

Small Cell Carcinoma of the Ovary of Pulmonary Type: Immunohistochemical and Ultrastructural Study A Case Report

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. INTRODUCTION

Small cell carcinoma of the ovary (SCCO) is a recently described tumor that occurs almost exclusively in the second, third, and fourth decades of life and is associated with hypercalcemia, which can be reversed by removing the tumor, in approximately two-thirds of the cases. Treatment remains ineffective. Surgical therapy such as salpingoophorectomy, total abdominal hysterectomy, omentectomy, and excision of locally occurring lesions and lymph node metastasis has been attempted.²⁾ Postoperative radiation therapy to the abdomen or pelvis alone or in combination with chemotherapy and chemotherapy trials including cis-platinum, vincristine, actinomycin D, cyclophosphamide, bleomycin, vinblastine, etoposide and

doxorubicin all provide questionable benefits.²⁵⁾ SCCO is an aggressive tumor and death occurs in approximately 18 months(range 1.5 - 66 months).²⁷⁾

In this report, we described a 36-year-old woman with small cell carcinoma, pulmonary type of the ovary (stage IV) and reviewed the literatures relating to this disease.

. CASE REPORT

A 36-year-old gravida 6 para 2, native Korean woman was admitted to the hospital with vague complaints of lower abdominal pain and the sensation of a rapidly enlarging pelvic mass.

The patient's past medical history was one of good general health. An annual exam 1 year prior to

admission was reportedly negative for any pelvic pathology. She was not taking any medication.

On preoperative evaluations of this patient, firm immobile bilateral adnexal masses were found on pelvic examination, and a $12 \times 10 \times 8$ cm³ nonuniform echogenic solid bilateral adnexal masses were confirmed on transvaginal ultrasonography. Pulmonary metastasis was confirmed by the pleural fluid cytology. The serum calcium level was not elevated in this patient (7.6 mg/dl). Serum markers (-hCG, -FP, CEA, CA 19-9) were all normal except CA125 (270.4 U/ml).

At exploratory laparotomy, a tumor mass of 12 cm in diameter on right ovary and a tumor mass of 8 cm in diameter on left ovary was found with numerous intraperitoneal masses ranging from 0.5 to 2 cm in diameter. Metastatic nodules of hepatic parenchyme and diaphragm were palpated (stage). The report of frozen section was as follows: cellular ovarian neoplasm with high mitotic rate composed of small cells, likely malignant germ cell tumor. Total abdominal hysterectomy with bilateral salpingoophorectomy, infracolic omentectomy, debulking of extraovarian tumor, and complementary appendectomy were performed. The tumor mass was not felt to be completely excised and the remaining mass was about 3-4 cm in diameter. The removed right ovarian tumor measured $14.5 \times 10 \times 8$ cm in size and its cut surface showed lobulated yellowish gray solid mass with areas of hemorrhage and cystic changes in the center. The left ovarian mass measured $3.5 \times 3 \times 2.5$ cm in size and gray white to brownish gray solid surface was noted on cut section (Fig. 1). Both ovarian tumors had similar features with each other. The tumor was composed of hyperchromatic small to medium sized tumor cells with scanty cytoplasm. They formed sheets, nest, cords, with areas of marked desmoplastic reaction. The tumor cells also had diffuse hyperchromatic chromatin in the nuclei and inconspicuous nucleoli. Areas of coagulative necrosis were present. Mitosis was frequent with occasionally atypical forms (Fig. 2). The results of immunohistochemical studies were as follows; LCA: negative, B-cell and T-cell

marker: negative, CK: positive, Desmine: negative, Vimentin: negative, GFAP: negative, -FP: negative, NES: focally positive, Chromogranine: negative. PAS staining shows positive granules in the cytoplasm of a few tumor cells. HMB45: negative, EMA: negative, S-100: positive in a few tumor cells, Nm23: negative, SMA: negative, HCH: negative, -antichymotrypsin: negative, Lysozyme: negative, CEA: negative. Immunostaining of p53 shows 50% positive reaction in the tumor (Fig. 3). On electron microscopy, junctional complex is noted between the cell membranes. The cytoplasm of the tumor cell has abundant glycogen particles, mitochondria, and some rERs (Fig. 4).

Fig. 1. The cut surface of the tumor shows yellowish gray, solid, lobulated appearance with central cystic and hemorrhagic areas.

Fig. 2. The tumor composed of hyperchromatic nucleated small to medium sized cells with scanty amount of cytoplasm and mitotic figures.

According to clinical features, the diagnosis of small cell carcinoma of the pulmonary type was made. Following her recovery from surgery, she received 4 cycles of chemotherapy (BEP regimen) consisting of 20 mg/m² cis-platinum Days 1-5, 100 mg/m² etoposide Days 1-5 and 15 mg bleomycin Day 2, 9, 16. Since

Fig. 3. Immunostaining of cytokeratin shows relatively diffuse positive reaction in the tumor cells.

Fig. 4. On electron microscopy, junctional complex is noted between the cell membranes. The cytoplasm of the tumor cell has abundant glycogen particles mitochondria, and some rERs ($\times 4,000$).

then serum CA 125 was 7.6 U/ml. CT scanning after the 3 cycles of chemotherapy showed improved liver metastasis but 1 month later, a suspicious nodular mass newly appeared in the anteroinferior segment of the liver. Another cycle of chemotherapy with the same regimen was performed. Afterwards, irradiation of the whole abdomen including liver was begun (2500 cGy/5 weeks) for salvage therapy.

She is in tolerable condition now and has been alive for 8 months since initial operation.

. DISCUSSION

Dickersin et al. first described small cell carcinoma of the ovary with hypercalcemia in 1982.¹⁾ They designated the tumors "nonspecifically" as small cell carcinoma because the neoplastic cells were of relatively small size and were of the epithelial type.

The histogenesis of SCCO, however, is obscure. In a recent study of six cases, Ulbright and co-workers postulated a germ cell origin for SCCO.⁴⁾ They interpreted their ultrastructural and immunohistochemical evidence as indicative of yolk sac differentiation. In two cases examined by electron microscopy, they found foci of intercellular nonhomogenous, electron-dense, basement membrane-like material between cells in addition to dilated cisterns of rER. The recognition of this intercellular basement membrane-like material in these neoplasms is therefore evidence of germ cell, and specifically yolk sac, differentiation. The presence of intracytoplasmic glycogen in tumor cells adds additional support to the theory of germ cell origin. But, James et al, did not find basement membrane-like material, other than lengths of basal lamina, and they are doubtful of the relationship of SCCO to yolk sac tumors or other germ cell tumors.⁹⁾

SCCO has distinctive clinical and pathologic features of the undifferentiated carcinoma of the ovary. These are frequently associated with hypercalcemia and small size of the tumor cells in contrast to that of undifferentiated carcinoma of the ovary. However, there is another type of SCCO, which resembles small cell carcinoma of the lung. The former one is called SCCO, hypercalcemic type and the latter SCCO, pulmonary type. The epithelial nature of the SCCO hypercalcemic type is suggested by ultrastructural features but the germ cell origin is also favored by others.^{9,10)} At present their origin is not yet established. The presence of neuroendocrine cells, identified by a positive argyrophil or argentaffin stain, explains the occurrence of primary ovarian carcinoid tumors and a small cell carcinoma.

The clinicopathologic features between SCCO of the pulmonary type and hypercalcemic type in the ovary are quite different. The SCCO of hypercalcemic type occurs in premenopausal patients (average age of 24 years), most of them are in the reproductive age group. Clinical presentation is almost similar to that of ovarian cancer in general but serum hypercalcemia is associated in 62%. At the time of laparotomy, the

tumor was almost unilateral. Contralateral ovary is occasionally involved by the tumor spreading to the abdominal region. But bilateral primary tumor has been reported. On gross examination the tumor is usually large, predominantly solid, soft, and tan-gray to creamy white, which may resemble a dysgerminoma or malignant lymphoma. The histologic features have characteristics of frequent follicle-like spaces, large cells with abundant cytoplasm and central nuclei containing clumped chromatin and a distinct nuclear envelope. There are also occasionally intracytoplasmic hyaline inclusions. Immunohistochemical findings are positive of cytokeratin in almost cases and neuron-specific enolase and parathyroid hormone related protein are also positive in the tumor of significant cases. The tumor occasionally shows staining for vimentin. Flow cytometry for DNA content shows diploid.^{1,5,11} The SCCO of pulmonary type occurs largely in perimenopausal and postmenopausal patients (mean 59 years). The tumor is bilateral in 45 % and may have paraneoplastic syndrome other than hypercalcemia, such as Cushing's syndrome and inappropriate secretion of ADH. The gross findings are yellow-tan, gray-white, of red-brown solid masses with occasionally necrosis. The microscopic features are tumors composed of small cells arranged in sheets and closely packed nests. Follicle-like spaces are rare. Coagulative necrosis and areas of extensive nuclear pyknosis are present. The tumor cells have scanty cytoplasm and small to medium sized hyperchromatic nuclei with indistinct nucleoli. Mitosis is frequent and occasionally atypical. Immunohistochemical staining of CK are almost positive as well as NES. Vimentin is negative. Flow cytometry shows aneuploid in many cases. The SCCO of pulmonary type is aggressive in biologic behavior.¹²

In this case, the clinicopathologic findings reveal the differentials of SCCO of hypercalcemic type, SCCO of pulmonary type, metastatic small cell carcinoma, malignant lymphoma, dysgerminoma, intraabdominal desmoplastic small round cell tumor, primitive neuroectodermal tumor, etc. We excluded SCCO hy-

percalcemic type by clinical features: age of patient, absence of hypercalcemia and bilaterality, and by histologic findings: frequent mitosis, tumor cell necrosis, etc. Metastatic SCCO was not considered because the known primary tumor site was not present. Malignant lymphoma was excluded by negative B-cell, T-cell, and LCA stain result. Granulosa cell tumor exhibited greater reactivity to vimentin and EMA, but our case was not. Cytokeratin stain shows positive result only in cases of carcinoma, and dysgerminoma, granulosa cell tumor, and intraabdominal desmoplastic small round cell tumor was excluded. So the diagnosis of SCCO of pulmonary type was given.

Most patients with SCCO have undergone more or less extensive surgery to remove the tumor or to obtain maximal debulking. Several chemotherapeutic agents have been tested.^{1,7} Although some temporary benefits have been reported, no single combination of chemotherapeutic agents has been curative in advanced cases of SCCO. There is some evidence that small cell carcinoma of ovary could be of germinal nature, on this basis we decided to treat this case as if they were affected by germinal neoplasia, i.e., with a BEP regimen as first-line chemotherapy. Although only five reported patients received adjuvant radiation therapy, the four survivors in that group suggest that it may have a role in the adjuvant therapy of this tumor. Patients who received radiation had a significantly better outcome($p=0.035$).¹⁰

The outcome for patients with SCCO is generally poor, but is related to staging and operability. Overall survival is 10%, with a recurrence free period averaging 10 months, but in stage Ia, about 20% are cured by surgery alone.^{2,7}

. CONCLUSION

We report a case of immunohistochemical and ultrastructural study of small cell carcinoma of the ovary of the pulmonary type (stage IV) with a review of the literatures.

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