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# A dramatic response to checkpoint inhibitor in a woman with small cell carcinoma of the hypercalcemic type of the ovary

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## HIGHLIGHTS

- This is the longest survival of a patient with SCCOHT under therapy with checkpoint inhibitors reported in the literature.
- This report emphasizes the importance of immunohistological testing for PD-L 1.
- Clinicians should consider off-label use of immune checkpoint blockade when treating this highly aggressive tumor.

## ARTICLE INFO

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## ABSTRACT

*Objective.* We present the rare case of a 21 year old woman with small cell carcinoma of the right ovary of the hypercalcemic type with dramatic response to checkpoint inhibitor.

*Methods.* Case report.

*Results and conclusions.* Our patient, a 22-year old woman with small cell carcinoma of the hypercalcemic type with hepatic metastases, is currently 43 months under treatment with pembrolizumab. Last MRI revealed no viable liver metastases nor other signs of recurrence. This is the longest survival of a patient with small cell carcinoma of the ovary under therapy with checkpoint inhibitors reported in the literature so far.
With this report we emphasize the importance of immunohistological testing for PD-L 1. Treating clinicians should keep off-label use of immune checkpoint blockade in mind when treating this highly aggressive tumor if all other treatment options fail.



## 1. Case report

We present the rare case of a 21 year old woman with small cell carcinoma of the right ovary of the hypercalcemic type.

The patient was first diagnosed in September 2019, when she was 20 years old, at a regional hospital in Germany. She presented with severe abdominal pain, sonography revealed a large tumor of 16.5 × 11 cm. An oophorectomy on the right side via laparotomy was performed. During surgery, the right ovary was twisted several times due to the large tumor mass. Macroscopically a 16.5 × 11 cm large tumor of the right ovary with necrosis and diffuse hemorrhage was seen. Histological analysis showed polymorph malignant cells with partly hyperchromatic nuclei forming follicle-like structures [see Figs. 1, 2]. Immunohistological staining revealed negativity for progesterone and estrogen receptors, inhibin, Wilms tumor-1 antigen (WT-1), paired box protein 8 (PAX8), thyroid transcription factor-1 (TTF1), caudal type homeobox 2 (CDX2) and gross cystic disease fluid protein 15 (GCDFP-15). Further immunohistological staining showed negativity for SMARCA4 and A2 (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 and 2). SMARC B1 was preserved. Cytokeratine (AE1/AE3) was partly positive. These pathognomonic changes prove the diagnosis of a small cell carcinoma of hypercalcemic type (SCCOHT).

The patient's serum calcium was slightly elevated to 2.8 mmol/l (reference values: 2.15–2.64 mmol/l) prior to the surgery. Following the oophorectomy on the right side serum calcium was within normal ranges and stayed within normal values during the course of disease. Tumormarker in blood was only tested after the surgery. Ca 125 was

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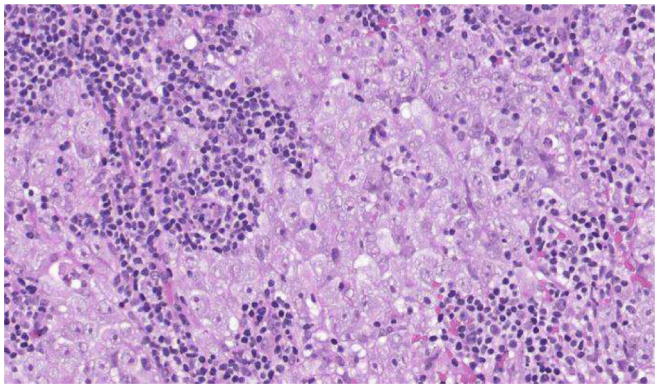

**Fig. 1.** Hematoxylin eosin staining: closely packed round cells with scant cytoplasm, small hyperchromatic nuclei, follicle-like structures.

slightly elevated with 42.5 kU/l (reference value: <35 kU/l). Other markers such as HE4 (human epididymal protein 4) and LDH (lactate dehydrogenase) were normal. During the course of disease, CA125 fell to normal values. External pathological examination classified the tumor as TNM (tumor (t) nodes (n) and metastases (m)) stage pT1a.

The patient was then referred to our specialized gynecological oncology center at Charité University Hospital in Berlin, Germany.

Following the histological diagnosis of small cell carcinoma of the hypercalcemic type of the ovary we performed a staging examination consisting of a positron emission tomography (PET)-scan.

Residual tumor was seen adjacent to the former right ovary. Also, a lymph node of the iliacal vessels on the right side was suspicious of metastasis.

Cranial MRI (Magnetic Resonance Imaging) revealed no cerebral metastases.

After in-depth counselling of the young patient an en-bloc resection of the uterus, left ovary and tube and peritoneum of the pelvis as well as ometectomy and bowel resection with an anastomosis of colon descendens and rectum was performed via laparotomy.

Histological analysis showed: uterus, left ovary, biopsies of peritoneum and omentum showed no evidence of tumor infiltration. Two para-aortic and one para-caval lymph node revealed metastases. Proliferation index (Ki67) was 60%. After completion of the surgery no residual tumor was detected intraoperatively.

TNM stage was pT3c N1 (3/7) L0 V0. FIGO stage III.

Owing to the patient's age hormonal replacement therapy with transdermal estradiol was given.

From January to April 2020 she received a total of 4 cycles of chemotherapy with cisplatin, etoposide and ifosfamid.

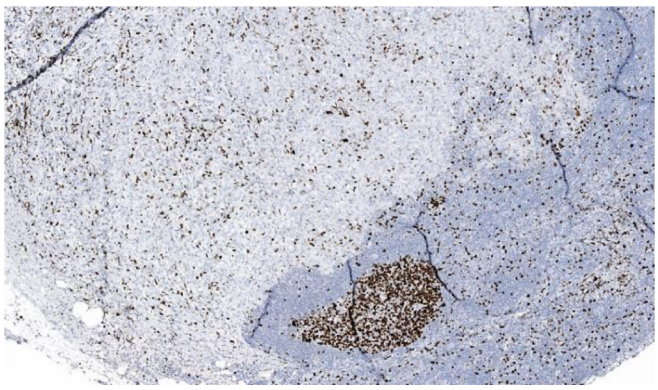

**Fig. 2.** ki67 staining.

Due to severe and prolonged cytopenia after these 4 cycles chemotherapy bone marrow puncture was performed, showing no tumor infiltration but toxic bone marrow damage.

After chemotherapy was completed a CT scan in April 2020 revealed new liver metastases in segment VII [see image 3]. Complementary MRI scan in June 2020 confirmed diagnosis of three liver metastases [two of those metastases are shown in images 4 and 5].

In July 2020 chemotherapy with cyclophosphamide was given, followed by application of pegfilgastrim, filgastrim and plerixafor and stem cell apharesis. High-dosage chemotherapy with carboplatin and etoposide was applied from September to October 2020 followed by autologous stem cell transplantation of a total of 2.85*106 (1,6*106 und 1,25 *106 million CD34+ cells/kg body weight).

Unfortunately, despite extensive treatment magnetic resonance imaging (MRI) in October 2020 showed new disseminated liver metastases [see image 6].

The case was discussed within our interdisciplinary tumor board and PDL (programmed death ligand) - testing was recommended. It was performed using the lymph node metastases. TC (tumor cells)-score was: 0%; IC (immune cell)-score 2% and CPS (combined positive score) was 2.

In November 2020 off-label use immunotherapy with the checkpoint inhibitor pembrolizumab given every 3 weeks was started.

Another MRI in December 2020 showed remission of hepatic metastases under therapy with pembrolizumab [see image 7].

In February 2021 computer tomography (CT)-guided puncture of a liver metastases in segment IV and VIII was performed. Histological analysis confirmed diagnosis of hepatic metastasis of the small-cell cancer of hypercalcemic type of the ovary but showed no viable tumor cells.

Brachytherapy of 20Gy with Iridium-192 in afterloading technique of hepatic segments IVa/VIII and VIII was done [see images 8,9].

MRI in March, PET-scan in June, MRI in September, December 2021 and July 2022 showed no tumor recurrence.

To date, in April 2023, therapy with pembrolizumab is being continued without any sign of recurrence 43 months after initial diagnosis of small cell carcinoma of the hypercalcemic type of the ovary [see image 10].

## 2. Discussion

Small cell ovarian cancer of the hypercalcemic type (SCCOHT) is a very rare and highly aggressive tumor with an extremely unfavorable prognosis. SCCOHT affects mostly young women. According to a review of 135 cases published in the literature average age at diagnosis is 23.4 years, ranging from 7 months to 71 years [1,2]. Symptoms at diagnosis are abdominal pain and palpable mass caused by an almost exclusively unilateral tumor [1]. Two-third of cases are associated with hypercalcemia, which may lead to acute pancreatitis [Young]. Symptoms are similar to those of epithelial ovarian cancer such as abdominal pain and bloating, palpable mass and gastrointestinal symptoms. Histological features include small, closely packed cells forming follicle-likes spaces. Immunohistological staining usually shows focal positivity for cytokeratins, vimentin and epithelial membrane antigen. p53 and CD10 and Wilms tumor antigen-1 (WT-1) expression have also been reported. In contrast to small cell carcinoma affecting originating in other organs SCCOHT lacks typical neuroendocrine differentiation. The tumor is driven by SMARCA4 mutations.

Around 50% of patients are diagnosed at stage I of the disease and 36% at stage III [1,2]. CA-125 may be used as a tumor marker as it is elevated in 75% of cases [1].

No randomized trials exist so far. In the largest series published by Young et al. 150 patients with SCCOHT were analyzed [2]. Within this cohort the vast majority of tumors were unilateral with an average tumor size above 15 cm. All patients were treated with surgery and adjuvant chemotherapy. Long-term survival is extremely rare, the large majority of patients die within the first two years after diagnosis [2]

and relapse within the first 12 months of initial diagnosis. Relapse occurs mostly multifocal in the peritoneum as in other types of epithelial ovarian cancer. Slightly improved survival was seen in patients above 30 years at initial diagnosis, histologically without large cells, with tumor size <10 cm and/or normal preoperative serum calcium [2].

Due to the rarity of the disease no specific guidelines exist. Treatment described in the literature usually includes laparotomy, hysterectomy with oophorectomy and peritoneal and omental staging because of the highly aggressive nature of the tumor [1]. Residual tumor is associated with adverse outcome [1]. However, patients are usually of childbearing age and fertility sparing approaches in early stages of the disease can be offered [3]. Surgery is usually followed by platinum-based chemotherapy, oftenly including carbo- or cisplatin, etoposide and vinca alkaloids. Radiotherapy has not been shown to be effective. The use of high-dosage chemotherapy followed by autologous stem cell transplantation has been described in the literature [4,5]. In our case, no lasting effect of this treatment could be observed.

So far, very few reports of using checkpoint inhibitors such as pembrolizumab as an off-label therapy in small cell carcinoma of the ovary were published [6,7]. Pembrolizumab is a humanized monoclonal antibody, a PD-1 inhibitor that prevents T cell PD-1/tumor cell PD-L1 interaction, which restores T cell–mediated antitumor immunity. Pembrolizumab has shown efficacy in treating melanoma, non-small cell lung cancer, genitourinary cancer, Hodgkin's lymphoma and others.

A guideline published in 2020 by the international SCCOHT Consortium also recommends evaluating the off-label use of immune checkpoint blockade if all other treatment options fail [8]. Jelinic et al. described three patients with SCCOHT who remained disease-free for 1.5 years [6]. This group also examined 11 cases of SCCOHT and detected PD-L1 expression, prominent T-cell infiltration and infiltration by CD68 + macrophages in 10 of 11 cases [4]. PD-L1 expression was detected in both tumor cells and stromal cells. T-cell infiltration was strongly associated with PD-L1 expression across all patients. These data suggest that SCCOHTs are immunogenic tumors and exhibit biologically significant levels of T-cell infiltration and PD-L1 expression despite the low mutational burden in these tumors. The authors suggest that the transcriptional program regulated by SMARCA4 may influence tumor immunogenicity [6].

Our patient, a 22-year old woman with small cell carcinoma of the hypercalcemic type with hepatic metastases, is currently 43 months under treatment with pembrolizumab. Last MRI revealed no viable liver metastases nor other signs of recurrence. This is the longest survival of a patient with small cell carcinoma of the ovary under therapy with checkpoint inhibitors reported in the literature so far.

With this report we emphasize the importance of immunohistological testing for PD-L 1. Treating clinicians should keep off-label use of immune checkpoint blockade in mind when treating this highly aggressive tumor if all other treatment options fail.

## Author contribution

J. Altmann: project development; data collection; data analysis; manuscript writing.

W. Schmitt: evaluation of pathological and immunohistological data; manuscript editing.

N. Bashian: evaluation of radiological data; manuscript editing.

J. Sehouli: project development; data collection; data analysis; manuscript editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2023.12.016.

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