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Paraganglioma of the testicle: A case presentation and review of the literature

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ABSTRACT

Paragangliomas are rare extra-adrenal neuroendocrine tumors and presentation within the scrotum is exceedingly rare. Only thirteen other cases have been reported in medical literature, with only one other case presenting within the testicle itself. We present the second known case of paraganglioma of the testicle in a patient who initially presented with a two-week history of right testicular pain with no associated dysuria and hematuria. Ultrasound imaging indicated a solid heterogenous mass in the right testicle concerning for malignancy and was treated surgically with right radical orchiectomy. Gross and histological investigation demonstrated a morphology and immunophenotype consistent with a paraganglioma.

Introduction

Paragangliomas are rare extra-adrenal neuroendocrine tumors, arising from neural crest precursor cell origin. They are also referred to as extra-adrenal pheochromocytoma, typically in older literature.[1] They may arise anywhere along the sympathoadrenal system, with less than 5% arising extra-abdominally.[2] While pheochromocytomas classically present with adrenergic symptoms due to catecholamine production, paragangliomas are less likely to be hormonally-producing and more likely to present with symptoms associated with tumor growth.[1] Paragangliomas within the scrotum are exceedingly rare. To date, only thirteen cases have been reported in medical literature, with only one other case presenting within the testicle itself (Table 1). We present the second known case of paraganglioma of the testicle in a patient who initially presented with a right testicular mass.

Case presentation

A 54-year-old man presented with a two-week history of right testicular pain with no associated dysuria or hematuria and self-examination notable for a right testicular irregularity. He had previous history of left renal cell carcinoma and left nephrectomy five years prior. The pain was described as dull in nature with no overt aggravating or relieving factors. Physical examination exhibited testicular and scrotal tenderness, with right varicocele noted but no abnormal testicular or scrotal masses. Ultrasound imaging indicated a $1.7 \times 1.6 \times 1.2$ cm solid heterogenous mass in the right testicle concerning for malignancy along with left varicocele and small bilateral complex hydroceles (Fig. 1). Computed tomography imaging showed no evidence of renal cell carcinoma or metastatic disease. There were prominent right inguinal lymph nodes which did not meet pathologic size criteria and bilateral pulmonary nodules. Tumor markers were all negative. He was treated surgically with a right radical orchiectomy.

Grossly, there was a $1.5 \times 1.5 \times 1.0$ cm well-circumscribed, yellow/white, gelatinous, firm mass situated at the lower pole of the removed testicle. The mass appeared to be abutting the tunica albuginea but did not appear to invade through. The remainder of the testicular parenchyma was tan-brown with seminiferous tubes that strung with ease. The epididymis and spermatic cord were grossly unremarkable. Histologically, the tumor was composed predominantly of epithelioid cells with granular, focally rhabdoid cytoplasm, cytoplasmic vacuoles, and focally with hyaline globules. The tumor cells were arranged in nested and focally trabecular growth pattern separated by fibrous septa. The tumor was a round well-defined nodule with rare scattered entrapped Leydig cell clusters and seminiferous tubules without infiltrative edges or evidence of intratubular germ cell neoplasia (Fig. 2). Immunoperoxidase stains were performed with the following results (Fig. 3):

- Positive: Vimentin, Synaptophysin, CD56, CD10, Beta-catenin (focal nuclear), S100 (rare stromal cells), Ki67 (~2%), CAM5.2 (very rare scattered positive cells)

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Table 1
Clinical data of previously published case reports of thirteen patients with paraganglioma presenting within the scrotum.

Case	Age	Location	Side	Size (cm)	Presentation	Metastases
Eusebi, 1971	37	Spermatic Cord	Right	2.5 diameter	Painless mass in scrotum present for 10 years	None
Soejima, 1977	52	Spermatic Cord	Left	4.5	Painless mass in scrotum	None
Bacchi, 1990	18	Spermatic Cord	Right	6.0	Painless mass in scrotum	None
Mashat, 1993	37	Spermatic Cord	Right	10.0 × 4.0	Painful mass with scrotal swelling	None
Attaran, 1996	40	Spermatic Cord	Left	1.5 × 1.5	Painless mass in scrotum	None
Young, 1999	52	Spermatic Cord	Right	1.5 × 1.5	Tender lump within spermatic cord	None
Abe, 2000	55	Spermatic Cord	Left	2.0 × 2.0	Painless mass in scrotum	Previous history of bilateral carotid body paragangliomas and bilateral pheochromocytomas
Garaffa, 2008	69	Spermatic Cord	Right	2.0	Weight loss, malaise, and mass above testicle,	None
Gupta, 2009	33	Spermatic Cord	Right	5.5 × 4.0	Mass in scrotum with dragging pain	None
Alataki, 2010	45	Spermatic Cord	Left	4.8 × 3.3	Painless lump in scrotum	None
Majdoub, 2013	50	Spermatic Cord	Left	2.7 diameter	Painless mass with scrotal swelling	None
Makris, 2014	40	Testicle	Right	17.5 × 10.0	Non-tender mass in scrotum	Bilateral lung nodules
Kwon, 2016	40	Spermatic Cord	Left	1.8 × 1.3	Painless mass in scrotum	None

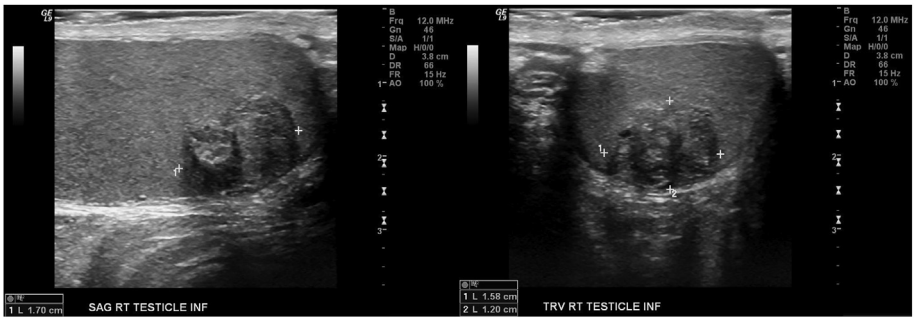

Fig. 1. Ultrasonographic imaging of the left testicle. Sagittal and transverse ultrasonography shows a solid heterogeneous mass in the bottom pole of the left testicle, measuring 1.7 × 1.6 × 1.2 cm. Testicular echogenicity is normal.

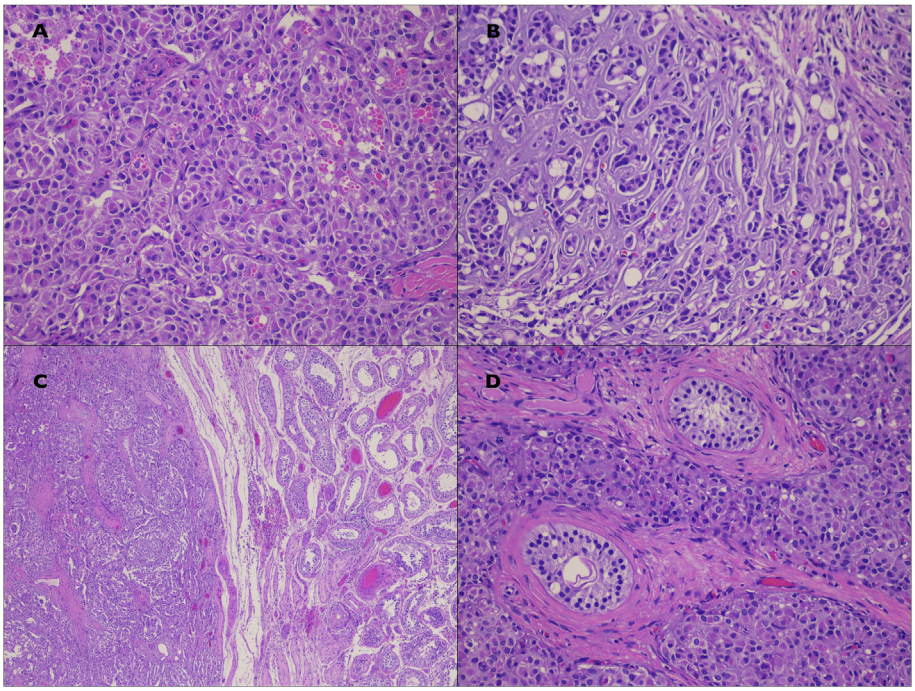

Fig. 2. Hematoxylin-eosin (H&E) staining. A) Epithelioid cells with eosinophilic cytoplasm arranged in sheets (200x). B) Similar cells arranged in trabecules (200x). C) Well-defined tumor nodule separated by a thin capsule from the surrounding testicular parenchyma (40x). D) Rare entrapped seminiferous tubules composed of mainly Sertoli cells (200x).

- Negative: Chromogranin A, Pankeratin, CK7, CK20, HMWK, WT1, Inhibin, Calretinin, MART1, RCC, PAX8, Podoplanin, CD30, CEA, Glypican, HepPar1, EMA, SALL4, OCT3/4, PLAP, AFP

Discussion

Paragangliomas and pheochromocytomas are rare tumors with an estimate annual incidence of about 2–8 per million. With paragangliomas accounting for just 10% of total pheochromocytomas,

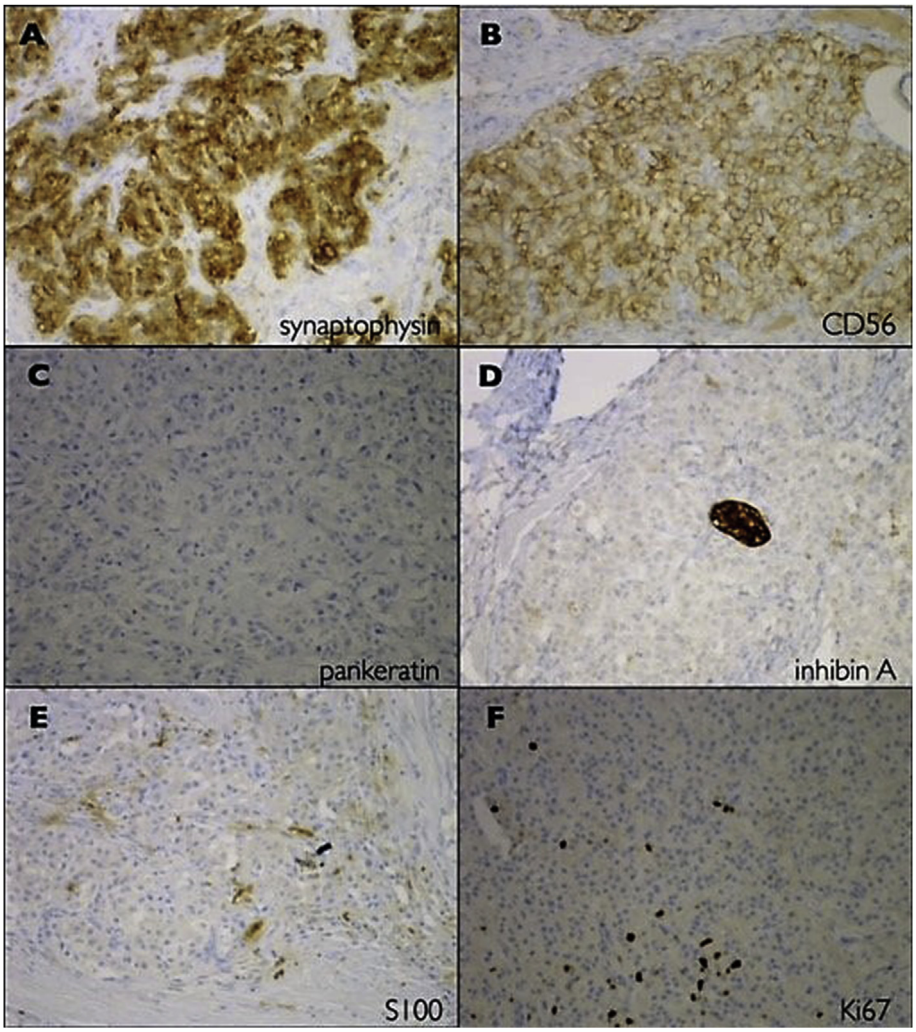

Fig. 3. Immunoperoxidase staining at 200x magnification. A) Synaptophysin diffusely positive cytoplasmic and membranous pattern in tumor cells. B) CD56 diffusely positive membranous staining in tumor cells. C) Pankeratin negative. D) Inhibin A negative tumor cells with positive Sertoli cells in entrapped seminiferous tubules E) S100 scattered positive stromal cells. F) Ki67 positive in ~2% of tumor cells.

paragangliomas within scrotum are exceedingly rare with only thirteen cases reported in medical literature and only one other case presenting within the testicle itself.[1] Due to the rarity of primary testicular paragangliomas, common tumors of the testicle and metastases had to be ruled out, presenting an interesting challenge in the differential diagnosis and a unique learning opportunity for future cases.

For our patient, the gross morphologic differential diagnosis included paraganglioma, testicular carcinoid tumor, Leydig cell tumor and hepatoid yolk sac tumor. The tumor's immunophenotype ruled out germ cell tumors (including yolk sac tumor), sex cord/gonadal stromal type testicular neoplasms (including Leydig cell and Sertoli cell tumors), and metastatic renal cell carcinoma. Testicular carcinoid was also ruled out due to the S100 and keratin expression patterns.[3] Presence of S100, specifically expressed by sustentacular cells, allows for the ruling in of paragangliomas and pheochromocytomas, although it may be sometimes absent. The immunophenotype was consistent with and supported a neuroendocrine tumor (positive synaptophysin, vimentin), more specifically a paraganglioma.[1,3] Interestingly, the tumor was negative for Chromogranin A, which is a very specific marker for paragangliomas. Chromogranin-negative paragangliomas and pheochromocytomas are virtually non-existent, so this brings another unique aspect of this case.[3]

Our patient's case also represented a case of benign tumor, which accounts for 90% of paragangliomas and pheochromocytomas. However, there is difficulty in differentiating between benign and malignant tumors pathologically, and malignant cases are only reliably diagnosed by the presence of distant metastases.[1,2] Immunoreactive staining of Ki-67/MIB-1, a marker for proliferative activity, has shown to be a promising tool in distinguishing between benign and malignant tumors. A proliferative activity value of greater than 3% produced a specificity and sensitivity of 100% and 50%, respectively, in predicting malignancy. Another study showed all benign tumors having a Ki-67 index of less than 1%. Our patient showed a Ki-67 value of approximately 2%, which sits in between the values of the two studies.[1] The prognosis for malignant tumors is relatively poor with five-year survival rates varying from 20% to 50%.[1,4] Although malignancy is rare, this does highlight the need of additional methods in determining malignancy, due to the poor prognosis conferred by these malignant tumors. Additionally, recurrence is another factor that must be considered. One study looking at abdominal extra-adrenal paragangliomas estimated a local-regional recurrence of 15% at 5 years and nearly 25% after 10 years, highlighting the necessity of follow-up and monitoring of these tumors due to the high possibility of recurrence.[5]

Conclusion

This case presents with a very rare diagnosis of paraganglioma within the scrotum and even exceedingly rarer presentation within the

testicle. This case demonstrates only the second documented case of an intratesticular paraganglioma in medical literature. Additionally, our patient presented with a unique Chromogranin-negative phenotype, which is virtually unseen for paragangliomas. These tumors within the scrotum are typically managed with a radical orchiectomy, due to the tumor's ability to metastasize, along with continued follow-up and monitoring, due to the possibility of recurrence. Although this particular location of paraganglioma is rare, it is the hope that these findings contribute to the continued study of this disease process.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eucr.2019.100847.

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