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Small cell carcinoma of the ovary of the hypercalcemic type (SCCOHT) – case report

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Summary

Small cell carcinoma of the ovary of the hypercalcemic type (SCCOHT) is a very rare malignant disease, seen mostly in young women, with a very poor prognosis. There is no standard treatment for patients with this disease and most literature is limited to short series or case reports. This report describes the case of a 34-year-old woman with aggressive course of SCCOHT and poor outcome. What proved difficult was the process of establishing the diagnosis due to non-specific first symptoms of disease and consequently the combined treatment of surgery and chemotherapy with concurrent side effects.

Key words: Ovarian cancer; Small cell carcinoma of hypercalcemic type.

Introduction

Primary small cell carcinoma of the ovary of the hypercalcemic type (SCOC – small cell ovarian cancer), is a rare form of cancer derived from this organ (about 1% of ovarian cancers). It belongs to the primary neuroendocrine tumors, and its presence is usually sporadic, with no familial circumstances. The tumor is usually diagnosed in adolescence and young adulthood, with the mean age of the patient being 24.3 to 34.5 years [1, 2], although incidence has been reported in both the first and the eighth decade of life [2, 3]. Tumors are usually solid and located almost exclusively unilaterally [4]. Cystic components of the tumor are observed as well as extensive areas of necrosis [5]. The initial symptoms are non-specific, consequently more than half of the cases are diagnosed in advanced stages of the disease [4]. Patients usually present with abdominal pain, a palpable mass/tumor in the abdomen, ascites, nausea or vomiting, and difficulty passing stool. Clinical symptoms of the cancer are non-specific beyond those symptoms associated with paraendocrine hypercalcemia. Extraovarian spread during surgery is observed in about half of the cases [5].

Case Report

A 34-year-old woman presented to the physician in December 2010 due to edema of the left groin and the left lower limb, as well as frequent urination. In the performed computer tomography scan of the abdomen and pelvis (December 12, 2010), enlarged left paraaortic lymph nodes up to 35mm in size and enlarged lymph nodes of the left common iliac artery measuring 20 and 30 mm were found. In January 2011, a fine needle biopsy of the left inguinal lymph node was performed. In the biopsied tissue sample (measuring 20 x 10 x 10 mm), neoplastic cells were not found, instead a fragment of adipose and fibrous tissue with a small focal area of bloody hemorrhage was observed. Additional diagnostic studies of the colon were performed – rectoscopy and colonoscopy of which neither displayed any pathology. March 2011, an abdominal ultrasonography (USG) was performed three times, which demonstrated enlarged retroperitoneal lymph nodes along the abdominal aorta, the left renal artery, bilateral common iliac arteries, the left external iliac artery, and the lymph nodes of the left groin (changes measuring up to 51 mm). The radiologist suggested, based on the topographic changes, non-Hodgkin's lymphoma as the initial diagnosis. In April 2011, a gynecologic examination was performed in which a tumor of the left ovary measuring about 50 mm was found. Simultaneously, laboratory results had shown elevated levels of LDH (1,794 U/L; normal range below 480 U/L), CEA (6.9 ng/ml; normal range 0.0 - 3.0 ng/ml), ESR (32 mm/h; normal range 3.0 - 15 mm/h). It is worth mentioning that the values of the tumor markers CA 125, CA 19.9, AFP, and beta-HCG were within normal limits. In April, the excision of the left-sided uterine adnexa was performed and a fragment of a lymph node was taken for testing. The enlarged lymph nodes along the major vessels described in the abdominal USG examination were not removed. The resected tumor had a diameter of about 80 mm and the cross-section was of a solid character. The intraoperative histopathologic examination revealed the presence of high-grade malignant cells that may correspond to lymphoid cells or a poorly differentiated tumor. The histological picture, on the basis of the immunohistochemical results, corresponded to, small cell carcinoma of the ovary of the hypercalcemic type G3, pT2 FIGO, pN0 [tumor composed of poorly differentiated cells with a very high proliferative index (Ki67 over 95%)], immunophenotype: CKAE1/AE3 +, EMA +, CK7 +, CD3 -, CD20-, WT1-, LCA-, CA125-, CHR + SYN + (single cells), and CD30-. In the final conclusion, the pathologist stated that the small cell carcinoma of the ovary of the hypercalcemic type, is the primary tumor of the ovary. The neoplasm was diagnosed as Stage IIIA according to FIGO classification. Shortly after the procedure the patient received chemotherapy, paclitaxel (175mg/m2) and car-

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boplatin (AUC 6). During ultrasound monitoring with a vaginal probe, a cluster of enlarged lymph nodes was detected in the left lower pelvis. During physical examination, soft tissue swelling in the left groin and the left thigh were noted. Additionally, there was a decrease in the size of the affected lymph nodes from 65.4 mm to 41 mm, and a reduction in the soft tissue swelling of the described area was noted after two courses of treatment with taxanes and platinum derivatives. A high toxicity reaction was noted in the patient due to the regimen of chemotherapeutics (neutropenia and thrombocytopenia were observed), requiring pegfilgrastim and steroid therapy. In August 2011, after the third course of treatment, in the face of persistent hematologic toxicity (thrombocytopenia, anemia, neutropenia), a trephine biopsy was performed to evaluate the bone marrow. The material obtained from the trephine biopsy was found to contain no metastatic cells. The immunohistochemical study demonstrated: MPO + about 60 - 70%, cytokeratin AE1/AE3, and CK7 negative. It was decided to use taxane, at a dose of 135 mg/m2 with cisplatin, at a dose of 75mg/m2 (75% of the recommended dose). In August 2011, in USG examination of the lower pelvis, an increase in the size of the monitored lymph node mass was observed. September 2011, the patient received the second line of treatment, and was treated with two courses of cytostatics - etoposide 200 mg/m2 and cisplatin 75mg/m2 (75% of the recommended dose). After the administration of the above treatment, again a progression was observed in the lesser pelvic lymph nodes, as well as an increase in the swelling of the left groin and left thigh. Nonetheless, a regression was observed in the lymph nodes of the abdominal cavity, in comparison to studies performed previous to the application of the second line of treatment with cytostatics, therefore it was decided to implement the next course of treatment according to the existing scheme. In early November 2011, the patient was hospitalized due to a significant degree of weakness, severe pain in the left lumbar region of the spine, and severe swelling of the left lower limb. In laboratory studies, neutropenia, hypomagnesaemia, and hyponatremia were found. In imaging studies - USG examination of the abdomen, a swelling of the tissues of the abdominal wall with the diameter of 25 mm was revealed. The paraaortal lymph nodes had increased in diameter to 47 mm and fluid was detected in the abdominal cavity. In the chest radiograph, fluid was found in both pleural cavities. In view of the ineffectiveness of the current treatment with cytostatics and the poor general condition of the patient, it was decided to discontinue chemotherapy. The patient died on November 21, 2011.

Discussion

Primary small cell carcinoma of the ovary is uncommon neoplasm. The present case proved that the diagnosis and treatment is really difficult and the outcome is poor.

There is no consistent information regarding the effectiveness of determining CA 125 in the diagnosis and monitoring of this form of ovarian cancer. Elevated levels of CA 125 in serum is observed in approximately 76.9% of cases, however, compared with serous carcinomas, these values are relatively low. The average concentration of this marker prior to treatment is estimated to be about 176 U/ml. It seems that there is no correlation between the level of the CA 125 marker and the size of the tumor or the concentration of calcium ions in the blood [1].

In a study of 150 cases of SCOC [4] it was found that 63% of patients with hypercalcemia in the serum were largely asymptomatic. The typical symptoms of hypercalcemia include: renal manifestations (polyuria, nephrolithiasis), lack of appetite, constipation, vomiting, abdominal pain, pancreatitis, hypertension, and symptoms of the central nervous system such as headache and disorientation. Some researchers believe that in women with high levels of calcium in the blood, determination of Ca 2+ in the course of treatment may be a useful tool to evaluate the effectiveness of therapy [6, 7].

The first description of ovarian small cell cancer dates back to the beginning of the 1980's, [8] and despite the progression of time, the prognosis of these patients is still very poor. The majority of patients, despite intense cancer treatment, die within two years of diagnosis (for Stage III disease according to FIGO, average life expectancy of patients is approximately six months [2]). Young *et al.* [4] presented data indicating the possibility of long-term survival among patients whose tumor, at the time of diagnosis, was limited to only one ovary (FIGO IA). Favorable prognostic factors include, patients over the age of 30, normal preoperative serum calcium levels, tumor size less than ten cm and the absence of large cells in the histological picture. From the series Harrison *et al.* [2], of 17 patients described, ten were diagnosed with Stage I of the disease; seven of them had a disease free period estimated to average 40 months after completion of therapy.

Due to the relatively low incidence of this cancer, and the variety of therapeutic regimens used in oncologic centers, a generally accepted standard of management has not yet been developed. Treatment is based on the execution of primary surgery, chemotherapy, secondary cytoreduction, and radiotherapy.

Surgery to remove the affected adnexa is necessary for the diagnosis and the assessment of the severity of the disease, but there is no unified position on the extent of the surgery in this group of patients. Unilateral removal of the adnexa or exclusively of the ovary is carried out in about 70% of cases [1]. Despite the generally very young age of patients, and the desire to maintain their fertility, because of the very dynamic course of the disease, with a short life expectancy, many surgeons do not implement conserving surgery but instead remove the uterus, the second adnexa, and the greater omentum [9].

In some women, the diversity of chemotherapy regimens used, the varying number of cycles of chemotherapy administered, and the addition of radiotherapy applied to the abdomen and pelvis, account for the considerable difficulty in evaluating the effectiveness of adjuvant therapy.

The analysis of literature covering a total of 136 cases of SCOC [1] proved that the greatest efficacy of chemotherapy regimens were those containing cisplatin or carboplatin, etoposide, and vinca alkaloids. In this study, in about 65% of the women who originally obtained complete remission, recurrence was found at approximately 11.5 months after the culmination of the first line of treatment.

Senekjian *et al.* [10] reported the results of treatment of five patients with SCOC receiving chemotherapy with VPCBAE

- vinblastine, cisplatin, cyclophosphamide, bleomycin, adriamycin (doxorubicin), etoposide. Four of the five women died within 11-18 months of diagnosis of the disease, whereas in one patient (FIGO IA), a 29-month disease-free period was achieved. During the course of the treatment, all the patients reported a high degree of hematologic complications, requiring an adjustment of dose in three of the cases. Additionally, severe neuropathy was present in one of the patients.

In a series of 17 patients described by Harrison *et al.* [2], all of the patients, after the initial surgery, received adjuvant chemotherapy, seven had additionally underwent radiotherapy. Eight women (five FIGO I, three FIGO III) received cisplatin with etoposide with or without bleomycin, and five of them (four FIGO I, one FIGO III) received radiotherapy at a later phase of the treatment. In women with Stage I disease, the median time observed without recurrence was 51 months. Two patients with FIGO Stage III died at six and seven months after the diagnosis of the disease. One of the patients that had been treated with additional radiation therapy, had achieved a disease-free period of over six months. Another four patients (three FIGO III, one FIGO IC) were treated with paclitaxel and carboplatin – in two of them, tumor recurrence was found after nine and seven months; in the remaining two, disease progression was already observed during the course of the treatment. The next three patients who were diagnosed with Stage IC disease received cisplatin, etoposide, paclitaxel , and carboplatin, two of which later receive additional radiotherapy treatment. In this subgroup, two women had attained a disease-free period of at least 16 and 54 months, only one achieved a partial response to the chemotherapy applied.

The study of Pautier *et al.* [9] included 27 patients who underwent surgical cytoreduction (with the excision of both adnexa, the uterus, the greater omentum, and the pelvic and para-aortic lymph nodes) before/during/and after the completion of chemotherapy and receiving four to six cycles of chemotherapy according to the PAVEP regimen (cisplatin, adriamycin, etoposide, cyclophosphamide). Of the 18 women who achieved complete clinical remission, ten received one course of high-dose chemotherapy of consolidating CARBOPEC (carboplatin, etoposide, cyclophosphamide) and subsequently received autologous hematopoietic stem cell transplantation (AHSCT). The results of such intensive treatment are encouraging - among the ten patients treated with high-dose chemotherapy (HDCT), at a mean follow-up of 37 months, seven patients still remained in complete remission, as opposed to five of the eight not subjected to HDCT, which were diagnosed with recurrent disease. One- and three-year survival for all patients included in the study were 58% and 49% respectively. It is worth noting that in the evaluated group of 17 patients, only five had Stage I disease according to FIGO.

Some researchers emphasize the important role of radiotherapy in the treatment of SCOC. Both Harrison *et al.* [2] and Young *et al.* [4] showed that the majority of women with long-term disease-free periods, in addition to chemotherapy, received radiation therapy within the pelvic and abdominal cavities. Favorable results of irradiation are explained by the fact that most frequently recurrence of disease occurs in the pelvis and the peritoneum.

Baeyens *et al.* [7] described a 19-year old female, kidney transplant patient, in which during the initiation of the transplantation, after exploration of the abdominal cavity, nodular changes were found in the right ovary, which proved to be SCCOHT. During the procedure, the right adnexa was excised, and all macroscopic residual tumors were removed from the abdomen (FIGO IA). The transplantation of the kidney was abandoned. Due to kidney failure, it was decided to suspend chemotherapy treatment, and the abdominal cavity was irradiated with a dose of 30 Gy and the pelvis with a dose of 44.8 Gy, yielding a greater than ten-year disease-free period.

References

[1] Estel R., Hackethal A., Kalder M., Münstedt K.: "Small cell carcinoma of the ovary of the hypercalcaemic type: an analysis of clinical and prognostic aspects of a rare disease on the basis of cases published in the literature". *Arch. Gynecol. Obstet.,* 2011, *284*, 1277.
[2] Harrison M.L., Hoskins P., du Bois A., Quinn M., Rustin G.J., Ledermann J.A., *et al*.: "Small cell of the ovary, hypercalcemic type - analysis of combined experience and recommendation for management. A GCIG study". *Gynecol. Oncol.,* 2006, *100*, 233.
[3] Distelmaier F., Calaminus G., Harms D., Sträter R., Kordes U., Fleischhack G., *et al*.: "Ovarian small cell carcinoma of the hypercalcemic type in children and adolescents: a prognostically unfavorable but curable disease". *Cancer,* 2006, *107*, 2298.
[4] Young R.H., Oliva E., Scully R.E: "Small cell carcinoma of the ovary, hypercalcemic type. A clinicopathological analysis of 150 cases". *Am. J. Surg. Pathol.,* 1994, *18*, 1102.
[5] Oliva E.: "Small cell carcinoma of ovary, hypercalcemic type: an update on an enigmatic neoplasm". *Pathol. Case Rev.,* 2006, 11, 43.
[6] Taraszewski R., Rosman P.M., Knight C.A., Cloney D.J.: "Small cell carcinoma of the ovary". *Gynecol. Oncol.,* 1991, *41*, 149.
[7] Baeyens L., Amat S., Vanden Houte K., Vanhoutte P., L'Hermite M.: "Small cell carcinoma of the ovary successfully treated with radiotherapy only after surgery: case report". *Eur. J. Gynaec. Oncol.,* 2008, *29*, 535.
[8] Dickersin G.R., Kline I.W., Scully R.E.: "Small cell carcinoma of the ovary with hypercalcemia: a report of eleven cases". *Cancer,* 1982, *49*, 188.
[9] Pautier P., Ribrag V., Duvillard P., Rey A., Elghissassi I., Sillet-Bach I., *et al*.: "Results of a prospective dose-intensive regimen in 27 patients with small cell carcinoma of the ovary of the hypercalcemic type". *Ann. Oncol.,* 2007; 18: 1985.
[10] Senekjian E.K., Weiser P.A., Talerman A., Herbst A.L.: "Vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin and etoposide in the treatment of small cell carcinoma of the ovary". *Cancer,* 1989, *64*, 1183.

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