Case Report

Metastatic epithelioid trophoblastic tumor in retroperitoneal nodes in a case of regressed germ cell tumor of testis: An extremely rare occurrence

Uma Sakhadeo*, Santosh Menon, Gagan Prakash[1], Sangeeta B. Desai

Departments of Surgical Pathology and [1]Surgical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

*E-mail: dr.uma14@gmail.com

ABSTRACT

Epithelioid trophoblastic tumor is an extremely rare tumor which occurs in women of the reproductive age group following a previous gestation. Its occurrence in male patients is remarkably rare, with only six cases reported in the English literature. Herein, we discuss the unusual occurrence of this tumor in a 31-years-old male patient as a component of non-seminomatous germ cell tumor. It presented as retroperitoneal metastasis with associated testicular microlithiasis (regressed germ cell tumor).

INTRODUCTION

Tumors of trophoblastic derivation other than choriocarcinoma are very rare in the testis but have been reported on occasion in association with other germ cell tumors. Their morphologic spectrum is analogous to the trophoblastic tumors of the female genital tract including epithelioid trophoblastic tumor (ETT) and placental site trophoblastic tumor (PSTT).[1] We describe a 31-year-old male patient who presented with left flank pain. Ultrasonography (USG) revealed a large retroperitoneal and pelvic mass with testicular microlithiasis. His serum beta-HCG was marginally raised (161 mIU/ml), whereas alpha fetoprotein (AFP) and lactate dehydrogenase (LDH) levels were within normal limits. The core biopsy of the retroperitoneal mass was reported as trophoblastic tumor. The patient received standard neoadjuvant chemotherapy. The left orchidectomy revealed features of a regressed germ cell tumor. His disease progressed and a desperation retroperitoneal dissection revealed metastasis of ETT and teratoma. The dilemmas of management are discussed.

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.iju_58_22

CASE REPORT

A 31-year-old male patient presented with left flank pain of 3 months duration. USG abdomen revealed a paraaortic retroperitoneal conglomerated nodal mass (6.5 cm × 5.8 cm) and pelvic necrotic nodal mass (9.2 cm × 7 cm) along left the external iliac vessels. His serum beta-HCG was marginally raised (161 mIU/ml), whereas AFP and LDH levels were within normal limits. USG testes revealed microlithiasis, there was no mass lesion computed tomography (CT)-guided core biopsy of the retroperitoneal mass was obtained and was reported as trophoblastic tumor based on the presence of an epithelioid pleomorphic tumor which expressed EMA, p63, and GATA3. It was negative for CD30, glypican 3, and OCT3/4. SALL4 immunohistochemistry was not done on this core biopsy. The patient underwent 3 cycles of standard BEP (bleomycin, etoposide, and cisplatin) chemotherapy. Response positron emission tomography (PET)-contrast-enhanced computed tomography (CECT) revealed a fluorodeoxyglucose (FDG)

Received: 14.02.2022, **Revised:** 12.05.2022,

Accepted: 15.06.2022, **Published:** 01.07.2022

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

avid retroperitoneal para-aortic nodal mass noted with areas of necrosis, measuring 5.1 cm x 3.7 cm x 4.4 cm, SUVmax 12.07 (previously measuring 4.65 cm × 3.1 cm × 4.4 cm, SUVmax 7.49). Thus, there was an interval increase in the size and metabolism of these masses as well as in metastatic bilateral lung nodules. Post BEP, left side orchidectomy and retroperitoneal node dissection (RPLND) were done and both did not reveal any tumor. The testicular tubules revealed microlithiasis ("burnt out" or regressed germ cell tumor), also noted was intertubular fibrosis and sclerosis with absent spermatogenesis [Figure 1a]. There was no GCNIS. He then received 2 cycles of TIP (paclitaxel, ifosfamide, and cisplatin). Follow-up PET-CECT, post-second-line chemotherapy at 2 months revealed an FDG-avid retroperitoneal para-aortic nodal mass noted, measuring 33 mm × 46 mm, SUVmax 5.09 (5.1 cm × 3.7 cm × 4.4 cm, SUVmax 12.07). Bilateral lung nodules were persistent. Serum beta-HCG at this stage was 2260 mIU/ml. A desperation RPLND was then performed and it revealed two tumor components. The predominant one was ETT which displayed sheets of moderately pleomorphic tumor cells of epithelioid [Figure 1b] morphology. The tumor was arranged in sheets and aggregates. There was focal eosinophilic hyaline-like material [Figure 1c]. There were large areas of hemorrhage and necrosis along with dispersed thrombosed vessels. The other component was a mature teratomatous component composed of fibrous stroma and cystically dilated glands lined by mucinous and columnar epithelium [Figure 1d]. The ETT component expressed AE1AE3, p63, and GATA3 [Figure 2a-c]. There was a focal expression of human placental lactogen (hPL) [Figure 2d]. SALL4, CD30, Oct3/4, and glypican 3 were all negative. Follow-up PET-CT after 2 months showed low-grade uptake in the retroperitoneal mass and lung nodules. Serum beta-HCG was 5489 mIU/ml. The patient was referred for palliative care.

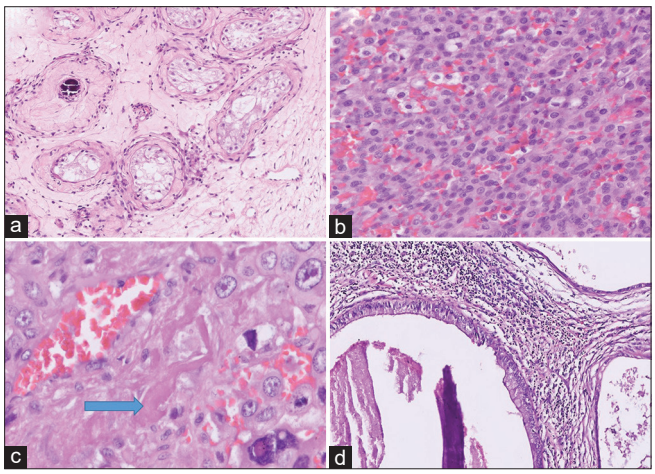

Figure 1: Hematoxylin and eosin sections: (a) Intratubular microlithiasis and fibrosis, thickening of basement membranes of the seminiferous tubules with interstitial edema in the left testis; suggestive of regressed germ cell tumor (×40). (b) Sheets of epithelioid tumor cells (×200). (c) Focal hyaline matrix (arrow) (×400). (d) Teratomatous component composed of cysts lined by ciliated epithelium (×100)

DISCUSSION

ETT is a distinct entity in the category of gestational trophoblastic tumors which also includes exaggerated placental site, placental site nodule, and PSTT. These entities are classified as extravillous trophoblastic lesions.[2] The term "ETT" was first introduced by Mazur and Kurman,[3] however, its first account was given by Shih *et al.* where they described its peculiar clinicopathologic characteristics in 14 female patients.[4] ETT is a malignant tumor of the extravillous trophoblasts of the chorionic type.[2] It typically occurs in females with antecedent gestation and mild-to-moderate elevation of beta-HCG level (<2500 mIU/ml)[5]. The occurrence of ETT in males is extremely rare with only six-documented cases[1,6,7] [Table 1]. Of these, one case was remarkably unique due to its occurrence in elderly male, extragonadal location (lung), and a coexisting pulmonary adenocarcinoma.[7] The remaining five cases showed an age range of 19–43 years; with mildly elevated serum beta-HCG except for one case (179,97 mIU/ml).[1,6] within our patient, beta-HCG was 161 mIU/ml at presentation, which further increased to 2260 mIU/ml and 5489 mIU/ml during the course of the disease. Post BEP therapy, he underwent left orchidectomy and RPLND, both of which did not show any residual tumor. However, the testis revealed fibrosis and intratubular microlithiasis, both of which strongly indicated a regressed germ cell tumor.[8] The follow-up beta-HCG (2260 mIU/ml) and PET-CT revealed disease progression. The patient received 2 cycles of second-line TIP chemotherapy and then underwent desperation RPLND, as the abdominal disease was unresponsive. The sections revealed ETT and teratoma. The ETT component expressed AE1AE3, GATA3, hPL (focal), and p63. SALL4 was negative. MIB-1 index was 50%. Similar to our case, all the cases documented in male patients demonstrated morphological and immunohistochemical features similar to the tumors occurring in female patients.[1,6,7] The classically described tumor in females also shows nests and cords of monomorphic epithelioid cells with

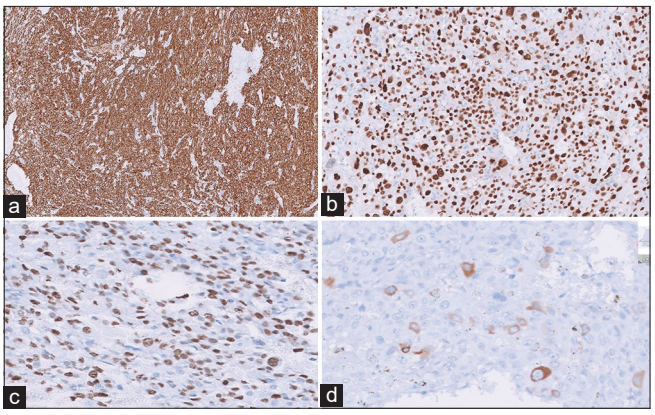

Figure 2: Immunohistochemistry: Diffuse expression of AE1AE3 (a), GATA3 (b) and p63 (c). Focal expression of hPL (d)

Table 1: Published cases

Year	Author	Age in years	Serum B-HCG (mIU/ml)	Site	Histological Diagnosis	Positive IHC	Ki67	Negative IHC
2009	Robert W. Allan	39	275	Left testis with para-aortic lymph node metastasis	Combined germ cell tumor in Testis and Metastatic ETT and teratoma in the para-aortic mass	HSD3B1, p63, cyclin E	25%	hPL
2012	Ju Sik Yun	69	Not done	Lung	Combined ETT and contralateral synchronous adenocarcinoma of the lung			
2015	Muhammad T. Idrees	19	247	Right testis	Combined ETT 5%; YST 70%; teratoma 25%	Inhibin, hCG, EMA, GATA3	10%	hPL, p63
2015	Muhammad T. Idrees	38	WNL	Left testis	Combined ETT 5%; EC 95%	Inhibin (focal), hCG (focal), hPL (focal), p63, PLAP	15%	
2015	Muhammad T. Idrees	43	WNL 8400 at first Recurrence	Precaval mass	Combined ETT (5%); teratoma (95%) Orchiectomy: EC, YST, teratoma	Inhibin (patchy), p63 (weak patchy)	25%	hCG, hPL, glypican 3 SALL4
2015	Muhammad T. Idrees	32	17997	Left deep chest mass	Combined ETT (95%); teratoma (5%) Orchidectomy: Teratoma, scar	AE1/3, GATA3, p63, HSD3B1, PLAP, 4H84	25%	hPL, CD10, OCT3/4, hCG, SALL4, glypican 3, MelCAM
Our case		32	161 2260 first recurrence 5489 second recurrence	Para-aortic	Combined ETT (60%); teratoma (40%) Orchidectomy: scar, Microlithiasis	AE1/3, GATA3, p63, hPL	50%	Glypican 3, Oct3/4, SALL4

IHC: Immunohistochemistry, ETT: Epithelioid trophoblastic tumor, WNL: Within normal limits, EC: Embryonal carcinoma, YST: Yolk sac tumour, hPL: Human placental lactogen, PLAP: Placental alkaline phosphatase, hCG: human-Chorionic gonadotropin, EMA: Epithelial membrane antigen

the characteristic eosinophilic hyaline matrix.[4,5] Idrees *et al.* have described three cases of ETT in males with an associated teratoma.[1] However, all three cases presented as testicular mass, unlike our patient. To the best of our knowledge, this is the first case of a regressed testicular germ cell tumor which developed epithelioid trophoblastic tumor at the metastatic site in retroperitoneum nodes. The non-expression of SALL4 and relatively low levels of beta-HCG ruled out the possibility of choriocarcinoma.[9] PSTT was a more plausible differential, however, PSTT can be distinguished as it is characteristically p63 negative and demonstrates extensive expression of hPL.[9] Focal expression of hPL is known as seen in our case.[5,10] Another distinctive feature of PSTT is diffuse expression of MelCAM. ETT only shows scattered expression if at all.[2,5] MelCAM was not done in our case. ETT and PSTT are chemoresistant, unlike choriocarcinoma.[2] Our patient also failed to respond to two lines of chemotherapy and was finally referred to palliative care following the RPLND.

CONCLUSION

We describe the first case of a regressed testicular germ cell tumor which presented as ETT at a metastatic site. It is of vital importance to identify these extravillous trophoblastic tumors in males as they are chemoresistant which may portend a graver prognosis as treatment options are limited.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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How to cite this article: Sakhadeo U, Menon S, Prakash G, Desai SB. Metastatic epithelioid trophoblastic tumor in retroperitoneal nodes in a case of regressed germ cell tumor of testis: An extremely rare occurrence. Indian J Urol 2022;38:230-3.