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Small cell ovarian carcinoma of the hypercalcemic subtype: a case report.

Tumor de células pequeñas del ovario del subtipo hipercalcémico: reporte de un caso

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Abstract

BACKGROUND: Small cell ovarian carcinoma of the hypercalcemic subtype (SCCOHT) is a rare and aggressive ovarian neoplasm that affects more frequently to young women, its landmark is the elevation of serum calcium and somatic mutations of the SMARC4 gen.

CLINICAL CASE: We present a case report of a 22 year old woman who attended to our emergency service due to a 48 hours long abdominal pain, at her arrival a transvaginal ultrasound was performed which showed a right adnexal, solid, 15 centimeters in size tumor, clinical examination was compatible with an acute abdomen. She underwent an emergency right salpingo oophorectomy because of the tumor was twisted, without other pathologic findings in the surgery. Serum markers where obtained, except for calcium, only lactate dehydrogenase was altered. The biopsy described a SCCOHT affecting the right ovary, because of these, a staging surgery (FIGO IIIC) follow by platinum-based chemotherapy and radiotherapy were performed, with good response from a clinical and imaging point of view. There are not been signs of recurrence up to her last appointment, in September 2019.

CONCLUSIONS: Regarding the treatment, there are no guidelines, but combine treatment: unconservative surgery along with chemotherapy and radiation seems to improve the outcome, despite this, the overall survival is low. Genetics techniques could play a key role in diagnosis and treatment.

KEYWORDS: Small cell ovarian carcinoma; Hypercalcemia; SCCOHT; Ovarian neoplasm; Mutations; Abdomen acute; Biomarkers.

Resumen

ANTECEDENTES: El tumor de células pequeñas del ovario, del subtipo hipercalcémico (SCCOHT), es una neoplasia ovárica rara y agresiva, que afecta sobre todo a mujeres jóvenes. Destacan la elevación del calcio sérico y las mutaciones somáticas del gen SMARC4.

CASO CLÍNICO: Paciente de 22 años que acudió a urgencias debido a un dolor abdominal de 48 horas de evolución. La ecografía transvaginal mostró un tumor sólido de 15 centímetros en el anexo derecho. El examen físico fue compatible con abdomen agudo. Se decidió la salpingooforectomía debido a que el tumor estaba torcido, sin otros hallazgos patológicos en la cirugía. Se obtuvieron marcadores séricos, excepto del calcio y solo la deshidrogenasa láctica se reportó alterada. La biopsia describió un SCCOHT que afectaba el ovario derecho; por esto se practicó una cirugía etapificadora (FIGO IIIC) seguida de quimioterapia con platino y radioterapia, con buena respuesta clínica e imagenológica. Hasta su último control médico en septiembre de 2019 se encontraba sin evidencia de recurrencia.

CONCLUSIONES: Si bien no existen guías de tratamiento, el combinado con cirugía no conservadora, quimio y radioterapia al parecer mejora el desenlace, aunque la supervivencia es baja. Las técnicas genéticas tienen una participación decisiva en el diagnóstico y tratamiento.

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PALABRAS CLAVE: Carcinoma de ovario de células pequeñas; hipercalcemia; SCCOHT; neoplasia de ovario; mutaciones; abdomen agudo; biomarcadores.

BACKGROUND

The small cell ovarian carcinoma is a rare and aggressive tumor with two subtypes: hypercalcemic (SCCOHT) and pulmonary (SCCOPT). The SCCOHT subtype represents < 1% of ovarian neoplasms, corresponding to the most frequent undifferentiated tumor in women under 40 years of age.[1] Up to this date, no more than 400 cases have been reported in English literature.[2] It presents with an elevation of serum calcium in about 2/3 of cases. Recent studies demonstrated the frequent inactivation of the germinal line and somatic mutations of the SMARC4 gene,[2] which can be used for diagnosis and treatment options.

The combined treatment seems to increase survival in a small number of cases. However, the prognosis is poor, with an overall survival of 16%.[1]

Here, we present a case of SCCOHT, found incidentally by an adnexectomy secondary to an ovarian torsion, which afterwards required staging and treatment.

CLINICAL CASE

The present study involved a 22-year-old woman, who was nulliparous, obese, a tobacco smoker with prior appendicectomy and tonsillectomy, and who was not using contraception at the time. There was no history of gynecological cancer in her family.

On March 14, 2017 she attended the gynecology urgency service of a public hospital in Santiago de Chile due to abdominal pain that she had been experiencing for 48 hours prior to arrival. At first examination, the patient was stable, the gynecologic exam was very poor because of the weight of the patient. A transvaginal ultrasound was performed, that showed a right adnexal solid tumor of 15 cm, With irregular edges and abundant free liquid in the posterior cul-de-sac. An exploratory laparotomy was decided and performed on the same day. In the operatory protocol 18 centimeters. Tumor was described from the right ovary with smooth edges but friable when touched, and that was twisted once over itself. A right adnexectomy was performed, no other lesions were described in the abdominopelvic cavity. The tumor along with peritoneal cytology were sent for biopsy analysis. The next day, tumor serum markers were obtained, with just lactate dehydrogenase was altered (1243 U/L (superior limit: 618U/L) abnormal. Serum calcium was not obtained because of the low prevalence of hypercalcemic ovarian tumors worldwide. The patient evolved favorably from a clinical point of view and was discharged. On April 20, the biopsy result (Nº 17-02039) described a small cell carcinoma, hypercalcemic type (SCCOHT), and the patient was derived to the local oncology unit.

On April 26, the oncology committee (formed by six oncology gynecologists, one radiation therapist and one medical oncologist) decided

to proceed with a staging laparotomy, which was performed on May 4. The surgical protocol described a supraumbilical and infraumbilical laparotomy, where the uterus and left adnexa looked healthy, but there was a suspicious nodule in the omentum, and lymph node metastasis in both external iliac territories and obturator fossa, and three metastases of up to four centimeters. In size in the paraaortic territory, that was intimately attached to the great vessels. No liver or gastric surface lesions were reported. Moreover, no diaphragm, colon, parietal peritoneum or mesenteric root infiltration was reported. A fast tumor biopsy reported neoplastic infiltration of the omentum. A total hysterectomy, left adnexectomy, cytoreductive lymphadenectomy of the external iliac and obturator fossa was performed. In addition, a sampling of paraaortic lymph node and peritoneum was obtained. The biopsy of this surgery (N º 17-03594) concluded that the samples corresponding to peritoneum and paraaortic lymph nodes were infiltrated by SCCOHT (immunohistochemistry positive to pan-cytokeratin). The rest of the samples were negative for neoplastic infiltration.

After the staging surgery, this case was cataloged as SCCOHT stage FIGO IIIC, with a residual mass of > 2 centimeters. Platinum based chemotherapy and radiotherapy, was then indicated after a review of the case and available literature by the oncology committee.

On June 28, a Positron-emission tomography (PET CT) was performed, which showed pathologic lymph nodes in the intercave-aortic, left paraaortic side, precava and left ileo-obturator territories. **Figure 1**

The patient received four cycles of chemotherapy and also radiotherapy on the paraaortic territory (45Gy/25 fraction scheme), between June 19 and December 20, without any severe secondary effects and with good response evaluated by PET CT. **Figure 2**

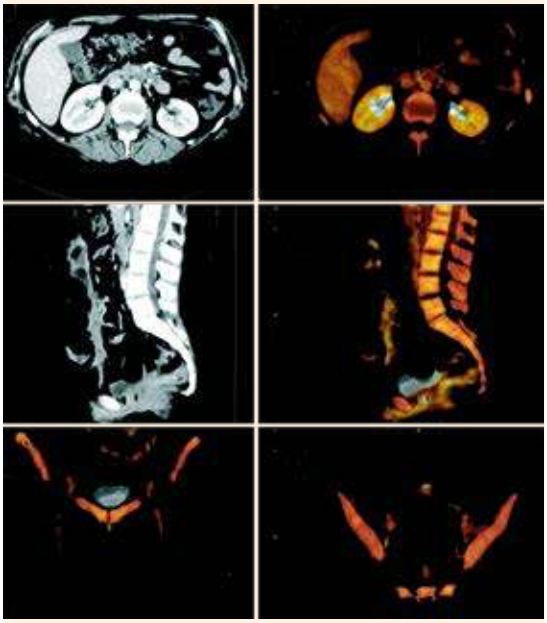


Figure 1. The arrow shows the pathologic lymph nodes in the intercave-aortic space at the kidney hilum SUV. [3,4]

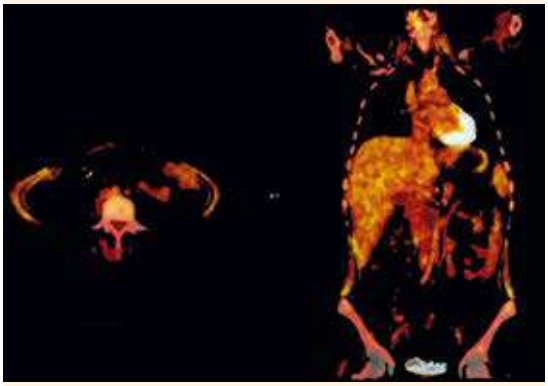


Figure 2. The image shows the decrease in size of the pathologic lymph nodes in the intercave-aortic space after combined treatment.

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Clinical and imagenological follow up every four months was performed without evidence of recurrence, however a year after the surgery she complained about climacteric symptoms, but because during her appointment she showed high blood pressure and a BMI of 41, and considering the lack of evidence on hormonal replacement therapy in patients with SCCOHT, the treatment prescribed included healthy habits, estriol ovules and selective serotonin reuptake inhibitors (SSRIs). Her last clinical follow up was on September 5, where a new computed tomography (CT) was performed and showed no signs of recurrence.

DISCUSSION

A literature review was performed in order to understand the relevance of this clinical case, this was performed between December 2019 up to May 2020, using the key word "SCCOHT" and "hypercalcemic ovarian tumor" in Pubmed obtaining 73 matches, however we only select four that where recently published more clinically focused.

SCCOHT is an extremally rare and aggressive tumor. In the study carried out by Young et al., 97% of the affected women were aged between 10 and 39 years 1.[3] Is frequently a unilateral tumor, with bilaterally informed in less than five percent of cases.[4]

Clinically, SCCOHT can present as a fast-growing unilateral pelvic mass, symptoms related to hypercalcemia are rare. By the time of the diagnosis more than half of the patients have developed metastasis, following patterns similar to epithelial ovarian carcinoma: peritoneum, lungs, liver and lymph nodes.[1]

Elevated serum calcium has been described in up to 62% of patients. This is believed to be secondary to PTH-related proteins produced by the tumor, which was observed in four of seven cases and it can be used for diagnosis and to evaluate the treatment response.[5] The calcium serum level also constitutes one of the three clinical elements associated with prognosis of the disease, where tumors bigger than 10 centimeters, that affect women under 30 years of age with elevated serum calcium levels have the worst outcome. The rest of the serum markers do not play a key role in the diagnosis of SCCOHT, neither the imaging techniques.[1] In this particular case, serum calcium was not obtained at the beginning of the treatment, due to the very low prevalence of this kind of tumor.

The tumor morphology is often described typically as small cells, with little cytoplasm and highly mitotic activity, with multiple necrosis areas. However, there are also describe a large cell variant, with a predominance of large eosinophilic cells that can be in association with previously describe morphology of SCCOHT, or as an exclusive pattern.[5] Since the diagnosis of SCCOHT is difficult, immunohistochemistry (IHQ) and molecular findings are key to achieve this outcome. IHQ is variable, usually broad spectrum cytokeratins, calretinin, CD10 and WT 1 are positive. While desmin, S100, inhibin and hormones receptors are negative.[5] Regarding the molecular aspect, studies have shown that the inactivation and bi allelic mutation or loss of SMARCA4 gene (which is involved in transcriptional regulation, DNA repair and mitosis) is present in almost all cases of SCCOHT (> 95% of cases), and seems to be the only mutated gene in this entity.[5,6] It is recommended to perform a SMARCA4 IHQ, however, it is not available in most of pathology laboratories.

There are no guidelines for its management. There has only been one prospective study published regarding SCCOHT management by Pautier in 2007. This study used a cohort of 27 patients (52.8% at stage FIGO IIIC) and

performed unconservative surgery followed or preceded by 4 to 6 cycles of platinum-based chemotherapy. Moreover, in the case of full remission, consolidation chemotherapy followed by autologous transplant of hematopoietic stem cells was carried out. 18 of the 27 patients achieved a full response after chemotherapy and unconservative surgery. However, there were pelvic recurrences, which led the authors to believe that pelvic radiotherapy would be needed[7]. This is confirmed in a multicenter study where it was shown prolong overall survival.[4] Also, if the cytoreductive surgery is not possible at the moment of diagnosis, to initiate the treatment with chemotherapy and perform an interval surgery is also feasible.[5]

Since the majority of women affected by SCCOHT are in reproductive age, fertility sparing surgery seems an interesting alternative. In the series published by Young et al, women affected with stage IA SCCOHT had better survival rate without recurrence when a bilateral salpingo-oophorectomy was performed compared with those with unilateral salpingo-oophrectomy (57% versus 23%).[3] However, these results did not reach statistical significance. Considering the poor survival rate and the limited number of cases, there are not guidelines regarding this topic. The genetic counseling for women affected by SCCOHT is recommended if it is possible.[5]

In a clinical trial currently in phase II, the role of an EZH2 inhibitor (tazemetostat) is being studied for the treatment of SCCOHT, considering that the loss or inactivation of SMARC4, leads to an overexpression of EZH2.[8]

CONCLUSIONS

We presented the case of a young women, whom after an emergency surgery for a twisted ovarian tumor was diagnosed with a SCOOHT, regrettably we did not obtain serum calcium at the moment the patient arrived, because of the low incidence of this type of cancer, however, and after the analysis of this clinical case, we request it along with other serum markers because it is widely available. The diagnosis was achieved through immunohistochemistry alone, since genetics techniques are not available in our country and imaging techniques do not allow differential diagnosis. The patient received staging surgery follow by platinum-based chemotherapy and radiation therapy because it is the most reported treatment, accomplishing in the clinical and imaging follow up, absence of recurrence.

We consider that the key messages are always request serum calcium along with other tumor serum markers in the presence of an ovarian mass, it is inexpensive and can be processed by any laboratory, it could be useful for diagnosis and follow up. Because this tumor affects primary to young women, more studies are necessary in order to assess the safety of fertility sparing surgery, but also to evaluate the treatment guidelines, until now unconservative surgery plus chemo and radiation therapy seems to be working for our patient. Finally, it is fundamental to spread the availability of the genetics techniques, since it has a role both in diagnosis and possible treatment.

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