Case Report

Current Opinion in Gynecology and Obstetrics Small Cell Carcinoma of the Ovary Hypercalcemic Type: A Case Report and Review of Literature

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Received: November 03, 2018; Accepted: December 21, 2018; Published: December 26, 2018

Abstract

Small cell carcinoma of the ovary hypercalcemic type (SCCOHT) is an exceedingly rare aggressive malignancy. It typically affects young women. Herein we aimed to report a case of a 28-year-old woman treated for SCCOHT in Salah Azaiez Institute. The tumor was revealed by a delay of menses. The imaging found a large mass of the right ovary. The patient underwent a bilateral salpingo-oophorectomy, a total hysterectomy and a pelvic and a para-aortic lymphadenectomy. She subsequently received 6 cycles of adjuvant chemotherapy. Three years later, she presented a metastatic bone relapse.

Keywords: Small cell carcinoma, Ovary, Hypercalcemia

Abbreviations: SCCOHT: Small Cell Carcinoma of the Ovary Hypercalcemic Type; BEP: Bleomycin; Etoposide and Cisplatin; EP: Etoposide and Cisplatin; HSCT: Autologous Stem Cell Transplantation

Introduction

Small Cell Carcinoma of the Ovary hypercalcemic Type (SCCOHT) is an exceedingly rare aggressive malignancy. Their first description was in 1982 by Dickersin et al. [1]. Currently there are more than 400 cases reported in literature. Most of the time it tends to affects young women with an average age at diagnosis around 23 years old [2]. This entity is often associated with hypercalcemia which decreases after reduction of the tumor burden. Due to the low cells differentiation, its origin remains unclear. It may derive from ovarian epithelium, sex-cord stromal cells or germ cells. The treatment is not yet well established but a combination of surgical resection and

chemotherapy is usually attempted. The prognosis is extremely bleak. Herein, we report a case of ovarian small cell carcinoma. We also discuss the existing bibliography regarding its clinical presentation and treatment.

Case Presentation

We report the case of a 28-year-old woman, had two children and a miscarriage, with no medical history, who consulted a gynecologist in September 2015 for a two-month delay of menses. The patient had a good general condition. The clinical examination was without particularity.

Pelvic ultrasound showed the existence of a cyst in the right ovary. Thereafter a computed tomography scan was performed. It revealed the presence of an expansive right latero-uterin lesion of dual component (tissue and fluid), with regular contours, which measured 15 × 8 cm. It was associated with retro-peritoneal and aortic lumbar lymph node enlargement. Blood test including serum tumor marker (CA-125) and serum calcium level were normal.

The patient was operated in two steps. She initially underwent a right Oophorectomy with resection of the tumor, then secondly, a total abdominal hysterectomy according to the Aldridge technique with a left salpingo-oophorectomy, omentectomy, appendectomy and pelvic and lumbosacral lymphadenectomy. Perioperative exploration revealed no evidence of invasion of other abdominal and pelvic organs, including no peritoneal carcinosis. Postoperative course was uneventful.

On macroscopic examination the right adnexal mass measured 15 × 11 × 8 cm, it was well limited with a smooth, glistening, and grossly intact surface. Cut surfaces were yellowish with a solido-cystic appearance. The solid component was predominant. The cystic cavities had a mucoid content. Some areas of cystic and hemorrhagic reworks were noticed.

Histological findings revealed tumor invasion of the right ovary and five lumbosacral lymph nodes (out of 10). Uterus, pelvic lymph nodes, omentum, appendix and left ovary were free from tumor invasion. Malignant tumor proliferation was made of densely arranged cells in pseudo follicular structures of variable size and included some eosinophilic material. Tumor cells were of small to medium size. They had a scanty cytoplasm and a rounded nucleus finely nucleated. In some areas, cells looked larger with more abundant eosinophil cytoplasm seeming like luteinized cells. The mitotic index was estimated at 10 mitoses per 10 high power fields. A mucinous type coating was present very focally. There were wide areas of necrosis and some lymph emboli. The reticulin formed a thin network arranged around juxtaposed cell islands (Figure 1). Immunohistochemistry revealed a focal positivity of EMA and CD10 and a high positivity for WT1 (Figure 2). Rare cells have been labeled with Synaptophysin and Vimentin. There was no evidence of cytokeratin staining, including for CK20, CK7, Chromogranin, PLAP, Inhibin, Calretinin, CD30, alpha-feto protein and CD 99. According to these findings, the pathological diagnosis was therefore a small cell carcinoma of the hypercalcemic type. The tumor was

classified as **stage IIIA1** (ii) according to the International Classification of Obstetrics and Gynecology (**FIGO 2014**).

Figure 1: Small cell carcinoma of the ovary hypercalcemic type: A case report and review of literature.

Meddeb Khedija et al., Microscopic findings of the small cell ovarian carcinoma, hypercalcaemic type

Figure 2: Small cell carcinoma of the ovary hypercalcemic type: A case report and review of literature. Meddeb Khedija et al., Immunohistochemical staining with WT1.

Adjuvant treatment: The case was discussed at a multidisciplinary team meeting. The decision was to make BEP regimen (Bleomycin 30 U day 1, Etoposide 100 mg/m² days 1-5, and Cisplatin 20 mg/m² days 1-5, every 4 weeks). After achieving six cycles of chemotherapy (4 BEP and 2 EP), the patient was in complete clinical and radiological remission.

Relapse: Six months later, the patient had a left parietal bone relapse. Brain magnetic resonance imaging showed a bulky expansive process centered on the left parietal bone of 78 × 64 × 44 cm. It was in hypo T1 signal and T2 hyper signal, heterogeneous and heterogeneously enhancing after Gadolinium injection, sparing necrotic spaces. The tumor had endocranial extension without signs of intracranial hypertension. It repressed the cerebral parenchyma without invading it and invaded the upper longitudinal sinus. The indication of surgery was not retained by surgeon. The patient was proposed for brain radiotherapy followed by palliative chemotherapy, but the disease went forward very quickly. After two weeks, she developed right hemiplegia and her general condition continued to deteriorate astonishingly. No treatment could finally be established during the relapse. She died on December 19, 2016 from her illness.

Discussion

The main complaints are not specific to the disease. The most common presenting symptoms included abdominal swelling, acute or subacute abdominal pain, vomiting, abdominal bloating or irregular menses like the case of our patient. Symptoms related to hypercalcemia may be associated such as fatigue, lethargy, polydipsia and polyuria [2]. It has been described particularly in young women with a median of 23 years [1,2].

Paraneoplastic hypercalcemia is often observed but is not consistent. In the largest series reported it has been objectified in about two third of cases [2]. The tumor is mostly unilateral (99%) and has right side predominance. On pathologic examination the tumor grossly measures around 15 cm in greatest dimension. The typically round and small neoplastic cells marks were different to that of other undifferentiated carcinomas of the ovary. There are also highly undifferentiated with hyperchromatic nuclei and brisk mitotic activity. It's characterized by follicle-like spaces (80%) containing eosinophilic fluid. Cysts lined by mucinous epithelial cell are present in 12% of cases [2,3].

In the first description of Dickerson et al. [1], the epithelial nature was mentioned but largely discussed because of the absence of specific characteristics usually observed in primary ovarian cancers of epithelial nature. In addition, undifferentiated carcinomas of epithelial origin are distinguished by their bi-laterality in half of the cases, as well as an appearance at a later age. On the other hand, follicle-like structures suggests the diagnosis of a granular cell tumor. Ulbright et al. have also supported the theory of a germinal cell origin and more

particularly of the yolk sac because of the similarities in epidemiological distribution and histological aspect [3]. In his review, Mc Cluggage et al. have reported in several cases the positivity of transcription factor SALL4 which is an immunohistochemical marker useful for germ cell tumors [4]. More recent studies have incriminated the deleterious germline mutation of SMARCA4 as an important factor in the spread of SCCOHT [5]. Lin et al. [6] demonstrated in a complete genetic profiling that inactivation of SMARCA4 was associated with 94% of SCCOHT cases analyzed.

The scarcity and aggressiveness of SCCOHT makes their treatment a challenge. There is currently no consensus concerning the optimal strategy of treatment. Callegaro-Filho et al. [7] analyzed a series of 47 patients treated by suboptimal surgery, chemotherapy, radiotherapy and autologous stem cell transplantation (HSCT). The recurrence rate was 74.5%. Nevertheless given the correlation between SCCOHT and germ cell tumors several authors encourage more intensive treatment regimens. In the only prospective study conducted to date, Pautier et al; performed tumor cytoreduction surgery then a semi-intensive chemotherapy with Cisplatin, Adriamycin, Etoposide and Cyclophosphamide followed by consolidation chemotherapy with Carboplatin, Etoposide and Cyclophosphamide and HSCT. The results were encouraging for the early-stage patients. The authors finally recommended combining pelvic radiotherapy and increasing doses of chemotherapy to reduce local recurrence and improve clinical outcomes [8]. In the era of immunotherapy and targeted therapy, a phase II trial is currently underway associating Tazemetostat (EZH2 inhibitors) with immunotherapy [9].

Most literature agrees upon the exceedingly gloomy prognosis of SCCOHT. Progression free survival is less than 10 % for advanced stages and about 33% for stage IA.

Conclusion

SCCOHT is a rare and distinct entity from other ovarian neoplasia. The germinal origin is strongly suspected. The diagnosis should be mentioned in front of any young women with an undifferentiated ovarian tumor composed of small cells. The treatment is not yet well established, however the authors recommend an aggressive multimodal strategy. The prognosis is poor and survival rarely exceeds 2 years due to rapid relapse and recurrence.

Declarations

We certify: That the proposal received a favorable opinion and consent of publication of the Ethics committee.

Data and material are available

Competing interest

No funding was required

References

1. Dickersin GR, Scully RE. Ovarian small cell tumors: an electron microscopic review. *Ultrastruct Pathol.* 1998;22(3):199-226. doi: <https://doi.org/10.3109/01913129809033472>
2. Young RH, Eichhorn JH, Richard Dickersin G, Scully RE. Ovarian involvement by the intra-abdominal desmoplastic small round cell tumor with divergent differentiation: A report of three cases. *Hum Pathol.* 1992;23(4):454-464. doi: [https://doi.org/10.1016/0046-8177\(92\)90094-J](https://doi.org/10.1016/0046-8177(92)90094-J)
3. Ulbright TM, Roth LM, Stehman FB, Talerman A, Senekjian EK. Poorly differentiated (small cell) carcinoma of the ovary in young women: evidence supporting a germ cell origin. *Hum Pathol.* 1987;18(2):175-184. doi: [https://doi.org/10.1016/S0046-8177\(87\)80336-2](https://doi.org/10.1016/S0046-8177(87)80336-2)
4. McCluggage WG, Oliva E, Connolly LE, McBride HA, Young RH. An immunohistochemical analysis of ovarian small cell carcinoma of hypercalcemic type. *Int J Gynecol Pathol.* 2004;23(4):330-336. doi: <https://doi.org/10.1097/01.pgp.0000139644.38835.9d>
5. Witkowski L, Goudie C, Ramos P, et al. The influence of clinical and genetic factors on patient outcome in small cell carcinoma of the ovary, hypercalcemic type. *Gynecol Oncol.* 2016;141(3):454-460. doi: <https://doi.org/10.1016/j.ygyno.2016.03.013>
6. Lin DI, Chudnovsky Y, Duggan B, et al. Comprehensive genomic profiling reveals inactivating SMARCA4 mutations and low tumor mutational burden in small cell carcinoma of the ovary, hypercalcemic-type. *Gynecol Oncol.* 2017;147(3):626-633. doi: <https://doi.org/10.1016/j.ygyno.2017.09.031>
7. Callegaro-Filho D, Gershenson DM, Nick AM, et al. Small cell carcinoma of the ovary-hypercalcemic type (SCCOHT): A review of 47 cases. *Gynecol Oncol.* 2016;140(1):53-57. doi: <https://doi.org/10.1016/j.ygyno.2015.11.004>
8. Pautier P, Ribrag V, Duvillard P, 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(12):1985-1989. doi: <https://doi.org/10.1093/annonc/mdm376>
9. Jelinic P, Ricca J, Van Oudenhove E, et al. Immune-active microenvironment in small cell carcinoma of the ovary, hypercalcemic type: rationale for immune checkpoint blockade. *J Natl Cancer Inst.* 2018;110(7):787-790. doi: <https://doi.org/10.1093/jnci/djx277>

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