Primary ovarian small cell carcinoma of the pulmonary type: A case report and review of the literature

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Summary

Small cell carcinoma of the ovary is a rare type of ovarian carcinoma with a poor prognosis. Two types should be distinguished: the hypercalcemic type and the pulmonary type.

We report the case history of a 54-year-old woman with both a Stage IIIC small cell carcinoma, pulmonary type and a well-differentiated endometrioid adenocarcinoma of the left ovary in combination with a Brenner tumor in the right ovary. A review of the literature on small cell carcinoma of the ovary is given and the findings of our patient are brought into perspective in terms of both histopathogenesis and treatment outcome.

Key words: Ovary; Small cell carcinoma; Surgery; Chemotherapy.

Introduction

Primary small cell carcinoma of the ovary is extremely rare. There are two types of primary small cell carcinoma of the ovary described in the literature: the hypercalcemic type and the pulmonary type. The first occurs in young women and is associated with hypercalcemia in approximately two-thirds of the patients. The pulmonary type is seen more in elderly women and has the identical microscopic features as small cell carcinoma of the lung.

In the present case report we describe a patient with a combination of the pulmonary type of small cell carcinoma and an endometrioid carcinoma in the same ovary. In the other ovary, a Brenner tumor was found. To our knowledge this is the first description of such a triple combination.

Case Report

A 54-year-old postmenopausal woman with a history of smoking and arterial hypertension treated with diuretics was admitted to our hospital because of a mass in the left ovary. Apart from this pelvic mass, clinical examination was completely normal. No abnormalities were discovered at routine blood examination and in particular calcium levels were normal. Only a slightly elevated alkaline phosphatase (104 U/l, normal: 36-95 U/l) was noted. CA 125 serum level, chest radiography and bone scintigraphy were also normal. Abdominal ultrasound showed a left ovary which had an irregular form and low resistance flow on Doppler. A subsequently performed computed tomography (CT) scan of the abdomen confirmed a mass in the left ovary with hypodense structures. No enlarged lymph nodes were seen. An explorative laparotomy was performed. An examination on frozen section confirmed malignancy and a suboptimal staging (total hysterectomy, bilateral salpingo-oophorectomy, omentectomy and removal of one lymph node) was performed. Morphologic and immunohistochemical examination of both ovaries showed a Brenner tumor in the right ovary and a well differentiated endometrioid adenocarcinoma with small cell carcinoma in the left ovary. The endometrioid carcinoma was composed of glands lined by columnar epithelial cells with oval hyperchromatic nuclei. There was mild anisonucleosis. The nuclei demonstrated a pseudostratification. There was distinct mitotic activity (Figure 1). The apical cytoplasm and the luminal secretion products were paraaminosalicylic acid (PAS)-positive. These tumoral glands were immunohistochemically negative for CA 125, CEA and synaptophysin. A minority of the cells expressed chromogranine. The small cell carcinoma consisted of small to medium sized tumor cells with hyperchromatic nuclei, indistinct nucleoli, and a high nucleo-cytoplasmic ratio. There was nuclear moulding. Rarely rosette-like structures were observed (Figures 1 and 2). The tumor cells in the small cell carcinoma were PAS-negative. Immunohistochemical stainings were positive for synaptophysin, weakly positive for chromogranin and negative for CEA and CA 125. The Brenner tumor in the right ovary consisted of well-defined solid bland transitional-like epithelium embedded in a dense fibroblastic stroma. The resected lymph node showed no malignant cells. After recovery from surgery, three courses of combination chemotherapy with cisplatin (30 mg/m^2/day), ifosfamide (1.5 g/m^2/day) and etoposide (150 mg/m^2/day) for three days were given once every three weeks.

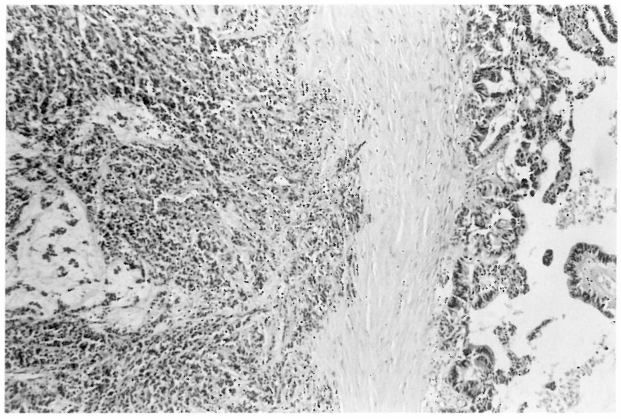

Figure 1. — The combination of small cell carcinoma (pulmonary type) and well differentiated endometrioid adenocarcinoma in the left ovary (magnification: 208 x).

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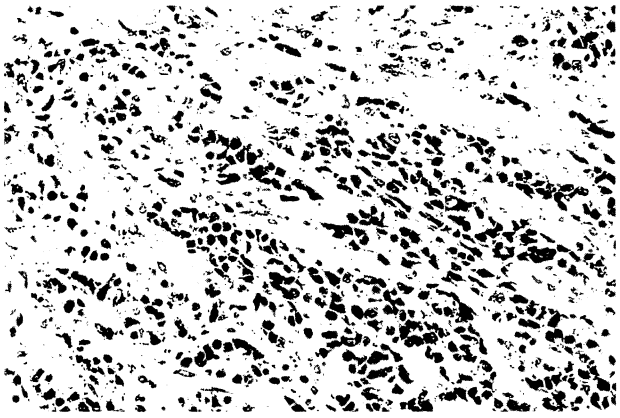

Figure 2. — Detail of small cell carcinoma of the pulmonary type (magnification: 248 x).

The tolerance to this chemotherapy was poor and consisted of hematologic toxicity, severe nausea and vomiting, alopecia and strong emotional instability. After completion of chemotherapy a CT scan showed no evidence of disease. Subsequently a second-look laparotomy with pelvic and paraaortic lymphadenectomy was performed by a gynecologic-oncologist. One of the lymph nodes in the paraaortic area still contained small cell carcinoma. The patient refused any further therapy, including radiotherapy. Nine months after the end of treatment, the patient developed liver metastases and a pelvic recurrence, and died five months later.

Discussion

Small cell carcinoma of the ovary is a rare type of ovarian carcinoma with a poor prognosis. Small series or sporadic cases have been reported in the literature. Small cell carcinoma of the ovary is divided in two types: the hypercalcemic and the pulmonary type.

The hypercalcemic type

In 1978, Scully described the first patient with a hypercalcemic type of small cell ovarian cancer [1]. Dickersin et al. further described this clinicopathological entity in 1982 stating that it was an undifferentiated carcinoma of unknown cellular lineage only occurring in the ovary [2].

Since 1982, 167 patients have been reported in the literature, almost exclusively occurring in women in their second through fourth decade of life, but on the average being young [3, 4].

Because this tumor type has been observed to occur in certain families a genetic basis has been suggested. Scully referred to Carinelli, who described three sisters with bilateral tumors in one family and described another family in which two cousins and two others, a mother and a daughter, were diagnosed with this tumor type [3].

The hypercalcemic type of small cell ovarian cancer is associated with paraendocrine hypercalcemia in 60% of patients [3-5] and normal or low phosphate with normal parathyroid hormone levels [6]. Hypercalcemia occurs in the absence of bone metastases, and improves after surgical removal of the tumor. This suggests an ectopic production of a hypercalcemic factor, such as prostaglandins, or a parathyroid hormone-like peptide. Except for one study in which immunohistochemical staining for PTH-related protein was found positive in five of seven small cell carcinomas, antibodies have not been able to detect such a peptide [6, 7, 17]. The clinical manifestations of small cell carcinoma of the hypercalcemic type are similar to those of other ovarian cancers and in only 2.5% of the patients clinical symptoms of hypercalcemia occur [3].

Small cell carcinoma of the hypercalcemic type shows solid, soft, cream colored tissue containing areas of necrosis or hemorrhage in larger masses [3]. Histologically the tumor is composed of small cells with scanty cytoplasm and with hyperchromatic nuclei containing a small single nucleolus. In about 50% of cases larger cells with abundant cytoplasm are present. The large cells may contain pale eosinophilic rounded globules that push the nucleus to the periphery of the cell [4]. There are solid parts as well as pseudofollicular structures filled with eosinophilic fluid [5]. Electron microscopic examination shows an abundant dilated rough endoplasmic reticulum [3].

The hypercalcemic type of small cell carcinoma should be distinguished from anaplastic carcinoma of müllerian origin, which has a bilateral presentation in 25% of cases, and from metastasis of small cell carcinoma of the pulmonary type, both occurring in older patients [5].

Several treatment options have been described, including 1) surgery alone with salpingo-oophorectomy, total abdominal hysterectomy, omentectomy and excision of local lesions and lymph node metastases, 2) surgery with postoperative radiotherapy to the abdomen or pelvis with or without chemotherapy or 3) chemotherapy alone or as adjuvant therapy after surgery with combinations of any of the following agents: cisplatin, vincristine, actinomycin D, cyclophosphamide, bleomycin, dacarbazine, vinblastine, etoposide and doxorubicin [3, 4, 7]. Benefit from adjuvant radiotherapy has been suggested only in Stage Ia [7]. The overall survival rate of patients with a Stage Ia tumor was 33% after one to 13 (average 5.7) years of follow-up [3]. In patients with more advanced disease, no long-term survivors have been reported [3].

The pulmonary type

The first 11 patients with a primary ovarian small cell carcinoma of the pulmonary type were described by Eichorn *et al.* in 1992 [8]. These tumors, which occur mostly in perimenopausal and menopausal women, have histologic, immunohistochemical and DNA-ploidy features (the majority are aneuploid) similar to those of small cell carcinoma of the lung [8]. There are only limited reports of this primary ovarian neoplasm and only six reports of this type of primary ovarian cancer have appeared since 1992 [9-12]. Sometimes they occur in combination with a mature teratoma [13, 14].

This tumor type is also known to occur in a variety of sites, including the prostate, urinary bladder, larynx, trachea, paranasal sinuses, esophagus, stomach, colon, pancreas, endometrium, cervix, breast and skin or soft tissue [9, 11].

Small cell carcinoma of the pulmonary type has microscopic features and a neuroendocrine profile of pulmonary small cell carcinoma. It is composed of small cells with scanty cytoplasm, oval to spindle shaped nuclei and inconspicuous nucleoli. The cells are arranged in closely packed

sheets, islands and trabeculae [15]. On electron microscopy the tumor has a paucity of intracellular organelles [8].

The histogenesis of this tumor type is unclear. It has been suggested that it can arise from stem cells or neuroendocrine-type cells of the surface epithelium that has the capacity for neuroendocrine and epithelial differentiation. This could explain the frequent mixtures of cell types. Also a teratomatous origin can not be excluded [12, 16].

This is the first time that a patient is described in whom a small cell ovarian carcinoma of the pulmonary type intermingled with an endometrioid adenocarcinoma in one ovary has been found together with a Brenner tumor in the other ovary. Combinations of two different histologies have been described earlier. In the original article of Eichorn *et al.* two cases of Brenner tumors were mentioned. In each patient the Brenner components were intermingled with nests of small cell carcinoma. Four other patients had a component of endometrioid adenocarcinoma intermingled with or adjacent to the small cell tumor [8]. In 1997, Fukunaga *et al.* published another case of a combination of endometrioid carcinoma and a small cell carcinoma of the pulmonary type [12]. Their findings suggest that primary ovarian small cell carcinomas of the pulmonary type have a tendency to develop in pre-existing benign or malignant ovarian tumors. Neuroendocrine cells have also been found in the past in endometrioid adenocarcinomas and Brenner tumors, which can in part explain our observations [8].

The clinical symptoms are comparable to those of other ovarian cancers, except that paraneoplastic syndromes other than hypercalcemia are observed (e.g., Cushing's syndrome [8]).

The differential diagnosis of this neoplasm includes metastatic small cell carcinoma from the lung and thymus, ovarian small cell type of the hypercalcemic type, carcinoid, a primitive neuroectodermal tumor, granulosa cell tumors, malignant lymphoma, intra-abdominal desmoplastic small cell tumor, Merkel cell carcinoma, metastatic melanoma or metastatic alveolar rhabdomyosarcoma [12]. We believe that in our patient it was a primary ovarian carcinoma and not a lung carcinoma because the initial chest X-ray was negative just as it was on subsequent examinations. Also the fact that the carcinoma was intermingled with an endometrioid adenocarcinoma, as well as the pattern of spread to the lymph nodes, point in that direction.

Generally, the prognosis is poor and only limited data on the treatment of this tumor type are available. Most patients described by Eichorn *et al.* died within one year or had an early recurrence [8]. In their series the only long-term survivor was treated with a combination of cyclophosphamide, cisplatin, doxorubicin, etoposide and vincristine after total hysterectomy and bilateral salpingo-oophorectomy with bilateral retroperitoneal lymph node dissection [8]. They suggested that patients with ovarian small cell carcinomas of the pulmonary type should be treated with agents known to be effective in small cell carcinoma of the lung. A patient described by Lim *et al.* was treated by total hysterectomy followed by six courses of cisplatin, etoposide and bleomycin given in a 2-week schedule. This patient was alive without evidence of disease 34 months after diagnosis [14]. A case with extensive disease described by Lo Re was treated with bilateral salpingo-oophorectomy and omentectomy followed by four cycles of single-agent cisplatin followed by three cycles of cisplatin and etoposide. At the end of treatment a partial response was obtained and the patient died 17.5 months after diagnosis due to recurrent disease [11]. Our patient was treated after surgery with a combination of cisplatin, ifosfamide and etoposide. She recurred nine months after the end of treatment, and died because of this five months later. Whatever treatment is employed, in general the percentage of patients surviving more than two years is low [11].

In conclusion, data on this type of tumor is scarce. There is no optimal therapy and prognosis remains poor.

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