thyroid-stimulating hormone 1.777 μIU/mL (1.777 mIU/L; reference range: 0.35–4.94 μIU/mL; 0.35–4.94 mIU/L) and free thyroxine 0.92 ng/dL (11.8422 pmol/L; reference range: 0.7–1.48 ng/dL; 9.0104–19.0506 pmol/L), both within normal limits. No additional cytologic or histologic examinations were performed.

Case 2

The cyst was initially measured 25 mm, had expanded to 50 mm over 9 years. No nodular components or contrast enhancement were observed. Meanwhile, a simple thyroid cyst 7 mm in diameter was detected on ultrasound examination, and no significant findings were noted on CT. The patient's thyroid-stimulating hormone level was 0.969 μIU/mL (0.969 mIU/L) and free thyroxine was 0.93 ng/dL (11.97 pmol/L), both within normal limits. Serum thyroglobulin levels were not measured in any of the patients.

Treatment

Case 1

An adrenal tumor or lymphangioma was diagnosed clinically, adrenalectomy was performed. A grossly thin-walled unilocular cyst was observed (Fig. 1B). Microscopically, the cyst was lined with monomorphic cuboidal epithelium (Fig. 1C) and contained a small number of psammoma bodies. No mitotic features were observed. Immunohistochemically, the epithelial and subepithelial follicular structures were positive for thyroid transcription factor-1 (TTF-1) (Fig. 2A) and thyroglobulin (Tg) and negative for steroidogenic factor-1 (SF-1). These results confirmed that the cysts were lined by thyroid follicular epithelium. No C-cells were detected. Both the lining and follicular cells had glassy nuclei with moderate pleomorphism and irregularity; however, there were no definite nuclear features of papillary thyroid carcinoma (PTC). Additional staining revealed that human bone marrow endothelial cell marker-1 (HBME-1) and galectin-3 were weakly positive (Fig. 2B and 2C), whereas CK19 was moderately positive (Fig. 2D) and there was diffuse positivity for CD56 (Fig. 2E). The Oncomine Dx Target Test Multi-CDx system (ODxTT), a next-generation sequencing (NGS)-based hot spot panel test, was performed using paraffin blocks. The test can detect 46 representative genetic variants of thyroid cancer, such as *RET*-fusion and alterations, *ALK*, *BRAF*, *NTRK*-fusion, *HRAS*, *KRAS*, and *NRAS* alterations. The results revealed that the cyst was negative for major driver alterations. Although mutation rates were low in thyroid cancers, a few alterations listed as "pathogenic" in Clin Var were detected (Table 1). Among them, *FGFR3* (p.Arg248Cys) and *HRAS* (p.Gly12Ser) mutations have not been reported in thyroid carcinomas. *PIK3CA* mutations, previously detected in 5% papillary carcinomas and 10% undifferentiated carcinomas were more frequent in poorly differentiated thyroid carcinomas than in differentiated thyroid carcinomas [15]. *PIK3CA* (p.Cys378Tyr) has not previously been reported in thyroid cancer.

Case 2

Clinically, ganglioneuroma or adrenal carcinoma could not be ruled out; adrenalectomy was performed. The gross finding (Fig. 1D) and histological findings, including immunohistochemical results, were almost same as Case 1 (Fig. 1E, Fig. 2F, and 2J). Whereas positive staining for HBME-1, CK19, and galectin-3 was observed (Fig. 2G–2I), the ODxTT result showed no major driver alterations for thyroid carcinomas. It revealed *HRAS* (p.Gly12Ala) mutations, which have not been reported in thyroid carcinomas previously (Table 1).

Outcome and Follow-Up

Case 1

Initial pathological diagnosis was a retention cyst. Subsequent detailed histological examination, including additional immunostaining, confirmed that the cysts were lined by thyroid follicular epithelium. During 6 months of follow-up, neither recurrence nor metastasis was observed.

Case 2

Initial pathological diagnosis was a Müllerian cyst. Subsequent detailed histological examination of both, including additional

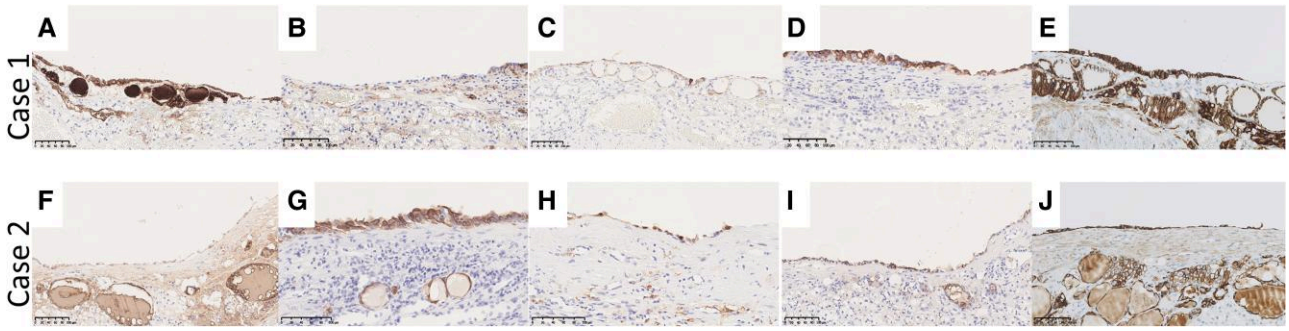

Figure 2. Immunohistochemical findings. Case 1 (A-E) and Case 2 (F-J). Dilated follicular structures adjacent to adrenal cortical cells were detected under the epithelium. A, F, Positive staining for thyroglobulin (Tg); B, G, HBME-1; C, H, galectin-3; D, I, CK19; and E, J, CD56 staining.

immunostaining, confirmed that the cysts were lined by thyroid follicular epithelium. During 1 year of follow-up, neither recurrence nor metastasis was observed.

Discussion

Our study aimed to report and analyze 2 cases of adrenal cysts lined by thyroid follicular epithelium. In both cases, imaging revealed an increase in the size of the cysts over time, along with abnormalities in the thyroid gland. Although the enlargements appeared to have occurred somewhat fast in both of the cases, this should not necessarily indicate malignancy. In benign thyroid lesions, findings such as glassy appearance in adenomatous nodules or Basedow disease, moderate pleomorphism in thyroiditis, and psammoma bodies in oncocytic follicular tumors or hyalinizing trabecular tumors, are typically observed. While these findings are not directly indicative of malignancy, in the present 2 cases, simultaneous occurrence of all 3 features seemed to be indicative of the possibility of malignancy.

While the thyroid gland was not examined cytologically or histologically in either case, it is important to note that PTC can be small, with sizes of < 10 mm in up to 36% of cases [16]. This characteristic does not completely rule out the possibility of thyroid cancer metastases. Moreover, the adrenal cysts in both patients demonstrated a progressive increase in size over time. Metastases to uncommon sites, such as the adrenal glands, are typically associated with advanced cases featuring more aggressive histological types. Such metastases often coincide with occurrences at common sites, such as the lungs and bones [17]. However, isolated metastases to the adrenal glands have been reported and do not necessarily indicate negative prognostic factors [18].

Various immunohistochemical markers have been utilized to assess the malignancy of thyroid follicular epithelium. Commonly employed markers include HBME-1, galectin-3, CK19, and, more recently, CD56 [19, 20]. In core needle biopsy studies, the sensitivity and specificity of each marker for malignancy were as follows: positive for HBME-1 (sensitivity 63.53%, specificity 81.81%), galectin-3 (sensitivity 89.41%, specificity 50%), CK19 (sensitivity 77.65%, specificity 63.63%), and negative for CD56 (sensitivity 55.29%, specificity 100%) [20]. The present study highlights the fact that when combined with targeted NGS (detecting 26 genes), negativity for CD56 or positivity in NGS can strongly indicate malignancy in both follicular and nonfollicular neoplasms. However, even if CD56 is positive, due to its low sensitivity, considering the positivity of the other 3 markers allowed an estimation of malignancy grade with a sensitivity of 88.71% and specificity of 92.3%. Since this study focused primarily on thyroid nodules, it is unclear whether it can be extended to adrenal cysts, as in our 2 cases. The adrenal cyst in Case 2 may not be ruled out as malignant because it was positive for HBME-1, galectin-3, and CK19, and retained CD56 expression. Nevertheless, relying solely on immunohistochemistry for estimating malignancy has limitations due to differences in the cases included in the study and the specimen collection methods.

Thyroid carcinomas exhibit various somatic driver mutations. The most common molecular changes in PTC involve *BRAFp.v600E* (29% to 69%) [21], followed by *RET* (approximately 28%; *CCDC6:RET* being most common) and *NTRK1/3* fusions (15%) [22]. In follicular thyroid carcinoma, the primary somatic mutation is *RAS* (30% to 50%). Specifically, *HRAS/NRAS* presented 61 frequently mutated codons, while KRAS exhibited 12 or 13 mutations. Additionally, PAX8::PPARG rearrangements were observed in 10% to 40% of cases [23]. Although our case, based on the ODxTT results, did not display any major genetic changes typically seen in thyroid cancer, it suggests the potential benign nature of the cyst lining the epithelium. However, ODxTT does not include all known driver mutations in thyroid carcinomas. A previous study reported that 25% of PTC cases had unidentified driver mutations when only representative mutations were examined. It was found that incorporating *EIF1AX*, *PPM1D*, and *CHEK2* mutations, and conducting gene fusion searches lowered this rate to 3% [24]. Therefore, the possibility of unknown driver mutations cannot be dismissed.

Considering other conditions, ectopic thyroid glands and teratomas should also be contemplated. Ectopic thyroid glands are typically found along the thyroglossal duct, particularly in the sublingual position [25]. Intrathoracic and intraabdominal cases have both been reported, with 14 adrenal cases described in detail (Table 1). Although the pathogenesis of ectopic thyroid tissue remains unclear, one hypothesis suggests an overdescent of the medial thyroid anlage-derived cells [14]. Previous cases were often cystic (12/14 cases). Similar to the present cases, there were no marked left-right differences (right: 6 cases, left: 8 cases), and most cases involved women (13 cases) with only 1 case involving a man. In previous cases, the possibility of metastatic thyroid cancer was ruled out because the cysts were serologically euthyroid, the thyroid gland was radiographically free of tumors, and the epithelium lining the cysts showed no obvious atypia. In routine clinical practice, lines of evidence that may clinically suggest adrenal cyst as a metastatic thyroid cancer include identification of

Table 1. Summary of previously reported ectopic thyroid cysts and our cases

Case	Age (years)	Sex	Side	Properties	Size (mm)	Thyroid gland status	Immunohistochemistry				Genetic findings	Ref. No.
							HBME-1	CK19	Galectin-3	CD56		
1	61	W	R	UC	35	normal	NR	NR	NR	NR	NR	[4]
2	50	W	R	MC	30	normal	NR	NR	NR	NR	NR	[5]
3	50	M	R	UC	NR	normal	NR	NR	NR	NR	NR	[5]
4	50	W	L	MC	30	normal	NR	NR	NR	NR	NR	[6]
5	67	W	L	MC	30	normal	NR	NR	NR	NR	NR	[7]
6	54	W	L	UC	16	normal	NR	NR	NR	NR	NR	[8]
7	61	W	L	Capsule of the adenoma	8	papillary carcinoma (4.5 mm)	+	—	—	NR	NR	[13]
8	38	W	L	UC	52	normal	+	+	+	NR	No *BRAF* or *KRAS* (codons 12, 13 and 61) alterations	[14]
9	59	W	L	nodular mass	50	normal	+	+	+	NR	No *BRAF* or *KRAS* (codons 12, 13 and 62) alterations	[14]
10	51	W	L	MC	33	few nodules with benign characteristics	+	NR	+	NR	NR	[9]
11	32	W	R	UC	40	normal	NR	—	—	NR	No *BRAFV600E* or *H,K* or *N-RAS* alterations	[10]
12	49	W	L	UC	20	normal	—	NR	—	NR	No *KRAS* (exon 2 and exon 3) alterations	[11]
13	39	W	R	MC	70	normal	NR	NR	NR	NR	No *BRAF, RAS* or *RET* alterations	[12]
14	29	W	L	MC	28	normal	NR	NR	NR	NR	NR	[3]
15	60	W	R	UC	57	multiple small nodules or cysts	focal+	+	focal+	+	*FGFR3* (p.Arg248Cys) (mr 0.013) *HRAS* (p.Gly12Ser) (mr 0.01) *PIK3CA* (p.Cys378Tyr) (mr 0.015) No *BRAF, RAS* or *RET* alterations	Our case 1
16	51	M	L	UC	50	simple cyst (7 mm)	+	+	+	+	*HRAS* (p.Gly12Ala) (mr 0.002) No *BRAF, RAS* or *RET* alterations	Our case 2

Abbreviations: L, left; M, men; MC, multilocular cyst; mr, mutation rate; NR, not recorded; R, right; UC, unilocular cyst; W, women.

abnormality in the thyroid on imaging, its progressive enlargement over time, an elevation in serum thyroglobulin levels, and the presence of imaging findings that raise suspicion of metastasis to other organs.

Additionally, HBME, galectin-3, and CK19 staining was performed in 3 cases; 1 case was only positive for HBME-1, and 2 cases were positive for all 3 markers, similar to Case 2. However, these 2 cases were positive only in focal areas where the epithelia showed squamous differentiation [14]. Moreover, gene alterations were examined in 5 of the 14 cases by NGS or real-time PCR, and no alterations were detected in *BRAF*, *H/N/K-RAS*, or *RET*. Though major alterations were not identified, including those in the present case, this does not constitute conclusive evidence to rule out malignancy. Ectopic thyroid tissue may have originally existed, and part of it may have acquired an unknown driver alteration. Primary adrenal teratomas are rare, with only 49 cases reported [26]. While only a few studies have detailed its histology, multiple layers of embryonic germ cells have been observed, and there has been no description of a monodermal teratoma containing only thyroid tissue. Similar to cases involving ectopic thyroid tissue, adrenal teratomas were more prevalent in women (women, 35 cases; men, 14 cases). While this sex difference is intriguing, the underlying reason for the predominance of adrenal teratomas in women remains unclear.

In conclusion, the 2 adrenal cysts with thyroid follicular epithelium described herein were considered malignant tumors with unknown driver gene mutations in thyroid carcinoma based on cellular atypia, and immunohistochemical results. Regarding cellular origin, an ectopic thyroid tissue origin is most plausible unless thyroid cancer is evident. Further case series and analyses are necessary to confirm the origin and malignancy of thyroid tissue in the adrenal gland. Although ectopic thyroid tissue is generally considered benign, the present case suggests that malignancy should be considered.

Learning Points

- Cysts covered with thyroid follicular epithelium may occur in the adrenal glands.
- Ectopic thyroid tissue and metastatic thyroid carcinoma are differential diagnoses, which are challenging to distinguish.
- Despite the absence of major gene alterations in thyroid carcinoma, the potential for malignancy could not be ruled out, considering the increase in cyst size over time and the presence of cellular atypia.

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Contributors

Pathological diagnosis, writing, review, and revision of the manuscript: M.K, Y.N, and T.I. Radiological evaluation: T.K. Clinical follow-up including surgery: H.F and K.S. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patients.

Data Availability Statement

The original data generated and analyzed in this study are included in this published article.

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