Ovarian small cell carcinoma of the hypercalcaemic type, a comprehensive review

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This review article aims at giving a comprehensive review of the literature on the hypercalcaemic type of small cell carcinoma of the ovary (SCCO-HT), addressing both clinical and pathological aspects, and to present a proposal for optimal therapy based on critical appraisal of literature findings. A literature search resulted in 250 reported cases with the largest retrospective series consisting of 150 patients. SCCO-HT has no specific clinical presentation, but occurs predominantly in young women. Hypercalcaemia is often but not always present at diagnosis. Both clinical and histopathological features discern SCCO-HT from the pulmonary type of SCCO and other ovarian tumours. Long-term prognosis is poor, with a mean survival of 18 months. Tumour stage is the most important prognostic factor. Most cases with a favourable outcome have been treated with surgery and multiple cycles of polychemotherapy including cisplatin or carboplatin and etoposide.

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Introduction

Small cell carcinoma of the hypercalcaemic type is a rare, highly malignant tumour of the ovary, first described in 1982 by Dickersin et al.[1] The cancer was originally termed small cell carcinoma of the ovary (SCCO) because of the typical microscopic appearance of uniform, closely packed small cells with scanty cytoplasm. Later, a large cell variant was also reported. This type of ovarian malignancy is different from the SCCO-pulmonary type, which has the same microscopic features as the small cell lung carcinoma. The occurrence of SCCO-pulmonary type in the female genital tract was extensively reviewed in 2007.[2] This article gives a comprehensive review of the available literature on the SCCO-hypercalcaemic type (SCCO-HT).

To select appropriate articles, a PubMed search was performed with various combinations of the following keywords: small cell carcinoma of the ovary, diagnosis, prognosis, therapy and pathology. Additional manuscripts were found by searching the reference lists of the retrieved articles. In total, approximately 250 cases were described, nearly all of them retrospectively. The largest series was reported by Young et al. and consisted of 150 cases.[3] One study prospectively described treatment of 27 SCCO patients with a median follow-up of 37 months.[4] Based on the findings from this literature

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query, the clinical presentation, laboratory findings, pathology, differential diagnosis, prognosis and treatment modalities will be described.

Clinical presentation and laboratory findings

Although there are no specific clinical manifestations of SCCO-HT, age at presentation and serum calcium level may contribute to the establishment of the diagnosis.

Age and presenting symptoms

SCCO-HT occurs almost exclusively in young women, in their second to fourth life decade; the average age of occurrence is 23.9 years.[3] Symptoms at diagnosis are not specific and similar to those of other ovarian tumours. Most common complaints are abdominal pain (~45%) and/or swelling (~40%) and urinary complaints (~20%).[3,5] Oligomenorrhea or amenorrhea are neither sensitive nor specific signs, but often striking because of the young and fertile age of the patient. Weight loss has been specifically reported in paediatric patients.[6]

Hypercalcaemia and CA-125

Despite its name, SCCO-HT is not always accompanied by hypercalcaemia: tumours with only small cells are associated with elevated serum calcium levels in 70% of the cases, tumours with a large cell component in only 57%.[3] Since other ovarian tumours are rarely associated with hypercalcaemia, elevated serum calcium levels in a patient with an ovarian mass strongly suggest SCCO-HT. However, clinical manifestations attributable to raised serum calcium levels (e.g. fatigue, lethargy, polydipsia and polyuria or, rarely, metastatic calcinosis) are only present in a minority (2.5%) of patients.[3,7] The cause of the elevated serum calcium level has not been elucidated as yet. It occurs in the absence of osseous metastases. In some cases, a parathormone-like substance was found, or some tumour cells stained for parathormone at immunohistochemistry, but this finding is inconsistent.[3]

The serum calcium level typically normalises after removal of the tumour and can raise in recurrence. As such, it is a useful tumour marker in the follow-up of the disease, even in cases in which the serum calcium level was initially normal.[3] Nevertheless, normal serum calcium levels do not rule out recurrence.[8] The clinical value of CA-125 is less clear, although levels can be raised at presentation and decrease under therapy.[9] Elevated CA-125 levels are possibly associated with peritoneal spread.[9,10] It must be noted that CA-125 elevation should be interpreted cautiously, as it can also occur in various non-malignant conditions (e.g. infection, endometriosis, menstruation and peritoneal irritation by intra-operative manipulation).[11]

Family history

There are reports of familial occurrence, suggesting a genetic basis for this cancer.[3,6,12,13] Familial cases may develop at younger ages than non-familial cancers and show genetic anticipation (i.e. reduction in the age of onset in successive generations).[6,13] One study noted an increased incidence of other solid tumours in first- and second-degree relatives of patients.[12]

Tumour spread and stage at diagnosis

Similar to other ovarian neoplasms, SCCO-HT occurs almost exclusively unilateral and spreads locally to the peritoneum. Pelvic and abdominal lymph nodes and distant metastases to liver, lungs, brain, bone and supraclavicular lymph nodes have been described.[3,6,10] Fifty percent of the cases in the Young series had stage I at diagnosis (33% of whom had stage IA), 5% had stage II, 43% stage III and 1% had distant metastases (Stage IV). Harrison et al. reported a similar distribution in 17 patients.[5] In contrast, in a recent series of 27 patients reported by Pautier et al., in which optimal staging was carried out, only a minority (5 out of 27) was diagnosed in stage I, and 14 patients had stage IIIC disease at diagnosis.[4]

Pathologic findings

Histopathologic examination of the tumour is essential for a correct diagnosis. Light microscopic alterations may overlap with other ovarian malignancies, in particular with the SCCO-pulmonary type, and immunohistochemical or electronmicroscopic examinations may be required to differentiate SCCO-HT from other entities.

Gross pathology

Tumour size can range from 6-26 cm, and its weight can reach 2500 grams.[14] The external surface,

which may be ruptured, can be lobulated, nodular or smooth.[3] The tumours are predominantly solid, but often have a cystic component too. Larger tumours usually contain areas of necrosis or haemorrhage.

Light microscopic findings

As a rule, the microscopic growth pattern consists of diffuse proliferating, closely packed, uniform cells. However, the malignant cells can also grow in nests, cords, clusters or in a mixture of these patterns. In 80% of the tumours, there are follicle-like spaces in varying sizes, generally filled with eosinophilic fluid (*Figure 1A*).[1,3] Foci of mucinous epithelium are present in 10-15% of the cases.

Except for the large cell variant, the most characteristic cell of the neoplasm is small and rounded, with scanty cytoplasm. The malignant cells have round to oval nuclei, which are similar in shape and size (*Figure 1B*). The nuclear envelopes are distinct; the chromatin irregularly clumped; many mitotic figures are present and small single nucleoli can often be seen. Larger cells with abundant cytoplasm and an eccentric nucleus are present in 50% of the tumours. When they predominate, the tumour is called the large cell variant of SCCO-HT.[1,3,15,16]

Immunohistochemical findings

Immunohistochemical stainings are negative for inhibin, α-fetoprotein, β-hCG, thyroid transcription factor 1 or desmin.[3,6,17,18] Epithelial membrane antigen is positive in one third of the cases, and intense staining possibly occurs more frequently in the large cell variant of SCCO-HT. [5,17] Vimentin staining is positive in about 50% of the cases whereas cytokeratin and neuron-specific enolase (NSE) staining is variable.

Electron microscopic findings and flow cytometric analysis

Abundant rough endoplasmic reticulum with distended cisternae is a characteristic feature of the hypercalcaemic type and is not seen in the pulmonary type.[1,15] In addition, the pulmonary type has neurosecretory granules in the cytoplasm, which are not observed in the hypercalcaemic type.[5,19-21] Flow cytometry can also differentiate between the 2 types. The hypercalcaemic type is uniformly diploid, in contrast to the aneuploidy seen in the majority (>60%) of pulmonary types.[8,15,22]

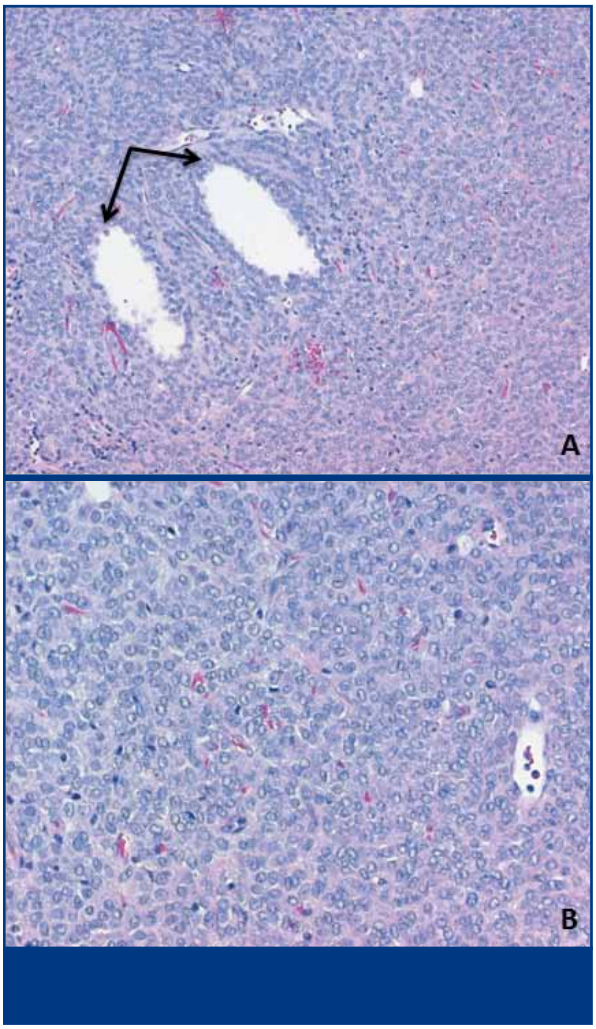

Figure 1. Characteristic light microscopic findings of the small cell ovarian carcinoma, hypercalcaemic type. (A) Follicle-like structures (black arrows, haematoxylin and eosin, 100x magnification). (B) Diffuse growth of small cells with scanty cytoplasm (haematoxylin and eosin, 200x magnification).

Histogenesis

The histogenesis of SCCO-HT remains unclear. Most primary ovarian cancers originate from the surface epithelial, the germ cells, or the sex cords. Based on microscopy findings, Dickersin et al. suggested an epithelial origin, but the young age of most patients with SCCO-HT and its aggressive behaviour strongly argue against his hypothesis.[1] Although a primitive germ cell origin was postulated too, SCCO-HT is nowadays considered as a distinct entity and classified by the World Health Organization (WHO) under tumours of uncertain origin and miscellaneous tumours.[18,23]

Table 1. Key differentiating findings between SCCO-HT and other ovarian tumours.[3,5,15]

Malignancy	Clinical and laboratory differences		Pathological differences
SCCO-pulmonary type	peri- and postmenopausal age 45% bilateral no paraneoplastic hypercalcaemia, can occur with other paraneoplastic syndromes (Cushing's syndrome, SIADH) associated with other types of ovarian neoplasms in the same ovary (Brenner, endometrioid)	LM HC EM FLOW	no follicle-like spaces (focal necrosis) no large cells nuclei ovoid-to-angulated with nuclear molding, indistinct nuclear envelopes, evenly dispersed chromatin, inconspicuous nucleoli. vimentin -, NSE often + normal endoplasmatic reticulum and neurosecretory granules present >60% aneuploid
Granulosa cell tumours	no hypercalcaemia raised oestrogen production mostly stage I	IHC	α-inhibin +
Intra-abdominal desmoplastic round cell tumour	2/3 bilateral	LM IHC	no follicles, prominent desmoplastic stroma desmin +
Germ cell tumours	raised serum βHCG and α-fetoprotein		

LM: light microscopy, IHC: immunohistochemistry, EM: electron microscopy, FLOW: flowcytometry

Differential diagnosis

SCCO-HT may be confused with other small cell malignant tumours affecting the ovary. First, SCCO-pulmonary type and metastases of a small cell lung carcinoma must be excluded. Secondly, desmoplastic round cell tumour, granulosa cell tumour, germ cell tumours and other rare non-epithelial ovarian tumours must be considered, including malignant lymphoma, primitive germ cell tumours, primitive neuroectodermal tumours, neuroblastoma, melanoma, metastatic sarcoma, and anaplastic carcinoma of Müllerian origin.[1,3,5,16] Clinical information and laboratory results as well as pathological findings may help differentiating between SCCO-HT and other tumours. An overview of the key differences with the most important differential diagnoses is presented in *Table 1*.

Prognosis

SCCO-HT is a highly malignant tumour with an poor overall prognosis. The average life expectancy is only 18 months and long-term disease-free survival (DFS) is uncommon.[9] The overall 1-year survival is about 50%.[3,4] A survival of >1 year post surgery without recurrence was seen in only 33% of the stage IA patients, 10% of stage IC patients and 6.5% of stage II, III and IV patients. However, more recent series reported a DFS of 70-100% in stage I patients, which may be explained by an understaging in Young's series.[4,5] Indeed, surgical staging was performed in only a minority of their cases. Other potential beneficial prognostic markers include age >30 years, a normal preoperative serum calcium level, tumour size <10 centimetres and absence of large cells.[3]

Therapeutic modalities

Since no controlled interventional studies have been performed, treatment principles are based on the approach of other ovarian cancers and expert opinion.

Surgery

All reported cases with long-term survival had surgical removal of the tumour. However, there is no consensus on the optimal extent of surgery, especially for tumours in early stages. Some have argued the aggressive behaviour of most SCCO-HT cancers warrants total abdominal hysterectomy and bilateral salpingoophorectomy, regardless of the tumour stage. Indeed, a trend for better outcome was seen in stage IA patients who underwent a bilateral salpingoophorectomy compared to those who had an unilateral procedure (57% survival without recurrence versus 23%).[3] In addition, extensive surgery allows optimal staging and might increase the effect of chemotherapy, as reported in epithelial ovarian

Table 2. Overview of chemotherapy schedules resulting in a favourable response.

Schedule	Components	Stage at diagnosis	Number of patients	Outcome (median follow-up)	Secondary outcome
VPCBAE	*0h:* vinblastine 6 mg/m² cisplatin 90 mg/m² *24h* cyclophosphamide 1g/m² bleomycin 15 U/m² *36h* doxorubicin (Adriamycin) 60 mg/m² etoposide 200 mg/m²	IA IC IIC IIIA IIIB IIIC	1 [29] 1 [19] 1 [29] 2 [29] 1 [9] 2 [25, 32]	CR (29 mo) CR (3 mo) CR (8 mo) CR (3mo) CR (25 mo) CR (48 mo)	 died at 3 mo died at 11 mo
BEP	bleomycin 18 U/m² on days 2, 9 and 16 cisplatin 20 mg/m² on days 1-5 etoposide 100 mg/m² on days 1-3	IC IIIC IV	1 [8] 1 [28] 1 [10]	CR (5 yrs) CR (68 mo) PR	 died at 7 mo
PVB	cisplatin 20 mg/m² on days 1-5 vinblastin 6 mg/m² on days 1-2 bleomycin 18 U/m² on days 2, 9 and 16	IB IIIB IIIC	1 [10] 1 [10] 1 [10]	CR (58 mo) CR (2 mo) progressive	 relapse at 2 mo
DEC	doxorubicin 40 mg/m² (days 1-3) etoposide 100 mg/m² on day 1 cyclophosphamide 500 mg/m² on day 1	IIIB (2nd line) IIIC (2nd line)	1 [10] 1 [10]	PR (3mo) progressive	died at 23 mo
PEI/PEC/ **PCAE** [4]	cisplatin 80 mg/ m² day 1/carboplatin etoposide 75mg/ m² (days 1-3) ifosfamide/cyclophosphamide (300mg/ m² (days 1-3)/melphalan (alkylating agent) doxorubicin (adriamycin) 40 mg/ m² on day 1 → in some cases, after inducing CR, **followed by high dose chemotherapy (mostly PEC) and BMT:** carboplatin 300-400 mg/ m² (days 1-4) etoposide 300-450 mg/ m² (days 1-4) cyclophosphamide 1600 mg/ m² (days 1-4)/ melphalan 180mg/ m²	IA I? IC IIC IIIB IIIC IV	3 [4] 2 [4] 2 [6] 5 [4, 27] 1 [6] 16 [4, 6, 27] 3 [4]	all BMT; CR (33 mo) CR (33 mo) 1 CR (26 mo) 1 BMT ; CR (18mo) 2 died 3 BMT after CR (1 2nd line) progressive 4 died [4] 6 CR, no BMT 6 BMT after CR (1 2nd line) 3 Progressive after PR, all died	 died at 63 mo 1 pelvic relapse and died, 2 CR (1 CR >10yrs) died at 3 mo 5 relapse; 2 CR* 2 pelvic relapse (1 CR*, 1 died) 4 CR (37 mo; 1 CR >14yrs)
Docetaxel	20 mg/m² (days 1, 8 and 15) used in 3rd line	IIIC	2 [14, 30]	CR (3,5 yrs)	

*CR: complete response, PR: partial response, BMT: bone marrow transplantation, *: after surgery, chemotherapy and radiotherapy*

cancers.[14,19] The high proportion of pelvic involvement in recurrent disease could be another argument in favour.[5] In contrast, others have proposed a more conservative surgical approach combined with chemotherapy, given the young age of most patients and the unilateral location in virtually all cases. Conservative surgery consists of a unilateral (salpingo)oophorectomy, total omentectomy, resection of any metastatic laesions from the peritoneal surfaces or the intestines, pelvic and peri-aortic lymphad-

enectomy, and performance of peritoneal cytology. This fertility sparing approach is supported by several case reports of young patients with stage II and III disease who survived for more than 2 years after surgery with uterine and unilateral ovarian conservation and adjuvant chemotherapy.[5,9,24-27] There is 1 case of long-term DFS after incomplete surgery (R2 resection) followed by chemotherapy.[25] A recent report of stage III disease in a 23-year old who was treated with neoadjuvant chemotherapy (BEP), fertility-sparing surgery and radiation of the para-aortal region made the authors plead for conservative approach.[28] Nevertheless, complete debulking (R0 resection) remains important since in Pautier's series all patients without extensive surgery died.[4]
When fertility-sparing surgery is opted for, a thorough surgical staging seems mandatory. Furthermore, the effects of adjuvant chemotherapy and radiation on ovarian function must be considered. No successful pregnancies have been reported after fertility-sparing surgery, but a normal menstrual function has been described after conservative surgery followed by intensive chemotherapy, including 7 cycles VPCBAE.[24,25,28]

Chemotherapy

Since most patients are young and otherwise healthy, aggressive chemotherapy is feasible and justified because of the malignant disease course, irrespective of stage of disease.[28] Young et al. could not show any benefit from chemotherapy in stage IA cases, but a variety of regimens was used, making it difficult to draw firm conclusions.[3] Also, the timing of chemotherapy (before or after debulking surgery) differs between reports. *Table 2* provides an overview of the different regimens that resulted in a favourable outcome.[29] Most evidence is present for the use of VPCBAE.

VPCBAE

This combination of vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin (adriamycin) and etoposide is the first regimen demonstrating any activity in the treatment of SCCO-HT.[29] In this first report, VPCBAE caused a rapid clinical response in patients with measurable disease, but the effect was short-lived.[29] Nevertheless, long-term survival after conservative surgery and this 6-drug treatment has been reported in patients with IIIC stage disease. However, this was at the cost of significant toxicity.[25] In 1 case, it even caused regression of a residual para-aortic lymphadenopathy.[25]

Triple therapies

Other potentially successful and less intense chemotherapy combinations are BEP (bleomycin, etoposide and cisplatin), PVB (cisplatin, vinblastine and bleomycin),[10] DEC (doxorubicin, etoposide and cyclophosphamide), and PEI (cisplatin, etoposide and iphosphamide).[6,8,10,19,28]

Taxanes

Whereas 2 studies described the successful use of docetaxel, an agent used in epithelial cancers, others have reported only limited efficacy with paclitaxel.[5,6,14,30]

Dose-intensive regimens

Since the response to chemotherapy is often short-lived, some authors attempted aggressive, high-dose consolidation chemotherapy, followed by autologous stem cell transplantation after induction chemotherapy. Pautier et al., who conducted a prospective trial in 27 patients, reported lower relapse rates among patients who received high-dose chemotherapy compared to those who were untreated, but there were more advanced stage patients (6 out of 8 patients stage IIIC versus 4 out of 10 patients stage IIIC in the treated group) in the group that was not treated with high-dose chemotherapy. Exceptionally long survival was reported by Christin et al. in 2 paediatric patients treated with high-dose chemotherapy followed by autologous bone marrow transplantation.[27]

Radiation therapy

Although several studies suggest that pelvic and/or abdominal radiation may be useful in adjuvant or palliative setting, it is unclear which patients might benefit from this treatment.[5,10] Radiation of the whole abdomen has a very important toxicity and the number of reported patients who received radiation therapy is small. In the original paper from Dickersin, 4 patients were treated with postoperative abdominal radiation without chemotherapy, 2 of which had a favourable response. In the Young's series, 4 out of 5 patients receiving radiation were long-term survivors.[3] Furthermore, there is 1 recent report of a >10 year DFS of a 17-year-old patient with a renal transplant, who was only irradiated af-

Key messages for clinical practice

1. SCCO-HT is a rare, highly malignant ovarian neoplasm that mostly occurs in young women in their second to fourth life decade, and appears with hypercalcaemia in two thirds of thecases.
2. Pathologists should obtain expert pathological advice to establish diagnosis and discern it from ovarian small cell carcinoma of the pulmonary type and other ovarian neoplasms.
3. Prognosis is poor, with a mean survival of 18 months. Beneficial prognostic factors are early stage, age >30, small tumour size and normocalcemia at diagnosis.
4. Since its aggressive behaviour, complete surgical debulking with pelvic and peria-ortic lymphadenectomy is warranted in all stages, but fertility-preserving techniques are feasible in selected cases.
5. All patients, irrespective of stage, should receive adjuvant multi-agent chemo-therapy, including at least etoposide and cisplatin or carboplatin.

ter surgery for stage IA disease.[31] Finally, Harrison et al. noted that most of the long-term survivors in their series received adjuvant radiotherapy.[5] Since the pelvis and the abdomen are the 2 most common sites of relapse, they proposed the use of abdominal radiation as first-line treatment. However, all of their patients also received chemotherapy, either concurrently with or preceding radiation therapy.

Treatment of recurrences

The recurrence pattern seems to be similar to that of epithelial ovarian cancer. Peritoneal metastases and retroperitoneal lymph nodes are often involved. Treatment of recurrence can consist of surgery, chemotherapy and/or radiation, the combination is mostly applied.

Conclusion

SCCO-HT is a rare ovarian neoplasm that should be considered in a young women with an ovarian mass, especially when hypercalcaemia is present. Expert pathological advice should be obtained to establish the diagnosis. Although no firm recommendations can be proposed for the treatment of this malignancy, we argue the aggressive nature of the tumour warrants multiple cycles of adjuvant chemotherapy after surgical tumour removal, irrespective of the tumour stage at diagnosis. In young patients that desire to preserve their fertility, conservative surgery including unilateral oophorectomy, omentectomy, resection of any metastatic laesions from the peritoneal surfaces or the intestines, pelvic and peri-aortic lymphadenectomy and peritoneal cytology is a reasonable option. In older patients, a total hysterectomy with bilateral salpingo-oophorectomy should be performed. Adjuvant multi-agent chemotherapy should at least include cisplatin or carboplatin and etoposide.[5,6,32] Docetaxel should be saved for second-line treatment. Since the young age of most patients, high-dose chemotherapy followed by stem cell transplantation is feasible. Although radiation therapy can be useful in some patients, we do not consider it as a first-line treatment because of the low numbers of patients.

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