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Case Report

Small Cell Carcinoma of Ovary Hypercalcemic type presented as back pain

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ABSTRACT

A young woman who presented to orthopedic department with referred back pain, hyper calcemic symptoms was worked up and found to be having ovarian mass. Small Cell Carcinoma of ovary hypercalcemic type is a highly malignant and prognostically poor tumor unique to the ovary. It is an undifferentiated carcinoma occurring in young patients and associates with hypercalcemia. Tumor morphology reveals sheets of anaplastic small cells with extensive necrosis and hemorrhage. Here we report a case of rare and aggressive histological type of ovarian carcinoma.

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1. Introduction

Small Cell Carcinoma of Ovary hypercalcemic type is a rare and enigmatic tumor accounts about less than 0.01% of ovarian neoplasms. It was first described in 1975. [1] In 1982 Dickersin et al reported eleven cases. [2] Young et al published retrospective analysis of 150 cases in 1994. [1] Estel R et al identified 80 cases in the literature between 1975 and 2010.[1] It effects young women and usually unilateral in presentation.[1,3,4] It is composed of small cells and considered as highly aggressive tumor with 50% of cases having spread beyond the ovary at the time of diagnosis.[3,5]

2. Case Report:

A 28 year-old female who was first seen by an orthopedic surgeon for persistent back pain, multiple bony pains, myalgia, abdominal and pelvic pain along with lethargy, fatigue and weight loss, and vague history of carpopedal spasms. She was treated symptomatically for few days. Her routine spinal radiographs were found to be normal and ultra sonography revealed an ovarian mass on the right side measuring 10x9x8 cm, Uterus and left side ovary were normal. There was no evidence of any lymph nodal enlargement. Keeping in mind as referred back pain she was send to gynecologist. Her General and per vaginal examination was unremarkable. Chest X ray and ECG were normal. Laboratory investigations were normal including CA 125, but serum calcium levels were raised.

Since the patient was young female with solid ovarian mass and has elevated serum calcium levels a provisional clinical diagnosis of Small Cell Carcinoma of Ovary hypercalcemic type was done. Total

abdominal hysterectomy and right salpingo oophorectomy was done. On gross examination the ovarian mass of 10x9x8 cm, weighed about 560 gm. Cut surface of the tumor was predominantly solid, pale white in color with areas of necrosis, hemorrhage and cystic degeneration [Figure 1].

Microscopically, the tumor was highly cellular showing diffuse growth pattern with small islands, trabeculae, cords and solid areas. Tumor cells were small, round to ovoid in shape with scant cytoplasm and hyper chromatic nuclei [Figure 2]. Few nuclei showed nuclear folding simulating nuclear grooves. The nucleoli were indistinct. Few mitotic figures were present. There were small cystic spaces lined by mucinous epithelium and occasionally follicle like areas with eosinophilic material seen.

Juvenile / adult Granulosa cell tumor, primary carcinoid tumor, lymphoma and Small cell carcinoma of ovary were considered in the differential diagnosis. To differentiate between these tumors a panel of immune marker studies were done. Tumor cells were negative for inhibin, epithelial membrane antigen, chromogranin A, common leukocyte antigen and placental alkaline phosphatase [Figure 3], but were positive for low molecular weight cytokeratin (CAM 5.2) [Figure 4] and WT1 [Figure 5].

We excluded granulosa, carcinoid and Lymphoid tumors since tumour cells were negative for inhibin, chromogranin A and common leucocyte antigen respectively. we considered diagnosis of small cell carcinoma of ovary due to positive staining for WT1 and low molecular weight cytokeratin (CAM 5.2).

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To know the status of hypercalcemia post operative serum calcium level was measured and it was normal. So preoperative elevated serum calcium level was attributed to the tumor. Hence the final diagnosis of small cell carcinoma of ovary, hypercalcemic type was made.

Figure 1: Gross photograph of small cell carcinoma of ovary, cut surface showing predominantly solid, pale white with areas of necrosis and cystic degeneration.



Figure 2: a, Tumor cells were small, round to ovoid with scanty cytoplasm and hyper chromatic nuclei. (H&E stain 200 x). b, Few nuclei showed nuclear folding simulating nuclear grooves and nucleoli were indistinct. (H&E stain 400 x).

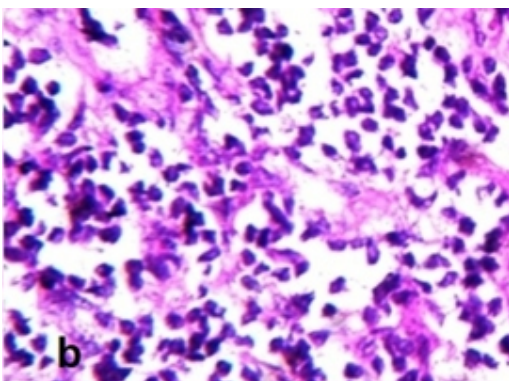
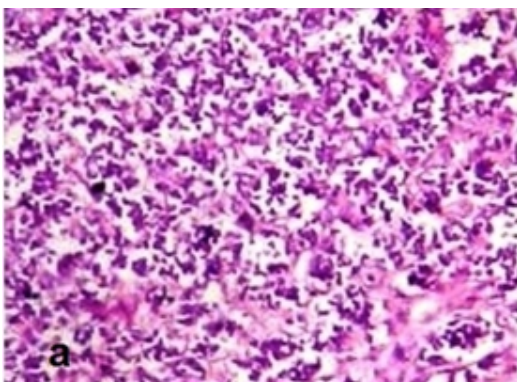


Figure 3: Immunohistochemical staining of the tumor cells showing negativity for inhibin (a), epithelial membrane antigen (b), chromogranin (c), commonleukocyte antigen (d) and placental alkaline phosphatase (e).(400x).

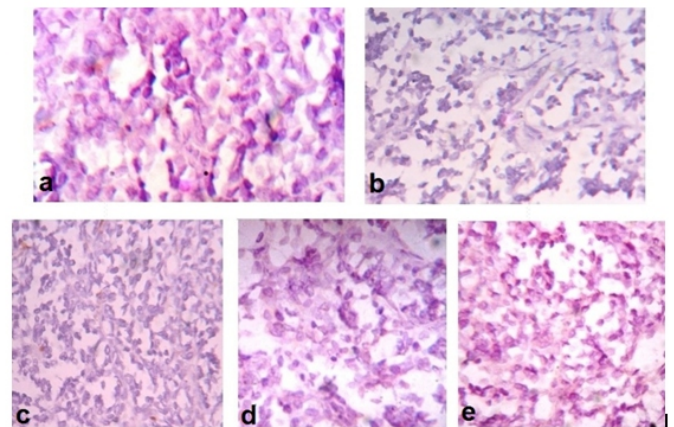


Figure 4: Immunohistochemical staining of the tumor cells showing positivity for Low molecular weight Cytokeratin (CAM 5.2). (Low Power).

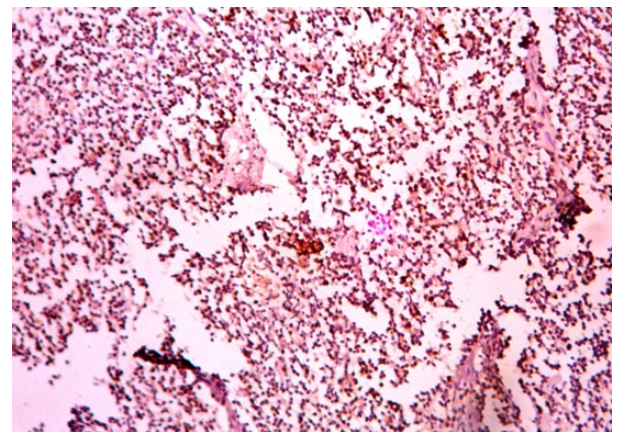
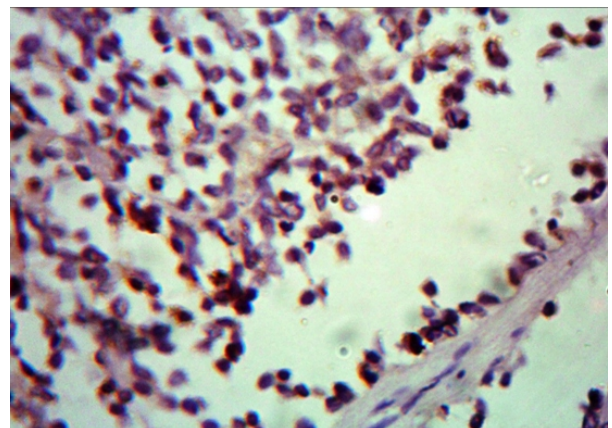


Figure 5: Immunohistochemical staining of the tumor cells showing positivity for WT1. (400x).



3. Discussion

Small Cell Carcinoma of Ovary is a rare, highly malignant, undifferentiated carcinoma which can occur in patients of age between 1 to 55 years with a mean of 23.9 years. [1, 3] usually it is unilateral in presentation and most of the patients have abdominal swelling or pain related to the tumor. [1, 3, 4] Hypercalcemia can be seen in 2/3rd of cases. [1] Development of hypercalcemia is unclear although parathyroid hormone related protein has been found in some cases. [6, 7]

Histogenesis of small cell carcinoma has not been definitely established. [6, 7]. By comparative genomic hybridization and electron microscopy the tumor appeared to be a distinct entity not related to any other ovarian tumors. [6, 7]

Small cell carcinomas of the ovary are generally large and predominantly solid, pale white to gray masses with necrosis, hemorrhage and cystic degeneration.[2,6,8] Microscopically tumor cells grow diffusely and may form small islands, trabeculae, cords or follicle like spaces with eosinophilic fluid.[2,4] Cells have scant cytoplasm and nuclei are hyper chromatic with prominent nucleoli.[2,6] Nuclear grooves may be rarely encountered.[2] The present case showed similar histology except for having indistinct nucleoli and having only few mitotic figures. Tumor staging is considered to be the most powerful prognostic factor than mitotic activity. [3, 5]

Tumors which can mimic small cell carcinoma are adult/juvenile granulosa cell tumour, malignant lymphoma, PNET and primary carcinoid of the ovary. Other tumors that can be considered in the differential diagnosis are malignant melanoma, metastatic alveolar rhabdomyosarcoma, small cell carcinoma of pulmonary type.[5] Occasionally small cell carcinoma with nested growth pattern is misdiagnosed as a dysgerminoma, a tumor with good prognosis, both can be associated with hypercalcemia. [2, 3, 5]

The tumor cells may show positivity for WT-1 protein and patchy moderate immunostaining for p53 and p16. [3, 9]

The tumors most consistently stain for low molecular weight cytokeratin (CAM 5.2) and in a significant proportion of cases stains for calretinin, CD10 and epithelial membrane antigen (30-75%). [3, 4, 5] Some cases also stain for vimentin, neuron specific enolase, chromogranin A and CD99. [4, 5] Occasional tumors reported PTH related protein or parathyroid hormone staining. [3, 5]. Importantly Small cell carcinoma does not stain for inhibin. [3] Lack of staining for inhibin, together with positive staining for cytokeratin and/or epithelial membrane antigen helps to differentiate small cell carcinoma from Juvenile/adult granulosa cell tumor. [9]

Hypercalcemia reverting to physiological level after complete resection of the tumor and appearing with recurrence indicates tumour of hypercalcemic type. Hence serum levels can serve as a marker for treatment response and recurrence. [3, 5]

In our case, tumor cells were positive for WT1 and low molecular weight cytokeratin (CAM 5.2) and negative for inhibin, epithelial membrane antigen, chromogranin A, common leukocyte antigen and placental alkaline phosphatase. Based on morphology and the immunohistochemical features together with preoperative hypercalcemia and post operative normocalcemia, this tumor was diagnosed as ovarian small cell carcinoma of hypercalcemic type.

Small cell carcinoma is an aggressive tumor and the survival rate is less than 20% and only about 33% of patients with stage IA survive. [3, 5, 10] Best treatment results in early stage disease have been achieved with a multimodality approach consisting of surgery, combination chemotherapy and radiotherapy. [3, 10] Effective treatment of patients with high stage tumors or recurrent disease has not yet been achieved. [3, 10]

4. Conclusion

Small cell carcinoma of ovary, hypercalcemic type is a rare and highly malignant, undifferentiated carcinoma. The diagnosis can be made clinically with an elevated serum calcium level in a young female with a solid ovarian tumor. Histomorphologically It needs to be differentiated from other small cell tumors of ovary in order to assess the prognosis of the patient and in early stage of disease for an aggressive follow up with multimodality therapeutic approach for better survival.

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