Small cell carcinoma of the ovary successfully treated with radiotherapy only after surgery: case report

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Summary

Small cell ovarian tumors are rare and highly malignant, occurring mainly in young patients. Early mortality is high due to the lack of an effective treatment. The first adjuvant therapy is usually chemotherapy. *Case:* During laparotomy for renal transplant in a 17-year-old girl, the right ovary exhibited a suspicious mass, whose pathological diagnosis was Stage 1A small cell ovarian tumor. Prognosis was poor (young age, hypercalcemia, tumor > 10 cm, and presence of large cells). Since chemotherapy is contraindicated for dialysed patients, only radiotherapy was given. The patient is still alive and disease-free ten years after diagnosis. *Conclusion:* This is the first case with a poor prognosis reported in the literature that has been successfully cured by surgery plus adjuvant radiotherapy only.

Introduction

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), is an extremely malignant tumor [2]. The treatment is often ineffectives, aggressive surgery is recommended as the primary treatment with further adjuvant chemotherapy [1-3]. Though this tumor seems to be both chemo- as well as radiosensitive, the long-term survival of patients who receive both adjuvant chemo- and radiotherapy is generally disappointing [1]: recurrence occurs on average 18 months after diagnosis [2]. We report a case of SCCOHT in a 17-year-old girl with several poor prognostic factors, who, after surgery, received radiotherapy as the only adjuvant therapy. She is still alive and has been disease-free for more than ten years.

Case Report

The patient, a 17-year-old female, suffered from terminal chronic renal insufficiency, secondary to proliferative mesangial glomerulonephritis, which had become corticoid-resistant. She had been under hemodialysis since the age of 13. In August 1994, serum calcium was 11.2 mg/dl and phosphorus 7.0 mg/dl; the levels of PTHi (intact parathyroid hormone) and alkaline phosphatases were normal. Since the patient did not receive any vitamin D, the diagnosis of adynamic osteomalacia was considered. Treatment with calcium kayexalate was initiated. Despite treatment, calcium levels remained high, reaching up to 12.8 mg/dl in September 1994. Even the non-compliance of the patient to this treatment was considered.

In October 1996 the patient underwent laparotomy for renal transplantation. She had experienced abdominal pain for several months before. During laparotomy a right ovarian mass (17 cm in diameter), showing a smooth wall with focal nodules, was discovered. No ascites or adenopathies were found. The right ovary was removed; pathological examination on frozen section revealed an undifferentiated malignant tumor. Debulking was optimal with no macroscopic residual disease. Biopsies were taken from the left ovary, iliac lymph nodes, peritoneal and epiploic tissues. Uterine curettage was also performed. Because of the presence of malignant disease, the renal transplantation was not performed.

The tumor weighed 850 g on sectioning; the tissue was partially solid and white with cysts containing coagulated blood. No ovarian tissue could be recognized. Microscopically the lesion was composed of small non-differentiated cells with scanty amphophil cytoplasm, arranged in clusters, cords or follicle-like structures; there were numerous atypical mitoses. Some tumor cells had abundant eosinophilic cytoplasm. Areas of hemorrhage and necrosis were observed. The histological diagnosis considered was that of a granulosa cell tumor (juvenile type). Because of high calcium levels, this diagnosis was however reconsidered since granulosa and germ-cell tumors can often be confused with small cell ovarian tumors. The histological slides were therefore sent to Prof. Robert E. Scully (Harvard Medical School, Boston, USA), who established the diagnosis of small cell ovarian tumor containing large cells. Immunohistological staining detected parathyroid hormone-related protein (PTHrP) in the tumoral tissue. The contralateral ovary, multiple peritoneal biopsies, the lymphatic ganglia and peritoneal cytology showed no evidence of malignancy. The tumor was thus classified as Stage 1A according to the FIGO classification.

Serum calcium levels returned rapidly to normal postoperatively.

Though there is no consensus concerning the adjuvant therapy, chemotherapy (usually the first choice) was not considered because of renal insufficiency. Since several poor prognostic factors were present (patient age < 20 year old, a large tumor > 10 cm, hypercalcemia and presence of large cells in the tumor [5]), whole abdomen radiotherapy was administered and started in December 1996. A dose of 30 Gy was delivered to the whole abdomen with the liver shielded at 22 Gy with a daily fraction

Revised manuscript accepted for publication December 3, 2007

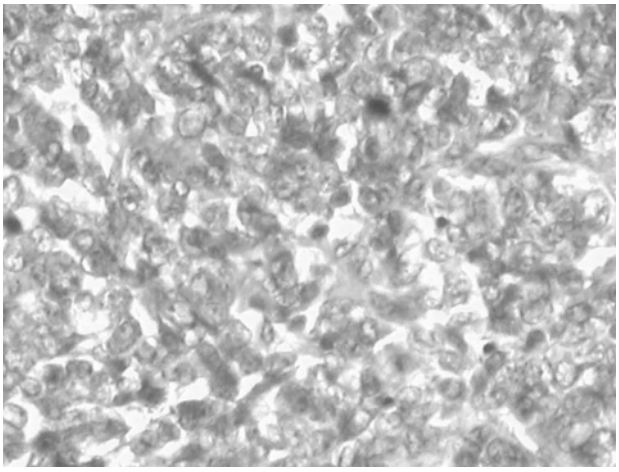

Figure 1. — Tumoral lesion composed of small and large non differentiated cells arranged in clusters. Numerous atypical mitoses are present (H&S x 40).

of 1.5 Gy. The treatment was then pursued to increase the dose to 40.8 Gy to the paraaortic lymph nodes and to 44.8 Gy to the pelvis. The treatment required 28 fractions over 40 days, using an 18MV linac.

In August 1997, the patient had a post-radiotherapy ileal occlusion which required ileotransversostomy. In December 1998, she underwent a renal graft, but reoccurrence of the segmental focal hyalinosis of the graft required a switch to plasmapheresis.

Yearly follow-up of this patient comprised a gynecological ultrasound, abdominal CT scan and blood analysis. The calcium levels remained normal. In 2002, a CT scan of the abdomen revealed a suspicious region in the liver; abdominal echography showed a focal hyperechogenic hepatic lesion (3 x 3 cm), which, after biopsy, was diagnosed as an adenoma. A new renal transplant was successfully performed in 2005.

Discussion

First reported in 1982 by Dickersin et al. [2], SCCOHT is a rare and highly malignant tumor. Several case reports had been published before Young *et al*. [4] reported the clinical and pathological features of 150 cases of ovarian SCCOHT. In that study, the mean age at tumor diagnosis was 23.9 years (range: 9-43). Clinical presentation is usually non specific, with initial symptoms of abdominal pain (as reported in our case) and/or swelling, an asymptomatic abdominal mass, irregular menses or amenorrhoea, fatigue, and lethargy. The preoperative serum calcium level was elevated in 62% of the cases, usually without clinical signs of hypercalcemia [1], such as in the present case. In 99% of the cases, the tumor was unilateral and voluminous (6 to 26 cm). Peritoneal extension was present in approximately half of the cases [1, 2].

There are two varieties of small cell carcinoma of the ovary [4, 5]: one is similar to the pulmonary type of small cell carcinoma and the other is less known and includes large cells ("large cell variant"), as reported in this case.

Histological diagnosis relies on the presence of nests, cords, clusters of small hyperchromatic round or oval cells diffusely or closely packed. The various patterns of growth are interrupted by follicle-like spaces. The neoplastic cells typically exhibit important mitotic activity. Young *et al.* [4] reported that 50% of the tumors had a variable component of cells with moderate to abundant amounts of eosinophilic cytoplasm, which sometimes contained large hyaline globules and large nuclei that are typically paler and have more prominent nucleoli than the small cells.

The genesis of small cell carcinoma remains obscure [5, 6]. Some evidence has been provided that small cell carcinoma of the ovary could be an inhomogeneous tumor which is either related to a germ cell tumor (co-expression of vimentine and cytokeratins, positivity for alpha 1 antitrypsine) or to an epithelial ovarian cancer (thin basal lamina, numerous desmosomes) [5]; it could even represent a distinct tumor entity [7]. The differential diagnosis with various tumors can be difficult and confused with granulosa cell tumors (because of the pseudo follicular structures, as in our case) [4], with sex-cord tumors, dysgerminoma, ovarian metastases of lymphomas, alveolar rhabdomyosarcoma or melanoma.

Hypercalcemia is often evidenced in patients having this kind of tumor and calcium levels usually return to normal after tumorectomy [1, 2]. The mechanism of such hypercalcemia is not fully understood. PTHrP produced by the tumor itself, has been implicated in the pathogenesis of tumoral hypercalcemia. PTHrP binds to PTH receptors in bone and kidney with equal affinity as PTH [1], leading to increased osteoclastic bone resorption and renal calcium reabsorption. The stimulation of increased bone resorption and renal tubular reabsorption of calcium results in persistent elevation of serum calcium levels. This hypothesis remains, however, not totally satisfactory. Postoperatively, these serum calcium levels are a marker of recurrence [2, 6].

Small cell carcinoma of the ovary is highly malignant and has a poor prognosis. The overall survival rate after five years is approximately 10%. Only 33% of the patients with a Stage 1A tumor, as in this case, were alive without evidence of recurrence 1 -13 years post surgery, 54% died within two years and recurrence occurred in 13% of the cases [4]. Since there is no consensus on the optimal adjuvant therapy, this makes the report of our case quite interesting. In 99% of the cases the tumor is unilateral and therefore unilateral salpingo-oophorectomy was usually performed; it is possible that bilateral salpingo-oophorectomy might be somewhat more curative, especially since recurrence in the contralateral ovary has been reported [1]. Young *et al.* recommended the latter procedure, despite no significant difference between the two modalities. A more aggressive therapy is even recommended in young women: hysterectomy and bilateral salpingo-oophorectomy followed by chemotherapy [2]. Some authors recommend, similarly to advanced ovary cancer, using immediately intensive polychemotherapy, with or without external

radiotherapy and bone marrow graft [8]. Due to the fact that SCCOHT is a rare tumor with a poor prognosis, no consensus is available about adjuvant therapy. The best results in the literature have been obtained with surgery followed by polychemotherapy plus radiotherapy [4, 5, 9]. In their review of 150 cases, Young *et al.* [4] reported that, among the five patients who received postoperative radiotherapy, four were still alive. It is only recently that Harrison *et al.* [5], from data collected in Australia, Canada and Europe, have advocated a multimodality treatment approach including surgery, chemotherapy and the addition of radiotherapy. It would suggest that radiotherapy could be more effective to cure this kind of tumor. Whole abdomen radiotherapy for treatment of ovarian cancer has also been stressed by Firat *et al.* [10], who reported ileal occlusion to be a classic complication, as seen in our patient. The case of our patient with a poor prognostic tumor, who received only radiotherapy and is still alive ten years later without recurrence, reinforces and strongly supports our hypothesis. Thus, we cannot agree with another recent review of SCCOHT in children and adolescents by Distelmaier *et al.* [3] who propose only multi-agent chemotherapy as adjuvant therapy.

Conclusion

When unexplained hypercalcemia is diagnosed in a young woman, the presence of an ovarian tumor must immediately be excluded. This case report illustrates how difficult a correct diagnosis is, but the presence of hypercalcemia can be helpful. Small cell carcinoma of the ovary, hypercalcemic type, is of poor prognosis and the survival rate after five years is usually around 10%. The type of optimal adjuvant therapy to recommend is unclear but, according to our case together with the literature, it appears that radiation therapy could be of prime importance.

Acknowledgment

The authors are grateful to Mrs M. Van Noten for secretarial assistance.

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