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Steroid Cell Tumor-Not Otherwise Specified: A Not So Rare Tumor of Ovary

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ABSTRACT

Steroid cell tumor-not otherwise specified accounts for sixty percent of the rare steroid cell tumors. These tumors are presumed to be of ovarian stromal cell origin. They are typically benign with one third of them exhibiting malignant behaviour. Androgenic manifestations are common and are the predominant complaints among these patients. They are slow growing in nature and are known for late recurrences. Surgery is the gold standard treatment for both benign and malignant variants. Early stages have good prognosis and good survival, inclusive of fertility sparing surgeries. There is no standard of treatment with respect to advanced stages management and is usually customized to patients. However, complete cytoreductive surgery plays a curative role in these cases similar to epithelial ovarian tumors and is the initial step. Adjuvant therapy has evolved over time and is not limited to taxane/platinum based chemotherapy. Hormonal therapy has shown promising results in recurrent cases and needs further validation.

Key words: Steroid cell tumor NOS; Surgery; Adjuvant therapy; Cushing's syndrome; Hormonal therapy

INTRODUCTION

Steroid cell tumor are rare ovarian parenchymal tumors and account for 0.1% of sex-cord stromal tumors. Earlier known as lipoid cell tumor, secondary to the appearance of their cell cytosol, is obsolete now. The WHO classifies them as pure stromal tumors arising from mesenchymal cells of ovarian stroma. These tumors have been sub-divided into stromal luteomas, leydig cell tumor and steroid cell tumor-Not Otherwise Specified (NOS). Half of these patients present with androgenic manifestations, 10% estrogenic and occasionally with features of cushing's syndrome and progestational changes. Symptoms vary from precocious puberty, amenorrhea, hirsutism to virilization. Around one third of these steroid cell tumors exhibit malignant behavior [1,2].

CASE PRESENTATION

Stromal luteomas account for 20%-25% and are benign in nature. Typically seen in post-menopausal women, manifest with abnormal uterine bleeding and virilization symptoms. Stromal hyperthecosis co-exists in 90% of cases. Treatment is

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surgical removal of the ovaries. Leydig cell tumor is a benign entity, predominantly located in the ovarium hilum [3]. The average age of presentation is 58 years and typically present with androgenic endocrine manifestations. These tumors are usually small (<2 cm) and have solid, well circumscribed appearances on gross examination. Histologically, they typically have well circumscribed polyhedral cells with eosinophilic cytosol with lipochrome pigments. Reinke crystal are characteristic of these tumors. Mitoses are rare and immuno-histochemistry shows positive for inhibin, melan A and calretinin [4].

Steroid cell tumor not otherwise specified: These tumors lack definitive tumor characteristic and account for 56%-60% of steroid cell tumors. Around 25%-43% of them are malignant in nature unlike the rest two entities [5]. The average age of presentation is 43 years. Patients usually present with symptoms/signs of androgen excess and in our practice, this has been the most common presentation of these patients (**Figure 1**).

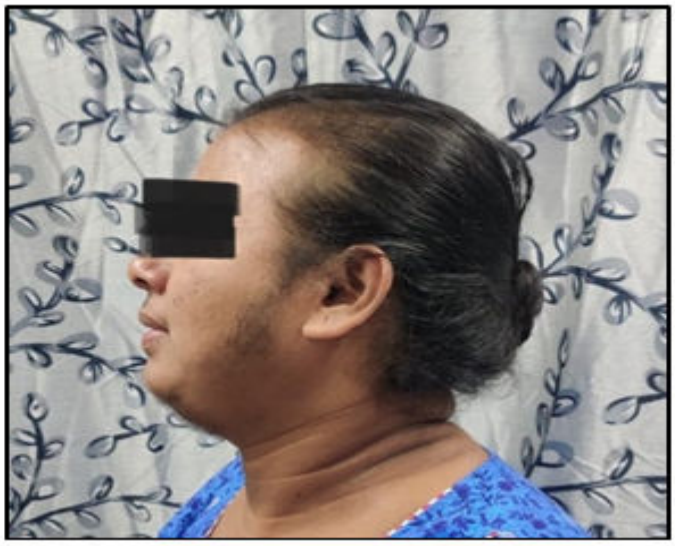

Figure 1: Receding hair line excess side burns.

The symptoms vary from hirsutism, receeding hair line, voice hoarseness and virilization (56%-77%). Other symptoms include sub-acute pelvic pain, abdominal distension, menstrual irregularities. Rarely they do present with abdominal distension, especially in advanced stages attributing to ascites. Bony metastases has been documented. Tumor markers serum inhibin and anti mullerian hormone, though non specific can be used as a surrogate marker for diagnosis and follow up. There is also elevation of serum testosterone and dehydro-epiandrosterone [6,7].

RESULTS AND DISCUSSION

Histopathological examination is crucial for diagnosis. Gross appearances reveal solid-cystic tumors with haemorrhage and necrosis varying from yellow to blackish areas. Histologically, these tumors exhibit expansile diffuse growth of large polygonal cells. The cells have abundant cytosol that range from eosinophilic (lipid poor) to pale vacuolated cells (lipid rich) [8,9]. Stroma ranges from scant to prominent fibrous bands. The nuclei are round with prominent nucleolus (**Figure 2**).

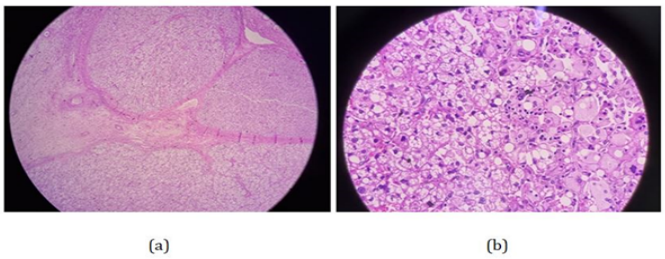

Figure 2: Histopathology of malignant steroid cell tumor-NOS. a) Fibrous stroma separating the cell clusters; b) Polygonal cells with multi-vacuolated cytosol, small round central nuclei.

Mitotic activity, necrosis are typically indicators of worse histology. Reinke crystals are absent. Hayes and Scully identified five pathological factors predictive of malignancy-two or more mitoses per high power fields (92% malignant); a tumor diameter of >7 cm (78% malignant); necrosis (86% malignant); haemorrhage (77% malignant) and grade 2 or 3 nuclear atypia (64% malignant) [10]. Immunohistochemistry shows positive for calretinin, inhibin and melan A and usually negative for FOXL2.

The staging for non-epithelial ovarian tumors is adopted from International Federation of Gynecology and Obstetrics (FIGO) of epithelial ovarian cancers. Conservative surgery can be offered to young women for ovary confined disease. Uterine endometrial curettage must be advocated before fertility preservation surgery, as they are hormone secreting tumors [11,12]. Total abdominal hysterectomy with bilateral salpingo-oophorectomy with complete staging is the standard of choice. Routine lymphadenectomy for staging purpose is not advocated, as nodal metastasis is very low. Complete cytoreduction surgery should be advocated for advance cases with tumor dissemination (**Figure 3**).

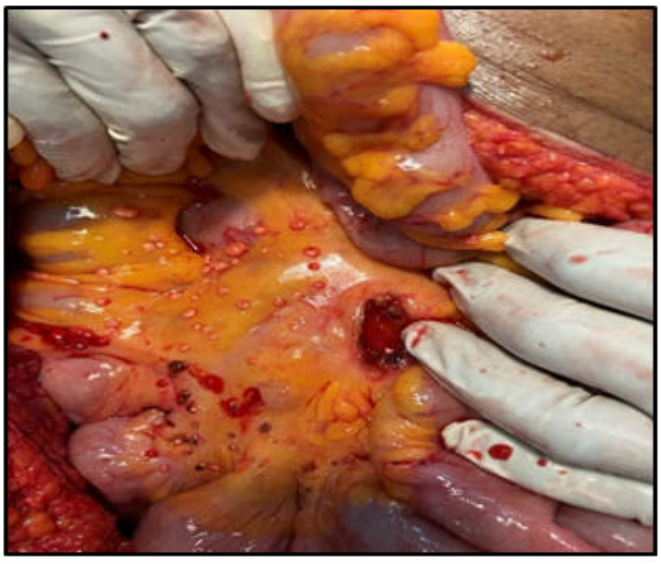

Figure 3: Multiple tumor deposits over mesentry-a case of malignant steroid cell tumor-NOS.

Management of advanced cases is challenging due to chemo-resistance and scarcity of trials. Surgical cytoreduction is the primary treatment for stage II-stage IV followed by adjuvant chemotherapy. Metastases to rare sites like bone, lung, liver and peritoneum have been documented [13]. Peritoneal metastasis are seen in around twenty percent of the cases. Platinum based chemotherapy has remained the first line of choice for sex cord stromal tumors with bleomycin, etoposide, cisplatin as the most preferred regimen. The efficacy of BEP in sex cord stromal tumor is limited, unlike germ cell tumors and also bleomycin comes with potential side effects, especially pulmonary fibrosis and secondary malignancy risk with etoposide. The choice of chemotherapy is not clear due to paucity of trials in these tumors and few recommended options include bleomycin, etoposide, cisplatin; carboplatin/paclitaxel; cyclophosphamide/doxorubicin [14].

The GOG 264, phase II trial randomly assigned women with newly diagnosed and recurrent chemo naive ovarian sex cord-stromal tumors to primary therapy with carboplatin and paclitaxel versus cisplatin, etoposide and bleomycin. They overall recruited 63 patients as study closed due to futility and difficult accrual. Further results on progression free survival is pending. There is potential role for use of targeted therapies and are underway. The ALIENOR trial showed better response rate with addition of bevacizumab among recurrent granulosa cell tumor. Bevacizumab has shown an overall response rate of 17% with stable disease in 78% in relapsed sex cord stromal tumors. Data on efficacy of other targeted agents is limited due to less cases and limited clinical trials [15]. Sex cord stromal tumors, unlike germ cell tumors, are not characterized by widespread genomic instability, but do have chromosomal abnormalities. Multi-kinase agent pazopanib has shown response in recurrent granulosa cell tumors. Hormonal agents like gonadotrophin releasing hormone analogues have shown promising results by inducing cellular apotosis. Their role has been evaluated in recurrent steroid cell tumor cases with remarkable responses in multiple studies. With the analogues, the hormonal assays typically show measurable reduction in their values and patients have symptomatic relief. The symptoms however recur with stoppage of these analogues and hence the need to administer for long duration.

CONCLUSION

Steroid cell tumors-NOS are not so rare tumors and advanced malignant steroid cell tumor-NOS can be wearisome to treat. Complete cytoreduction is the key prognostic factor as seen with epithelial ovarian tumors. Androgenic symptoms take time to revert and require post-operative hormonal assay monitoring. Adjuvant chemotherapy is required for stage II-IV patients and platinum based therapy is the preferred first line regime. Management of recurrent cases have to be individualized and options range from taxane/platinum combinations to GnRH analogues to targeted therapies.

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