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Ovarian Steroid Cell Tumor, Not Otherwise Specified: a case series

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ABSTRACT

Case series of Ovarian Steroid Cell Tumor Not Otherwise Specified is being reported in a child and two post-menopausal females. Hormonal symptoms were present in all of them. Two of three had malignant potential. The clinical presentation and histopathologic features and treatment of this extremely rare variety of sex cord stromal tumor has been discussed.

Keywords: children, histopathology, immunohistochemistry, malignant potential, not otherwise specified, ovarian steroid cell tumor

INTRODUCTION

Steroid cell tumors (SCT) were first described by Scully in 1979 and Steroid cell tumors, not otherwise specified (SCT, NOS) are a rare subgroup of sex cord stromal tumors accounting for less than 0.1% of all ovarian tumors. The largest study till date on these tumors was by Hayes and Scully who described 63 cases.[1]They are usually seen in adults with the mean age of 40 years and are very rare in children. They have endocrine secreting potential and patients most commonly present with androgenic manifestations; hirsutism and virilization in adults &heterosexual precocity in children. While most are benign, malignancy has been reported in one third of the cases. Based on the cell of origin, they are divided into three subtypes: stromal luteomas arising from ovarian stromal cells, Leydig cell tumors arising from Leydig cells in the hilus, and steroid cell tumors, not otherwise specified (NOS) when the lineage is unknown. The NOS subtype makes up around 60% of SCTs and tends to affect adult females.[1-3] Very few cases of SCT, NOS including malignant forms have been reported even in children in the literature.[4,5] We herein report three cases of ovarian SCT, NOS diagnosed within a span of 12 years (2008-2020) with a comprehensive analysis of the various aspects of their clinical presentation, treatment and pathological features of this rare entity.

CASE 1

A four years old child presented with increase in facial hairs, abdominal pain and distension. On physical examination she had clitoromegaly, cushingoid moon facies, deepening of voice and weight gain. Contrast enhanced computed tomography (CECT) revealed heterogeneously contrast enhancing solid mass in right ovary along with minimal free fluid in the abdominal cavity. Serum LDH, β-hCG and α-FP levels were within normal biological reference interval with very high serum testosterone level [Table-1] and high cortisol level (23.8µg/dl; normal <0.9µg/dl). Serum TSH, FSH, LH, prolactin, 17-hydroxyprogesterone and aldosterone were also within normal limits. Left salpingo-oophorectomy was performed. The final diagnosis from histopathology and immunohistochemistry was rendered as steroid cell tumor, NOS with malignant potential [Table-2]. A combination chemotherapy consisting of cisplatin, vincristine, and bleomycin was planned but the patient refused to take. She had been followed up closely and no recurrence or metastasis has been documented till date.

CASE 2

A 55 years old postmenopausal woman presented with increase in facial hairs, change of voice and abdominal distention with pain for two months. On examination, she was found to have breast atrophy, ascites and lump in the abdomen. A CECT was performed. It revealed a contrast enhancing solid mass with hemorrhage and necrosis in left ovary. Serum testosterone level was high [Table-1]. Serum tumor markers were within normal limits except slightly elevated level of CA-125 (155U/ml; normal<35U/ml). Exploratory laparotomy was performed. The mass was removed and sent for intraoperative frozen section consultation, followed by a total hysterectomy, bilateral salpingo-oophorectomy, left pelvic lymph node dissection and partial omentectomyAscitic fluid cytology was negative for malignant cells. The final diagnosis after histopathology and IHC confirmation was given as SCT, NOS, benign. Her CA-125 level normalized after surgery. She has been living disease free at 12 months of follow-up.

CASE 3

A 68 years old post-menopausal woman complained of excessive post-menopausal bleeding, alopecia and increase in facial hairs. After initial physical examination, a CECT was performed. It revealed a heterogeneously enhancing solid mass in left ovary along with necrosis and hemorrhage. Serum biochemical and tumor markers were evaluated. All the parameters were within normal limits except serum testosterone, estrogen (85pg/ml; normal 0-30pg/ml for age) and Inhibin B levels (23.5pg/ml; normal <5pg/ml for age). Exploratory laparotomy was planned for frozen section consultation. In frozen section, differential diagnoses were offered as either a Leydig cell tumor or steroid cell tumor with nuclear atypia, mitotic activity and necrosis. Following removal of tumor and frozen section confirmation, a total hysterectomy, bilateral salpingo-oophorectomy, left pelvic lymph node dissection and partial omentectomy were performed. Ascitic fluid was sent for cytological examination and it

Table-1: Clinical and demographic details of the patients

Characteristics		Case 1	Case 2	Case 3
Age (in years)		4	55	68
Symptoms		Androgenic	Androgenic	Androgenic+Estrogenic
	Tumor laterality	Right	Left	Left
	Tumor size (cm3)	16.5x10x8	9.5x6.5x4.5	7x6x3
Radiology	Ascites	Mild	Moderate	Moderate
	Metastases	Absent	Absent	Absent
Serum T level in ng/dl		266 (N:7-20)	320 (N:<40)	375 (N:<40)
Treatment		RSO	TH+BSO+LPLND+PO	TH+BSO+LPLND+PO
Follow-up (in months)		18	12	6
Current status		LWOD	LWOD	LWOD

NOTE: T-Testosterone; RSO-Right salpingo-oophorectomy; TH-Total hysterectomy; BSO-Bilateral salpingo-oophorectomy; LPND-Left pelvic nodal dissection; PO-Partial omentectomy; LWOD-Live without disease.

Table-2: Pathological findings of cases

	Characteristics	Case 1	Case 2	Case 3
HPE	Gross appearance	Solid, Encap, SS, Necr, Hem	Solid, Encap, SS	Solid, Encap, SS, Necr, Hem
	Histologic cell type	Clear + Eosinophilic	Clear	Eosinophilic + clear (focal)
	Cellular atypia*	Moderate	Mild	Moderate
	Mitotic count/10HPF*	3-4	0-1	10-12
	Necrosis and hemorrhage*	Present	Absent	Present
	Lymphovascular emboli*	Absent	Absent	Absent
	Capsular invasion	Absent	Absent	Absent
	Ovarian surface	Free	Free	Free
	Pathological diagnosis	SCT, NOS (Malignant)	SCT, NOS (Benign)	SCT, NOS (Malignant)
IHC	Vimentin	Positive (++)	Pos (+), focal	Pos (+++)
	AE1/3	Positive (+), focal	Negative	Positive (+), focal
	EMA	Negative	Negative	Negative
	Inhibin	Positive (++)	Positive (+++)	Positive (+++)
	Calretinin	Positive (++)	Positive (++)	Positive (++)
	Melan A	Positive (+)	Positive (++)	Positive (+++),
	MIB1 (%)	5	1-2	25-30
	PLAP	Negative	Not done	Not done
	OCT3/4	Negative	Not done	Not done
	Synaptophysin	Negative	Not done	Focal positive
	INI-1	Retained	Not done	Not done
HPE of the other ovary		NA	Unremarkable	Stromal hyperplasia
Endometrium		NA	Weak proliferative	Hyperplasia without atypia
Lymph node metastasis		NA	Absent	Absent
Omental deposit		NA	Absent	Absent
Pathological stage (TNM)		NA	pT1a	pT1a

*NOTE: *Pathological features associated with malignant potential along with tumor size >7cm. Encap-Encapsulated; SS-Smooth surface; Necr-Necrosis; Hem-Hemorrhage; SCT, NOS-Steroid cell tumor, Not otherwise specified; AE1/3-Anion Exchanger 1/3; EMA-Epithelial membrane antigen; MIB1-Antibody to Ki67 antigen; PLAP-Placental alkaline phosphatase; OCT3/4-Octamer-binding transcription factor 3/4; INI-1-Integrase interactor 1; NA-Not applicable; TNM-Tumor node metastasis.*

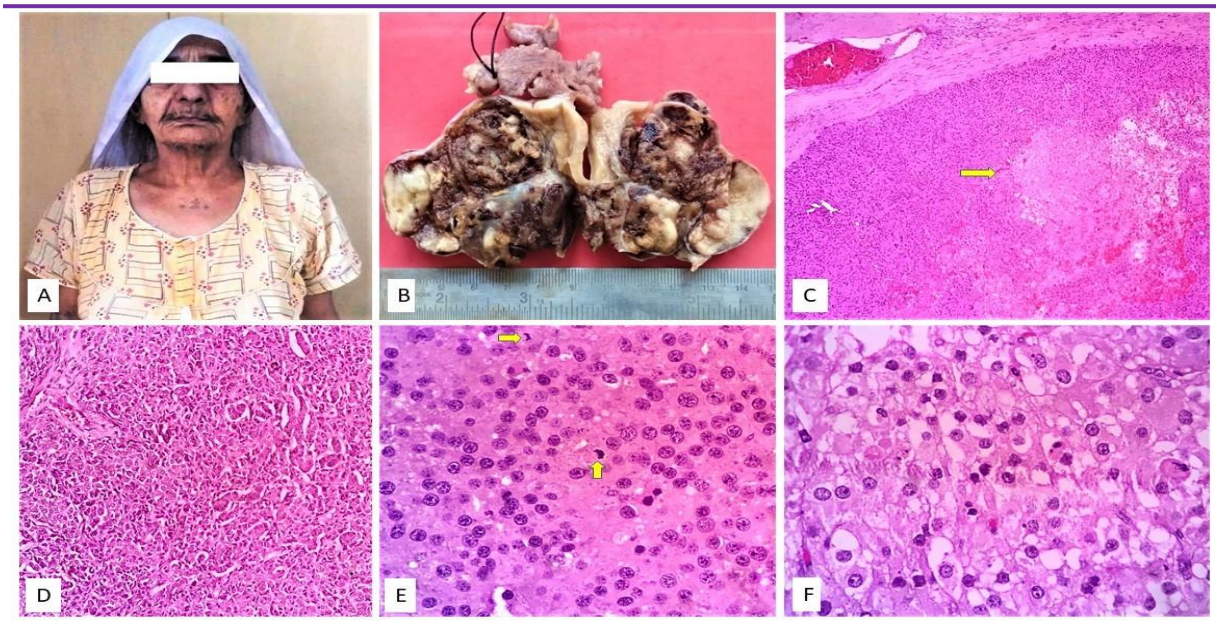

Figure-1: A: Patient in case no. 3 with hirsutism (written permission of the patient obtained for the image); B :Steroid cell tumor,NOS (Case no. 3); Gross picture showing a tumor involving ovary with solid pale yellow to hemorrhagic and necrotic cut surface; C: Solid circumscribed tumor with area of coagulation necrosis (yellow arrow) (H&E, 4x); D: Tumor cells arranged in solid tubules and interlacing cords resembling Sertoli cell tumor (H&E, 10x); E: Moderately pleomorphic tumor cells having round nuclei, abundant eosinophilic granular cytoplasm and prominent nucleoli; Atypical mitosis evident (yellow arrows) (H&E, 40x); F: At areas, cells have abundant eosinophilic to clear vacuolated cytoplasm (H&E, 40x); NOS- Not otherwise specified; H&E- Hematoxylin & eosin.

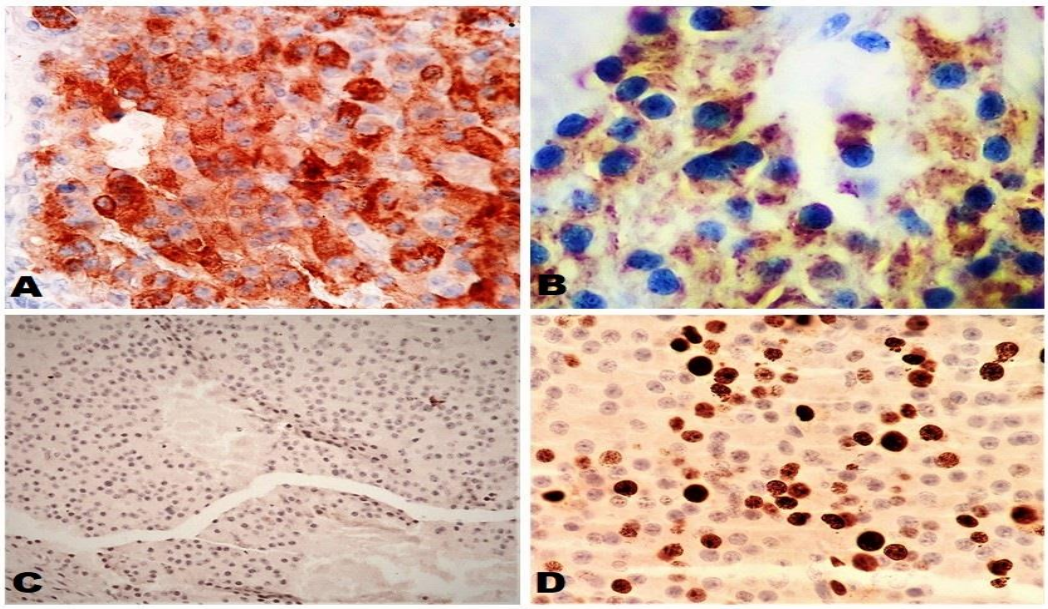

Figure-2: Immunohistochemistry in steroid cell tumor, NOS (case no. 3): A: Strong and diffuse Inhibin A expression by tumor cells (IHC, 40x); B: Melan-A expression (IHC, 40x); C: EMA negativity in tumor cells (IHC, 20x); D: High Mib-1 index (IHC, 40x); IHC- Immunohistochemistry; EMA- Epithelial membrane antigen

was free of tumor involvement. Final diagnosis was given as SCT, NOS with malignant potential [Figure-1 and 2]. The patient was advised close follow up as she was not medically fit for chemotherapy regimen. Till date, she is living disease-free without any recurrence or metastasis.

DISCUSSION

Among the three subtypes, SCT, NOS account for approximately 60% and usually occur in adult women with a mean age of around 40 years. Most of them have endocrine potentials and only 25% are non-functional. Among the patients with SCT, NOS, 56-77% present with androgenic manifestations and virilization such as hirsutism, acne, clitoromegaly, deepening of voice, temporal baldness, amenorrhea and breast atrophy. Estrogenic manifestations such as menorrhagia, postmenopausal bleeding, endometrial hyperplasia or carcinoma have been found in 6-25% of cases. Only 6-10% are associated with Cushing's syndrome.[2, 6,7] All three cases (one child and 2 post-menopausal women) of the present study presented with androgenic features, along with Cushingoid features in case 1 and hyperestrogenism in case 3.

Steroid cell tumors (NOS) are solid, occasionally lobulated, masses which are usually well-encapsulated without surface vegetations. The malignant tumors frequently show necrotic and hemorrhagic cut surface, as in case 1 and 3 of the present study. Microscopically, they are composed of either predominantly small round cells with eosinophilic granular cytoplasm, as seen in case 3 or large round to polygonal cells having clear to vacuolated cytoplasm, similar to case 2 of our study. The cells are arranged in nests, cords or columns separated by fibrous septa. It is not unusual to find mixture of these cell types in a same tumor as in case 1. The overall structure of the tumor resembles zona glomerulosa and fasciculata of the adrenal cortex.[8-10]

SCT, NOS previously called lipoid cell tumor should be considered as a possible differential diagnosis for clear cell tumors of abdomen, which also include clear cell renal cell carcinoma and adrenocortical tumors specially when associated with androgenic changes in a child with elevated cortisol level, as presented in the case 1 of the present series. Other close differential diagnoses to be considered are germ cell tumors/dysgerminoma and malignant extra-renal rhabdoid tumor. Dysgerminoma usually show sheets of clear to vacuolated cells traversed by fibrovascular septa and prominent lymphocytic infiltration. It expresses PLAP and OCT3/4.[11] Extrarenal rhabdoid tumor shows predominantly rhabdoid cells with hyaline cytoplasmic inclusion and losses INI-1 expression.[12] Clear cell renal cell carcinoma expresses EMA, PAX 8, CD10 and RCC antigen.[13]

Immunohistochemically most of the SCTs are positive for calretinin, inhibin and Melan A. All three cases discussed here showed diffuse strong immunoreactivity for calretinin and inhibin (Figure 2A), while the expression of Melan A was heterogenous, varying from weak and diffuse (case1) to strong and focal (case 3, Table 2, Figure 2B). While SCTs are uniformly negative for EMA (Figure 2C), some of them may show reactivity for cytokeratin usually in focal and weak manner,

unlike in epithelial malignancy, which was a close mimicker in the patients (case 1 and 3) discussed herein.[2,9] All the three cases showed consistent vimentin expression as documented in most other studies.[2,3] Among all the markers, inhibin and calretinin are consistently positive and hence are most reliable for diagnosis of SCT, likewise EMA is consistently negative and when present the diagnosis of SCT, NOS has to be questioned.

While most of the steroid cell tumors (NOS) are benign, 25% to 43% of cases behave as clinically malignant. Malignant neoplasms are commonly associated with identification of five pathological features described by Hayes and Scully, such as the presence of $\geq$2 mitoses per 10 high power fields, vascular invasion, grade 2 or 3 nuclear atypia, necrosis or hemorrhage and a tumor size greater than 7cm.[1,2,4] It is very crucial to look for these pathological features in order to identify potentially malignant tumors as they are associated with aggressive behavior. We herein also identified two cases (case1 and 3) with pathological features suggestive of malignant behavior.

Surgical intervention is the most effective treatment for steroid cell tumors, NOS. Radiation or chemotherapy should be given to malignant tumors. Distant metastases are the only direct evidence of malignancy, however when the high-risk features are identified pathologically, they should be considered as potentially malignant and treated with chemotherapy along with long term follow-up. There are no well-defined chemotherapy regimens for management of steroid cell tumor. However, PVB (cisplatin, vincristine, and bleomycin) or BEP (bleomycin, etoposide, and cisplatin) has been recommended by some authors.[2,11] Gonadotropin-releasing hormone agonists can be used as postoperative adjuvant therapy in metastatic or aggressive disease.[5]

CONCLUSION

The present series highlights, the importance of histomorphology and immunohistochemistry to establish a final diagnosis as well as to identify its malignant potential along with clinical manifestations, blood biomarkers and radiological investigations. Malignant tumors behave aggressively and require chemotherapy. No chemotherapy regimen has been standardized due to its overwhelming rarity. Long-term follow up is essential.

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