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Case Report

Small cell carcinoma of the ovary with hypercalcemia: Case report and review of the literature

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Abstract

We describe here the case of a 23-year old woman with small cell carcinoma of the ovary of the hypercalcemic type (SCCOHT) with SMARC-A4 mutation who benefited from surgery in two steps leading to a total hysterectomy with bilateral salpingo-oophorectomy, omentectomy, pelvic and lombo-aortic lymph nodes dissection. She also received 6 courses of poly-chemotherapy after the surgery. A close follow-up was then performed by clinical examination every three months with determination of serum calcium and CA125 level as well as imaging with thoraco-abdominal CT scan. To date, the patient has a disease-free survival of more than 9 years. We also reviewed the literature on this topic and discuted the new diagnostic and prognostic genetic tool SMARC-A4 mutation.

Introduction

Small cell carcinoma of the ovary with hypercalcemia (SCCOHT) is a rare neoplasm of the ovary with an aggressive character resulting in a very poor prognosis. This tumour type mainly affects young patients, especially in the second and third decade of life [1]. Hypercalcemia is found in more than 60% of the cases, but is rarely symptomatic at the time of diagnosis. If hypercalcemia is present at the moment of diagnosis, it may serve as "tumour marker" for the follow-up of the patient [1,2]. Historically, Scully reported a first case of small cell carcinoma of the ovary with hypercalcemia in 1979 [3], but it is only in 1982 that Richard Dickersin and colleagues defined this ovarian tumor as a particular entity with 11 reported cases [2]. Later, a larger retrospective study by Robert H. Young et al., described 150 patients presenting a small cell carcinoma with hypercalcemia. To date, it is largest series reported in the literature [1]. More recently, mutation of the SMARC-A4 gene coding for Brg-1 protein was reported as characteristic of SCCOHT [4].

The treatment of this disease is primarily surgical, frequently associated to chemotherapy. In some cases, radiation therapy is given to patients. The prognosis of these patients is very poor with a 5-year survival rate of 10 % [1,5]. We report a patient successfully treated by surgery and combined chemotherapy, who remains disease-free more than six years after initial diagnosis.

Case Report

A 23-year old female patient consulted in our department for an abdominal pain since three weeks. She had one pregnancy with vaginal delivery a few months earlier and was subsequently under oral contraception. The clinical examination revealed a large pelvic mass, with abdominal pain and fever over 39°C. Transvaginal echography showed a heterogeneous mass of about 14 cm in diameter. An abdominal computed tomography (CT)-scan confirmed the heterogeneous mass

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and a small amount of liquid in the pouch of Douglas and parieto-colic gutters. There was no evidence of carcinomatosis (Figure 1). Chest CT-scan was unremarkable. Biological investigations revealed a serum calcium level at 13.57 mg/dl (normal range 8.80 - 10.40 mg/dl) with a parathyroid hormone at less than 3 pg/ml (normal: 16-81pg/ml). CA 125 level was slightly increased to 40.8 U/ml (normal<25U/ml), whereas carcino-embryonic antigen (CEA) and alpha-foetoprotein were normal. Because of a persistent significant abdominal pain, the large adnexal mass, fever and an altered general status, we decided to carry out a diagnostic laparoscopy without delay. At laparoscopy, the large heterogeneous mass of the right adnexa was twisted by one turn on its pedicle. The right fallopian tube was normal as well as the left adnexa and the uterus. Careful examination of the peritoneum showed no sign of carcinomatosis and the liver was normal (Figure 2). Given the suspicious nature of the ovarian lesion, conversion into laparotomy by Pfannestiel incision was decided and a right salpingo-oophorectomy was performed. Frozen section of the mass revealed a poorly differentiated aggressive anaplastic carcinoma. The procedure was accordingly completed by a right ilio-obturator lymphadenectomy associated with an infra-colic omentectomy.

The pathological analysis confirmed a right ovarian mass of 14 x 10 x 5 cm, weighting 380 g, with no sign of capsule rupture (Figure 3A-3B). Microscopic analysis showed the tumour was made of small cells with scanty eosinophil cytoplasm and irregular hyperchromatic nucleus, often harbouring a nucleolus. The mitotic index was high. Follicle-like cavities containing a lightly eosinophilic fluid were noticed inside the tumour (Figure 3C-3E). Immunohistochemical analysis (Table 1 for used primary antibodies) showed a prominent cytoplasmic labelling of vimentin in most cells, of synaptophysin in many cells but of chromogranin in only a few cells. Very rare cells showed cytoplasmic immunolabelling with an anti-parathormone antibody (Figure 3F-3H). A few cells showed a strong nuclear immunolabelling of p53 protein. There was no immunolabelling of cytokeratins AE1-AE3, CD99, smooth muscle actin, estrogen receptor alpha, progesterone receptor and only few cells showed immunolabelling of epithelial membrane antigen (CA 15.3). The diagnosis of small cell carcinoma of the right ovary, hypercalcemic type (SCCOHT) was proposed. Absence of immunolabelling of Brg-1 in the nucleus of neoplastic cells prompted us to look for a mutation of SMARC-A4. DNA was extracted from neoplastic cells and SMARC-A4 gene was amplified with the TruSeq Custom Amplicon kit (panel_diag_UGS_V1.1) and sequenced

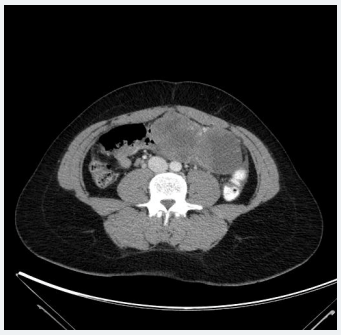

Figure 1: Abdominal CT-scan: large heterogeneous right adnexal mass. No evidence of ascites and carcinomatous.

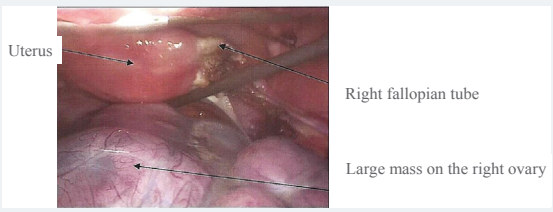

Figure 2: Abdominal CT-scan: large heterogeneous right adnexal mass. No evidence of ascites and carcinomatous.

Table 1: List of used antibodies.

Antigen	Host/Ig type	Clone	Source	Dilution
Bcl-2	Mouse IgG1, k	124	Dako	1/18
Brg-1				
Calretinin	Rabbit Ig	Polyclonal	ImmunoLogic	1/100
CD56 (N-CAM)	Mouse IgG1	1B6	NovoCastra	1/50
Chromogranin	Mouse IgG1, k	LK2H10	Hybritech	1/5000
Cytokeratins AE1-AE3	Mouse IgG1, k	AE1/AE3	Dako	1/60
Cytokeratins CAM5.2	Mouse IgG2a	CAM 5.2	Becton Dickinson	1/25
Cytokeratins CK22	Mouse IgG1, k	Mixture	Biomeda	1/400
Epithelial membrane antigen	Mouse IgG2a, k	E29	Dako	1/200
Estrogen receptor alpha	Rabbit IgG	SP1	Thermo Scientific	1/300
Inhibin alpha	Mouse IgG2a	MCA951R1	Serotec	1/100
$p16^{INK4a}$	Mouse IgG1	G175-405	Becton Dickinson	1/300
p53	Mouse IgG2b, k	DO7	Biocare Medical	1/1000
$p57^{KIP2}$	Mouse IgG2b, k	KP3	Thermo Scientific	1/300
Placental alkaline phosphatase	Rabbit Ig	Polyclonal	Dako	1/500
Progesterone receptor	Mouse IgG1	1A6	NovoCastra	1/50
Retinoblastoma gene protein	Mouse IgG1	13A10	NovoCastra	1/250
Parathyroid hormone	Rabbit Ig	Polyclonal	LabVision	1/50
Synaptophysin	Rabbit Ig	Polyclonal	Zytomed Systems	1/100
Vimentin	Mouse IgG1, k	V9	Dako	1/400
Wilm's Tumor-1	Mouse IgG1, k	6F-H2	Dako	1/100

Becton Dickinson, Erembodegem, Belgium; Biocare Medical, Concord, CA, USA; Biomeda, Foster City, CA, USA; Dako Denmark A/S, Glostrup, Denmark; Hybritech, San Diego, CA, USA; ImmunoLogic, Duiven, The Netherlands; NovoCastra, Leica Biosystems, Newcastle upon Tyne, UK; LabVision, Newmarket, UK; Thermo Scientific, Fremont, CA, USA; Zytomed Systems, Berlin, Germany

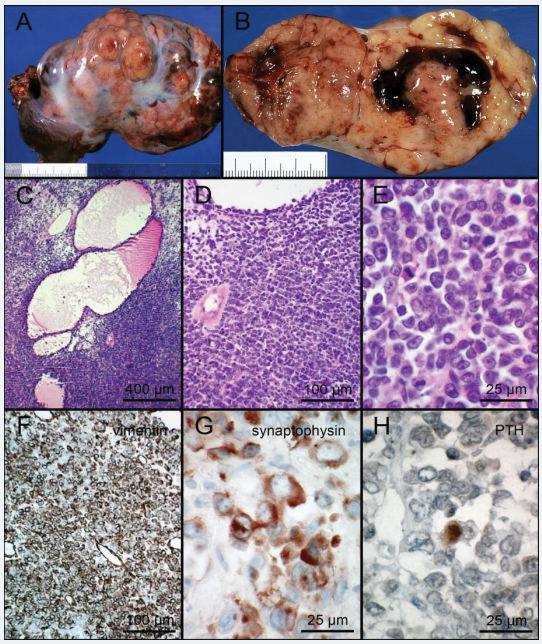

Figure 3: 3A,3B: macroscopic views of the surgical specimen (A: external view / B: section of the tumour); 3C,3D,3E: microphotographs showing small cells with scanty cytoplasm and hyperchromatic nucleus. A mitotic figure is visible at E.
3F,3G,3H: immunohistochemical labelling of vimentin (F), synaptophysin (G) and parathormone (PTH, H). Scale bars represent the indicated lengths.

with Illumina MiSeq, revealing the homozygous non-sense mutation c.2866del (p. Leu956*). DNA was also extracted from peripheral blood mononuclear cells but the SMARC-A4 mutation was not found, indicating a somatic mutation in ovarian cells. No metastasis was found in the 13 lymph nodes of the right lymphadenectomy and the omentum was free of neoplastic infiltration. No cancer cell was found in the peritoneal fluid. Tumour was thus staged as FIGO IA.

Serum calcium normalized a few days later, after the patient also received hyperhydration (3 l of saline in 24 h).

Post-operatively, an 18-fluorodeoxyglucose positron emission tomography (FDG-PET) scan, was performed in order to establish the full initial extension status of this aggressive tumour. It showed no sign of metastasis or remaining disease (Figure 4).

Because of the poor prognosis, the patient then received 6 courses of chemotherapy combining cisplatin and etoposide despite the low FIGO stage. After completion of the chemotherapy, a second step surgery was performed with total hysterectomy, left salpingo-oophorectomy and left ilio-obturator and lombo-aortic lymphadenectomy. The pathological analysis showed no residual tumour and no metastasis in the lymph nodes. Upon completion of treatment, the patient was followed clinically, biologically (serum CA125 and calcium levels) as well as radiologically (thoraco-abdominal CT scan) every 3 months for 3 years and then every 6 months for up to 5 years. She is now followed clinically and biologically once a year. To date, 9 years after diagnosis, there is no sign of recurrence. Indeed, the gynecological examination, the biology and the last CT-scan were all normal. Because of her young age and to avoid premature menopausal symptoms, the patient was placed under hormonal replacement therapy in the form of a transdermal estrogen-releasing gel (Oestrogel®, Besins Healthcare) a few months after the second operation.

Discussion

We here report a case of small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) with SMARC-A4 mutation, with one of the longest follow-up without recurrence of the disease found in the literature. The patient is currently alive, free of disease and in good conditions 9 years after the end of therapy. In order to conduct a complete review of SCCOHT, we searched all English and French literature on the subject (PubMed, with small cell carcinoma of the ovary of the hypercalcemic type as key words). The review is detailed in Table 2. Patient and disease characteristics are discussed below. SCCOHT is a rare tumour primarily affecting young women [1]. We found only 236 patients in the literature [Table 2], with an average age of 22.1 years. However, the disease can occur at a very young age with documented cases in a 14 month-old child [6] and an 8 year-old girl [7]. Its clinical presentation is often unspecific, with abdominal pain, nausea, weight loss and impairment of general health [1]. Some more atypical clinical manifestations have also been described such as acute pancreatitis as initial signs [8,9]. Usually, the lesion is unilateral (99% of cases), with an average size of 15 cm. half of all cases are diagnosed at stage I (two thirds at stage IA and one third at stage IC), 45% at stage III and 5% at stage II or IV [1].

In two-thirds of cases, hypercalcemia is observed but only a minority of patients is symptomatic at the time of diagnosis. Symptoms of increased calcium levels include

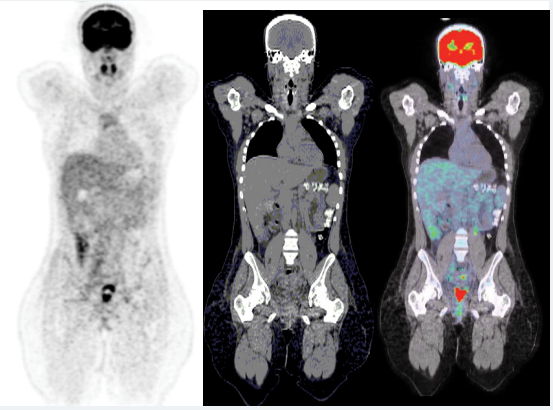

Figure 4: Pet-scan 3 days after the operation showing no sign of distant metastasis of the ovarian carcinoma.

Table 2

Year of publication	Authors	Number of patients	Age	Stade FIGO	Surgery	Chemotherapy	Radiotherapy	Survival
1982	Dickersin and al,	11 patients	average : 22 years		yes		unknown	
1994	Young and al,	150 patients	average : 23,9 years	35 % de stade Ia, 15 % de stade Ib/c, 50 % de stade III et 5 % de stade II et IV	yes		unknown	
1994	William and al,	1 patient	31 years	stade IC	yes	Cisplatine/Etoposide/Bléomycine	no	5 years without reccurence
1996	Idei Y and al,	1 patient	46 years	stade IIIc	no	non	no	1 month
1999	Scott and al,	1 patient	14 months	stade Ia	yes	Vincristine, Etoposide, cyclo, cisplatine et doxorubicine	no	22 months without reccurence
1999	Lamovec and al,	2 patients	40 et 21 years				no	
2004	Lei Chen and al,	1 patient	37 years	stade IC	yes	Paclitaxel/ Carboplatine	no	27 months without reccurence
2004	Bourgain and al,	1 patient	19 years	stade Ic	yes	no	no	20 months
2004	Wynn and al,	1 patient	27 years		yes	Carboplatine / Placlitaxel	no	16 months without reccurence
2005	Harrison and al,	17 patients	average : 34,5 years	70% stade I et 25 % stade III and 5 % unknown	yes	yes	60% yes	unknown
2005	Popiolek and al,	1 patient	35 years	stade III	yes	Cisplatine/ Etoposide	no	22 months without reccurence
2005	Kedzia and al	2 patients	13 et 16 years	stade Ic et stade IIIb	yes	yes	no	< 1 year (2x)
2006	Chen Fan and al,	1 patient	26 years	stade Ia	yes	unknown	unknown	unknown
2007	Pautier and al,	27 patients	Average : 25 years	5 stade I,4 stade II c, 17 stade III/IV and one unknown	yes	PAVEP	yes	Average 30 months
2008	Isonishi and al	3 patients	24,37,25 years	IIC, IIIC, IIIc	yes	yes	no	>4 years, 4 et 9 months
2008	Cheng et al	1 patient	14 years	stade IV	yes	yes	no	5months
2012	Matt McDonald et al,	2 patients	23 et 11 years	stade IIC / stade Ic	yes	Cisplatine/ paclitaxel	yes	11 and 18 months
2012	Zaied and al,	1 patient		stade Ic	yes	Etoposide/Bleomycine/Cisplatine	no	2 months
2012	Arvind Bakru and al,	1 patient		stade IIIa	yes	VPCBAE	no	6 months
2012	Wallbillich and al,	3 patients	24,28,26 years	unknown	yes	yes (VPCBAE)	no	33, 16 and 1 months without reccurence
2012	Stephens B	1 patient	21 years	stade IIIC	yes	VPCBAE	yes	5 months
2012	Woopen and al,	4 patients	25,29,18 and 24 years	stade Ia (2x), stadeIIb, stade IIIc	yes	PAVEP/cispl,etoposide, paclit, carbo	no	22 months (3x) and 15 months for stade IIIc
2012	Otte A and al,	1 patient	31 years	stade Ia	yes	no	no	13 months
2012	Bakhru and al	1 patient	14 years	stade IIIa	yes	VPCBAE	no	6 months
2013	Kopp and al,	1 patient	5 years	stade IV	yes	cispl/doxo/etoposide/ cyclo+ graft original cells	no	6 months
2014	Gribi and al	2 patientes	10,11 years	stade a	yes	vinblastin, cisplatin , bleomycine	no	3years and 7 years without reccurence
2014	Bahri and al,	1 patient	34 years	stade Ia	yes	PAVEP	yes	9 months without reccurence

2015	Callegaro-Filho and al,	47 patients	Median age : 30 years	34% stade I, 12,8% stade II,**48,9% stade III** and 4,3 % stade IV	yes (83,3% chemotherapy alone / 9,5% chemotherapy and radiotherapy	Cisplatin/Carboplatin/Etoposide(38,8%) / VPCBAE (25,6%)	yes (9,5%)	14 months
2015	Lavrut and al,	1 patient	14 years	stade IV	yes	PAVEP-CARBOPEC regimen	yes	4 months
2015	Moens-Sosnowska and al	2 patients	21 years and 35 years	stade IV and IIIB	no, yes	6 placlitaxel + carboplatin/ 3 lines of combination chemotherapy	no	6 months/ 1 year
2015	Park and al,	1 patient	19 years	no specified	yes	no specified	no specified	no specified
2016	Kascak and al,	1 patient	24 years	no specified	yes	Cisplatin/Etoposide	no	10 months
2016	wand and al	1 patient	29 years	no specified	yes	Carboplatin / Placlitaxel	no	alive
2016	Steward and al	1 patient	14 years	stade Ia	yes	bleomycine, etoposide and,cipslatine - BEP	no	11 years without reccurence
2017	Witkowski	4 patients	28 years	stade IC, IIIb(2x), unknow	yes	cisplatin/Etoposide	yes	alive,3 months,14 months and 3 weeks
2017	Ghazi and al,	1 patient	35 years	stade IIIc	no	no	no	no specified
2018	Gerday et al,	1 patient	23 years	Stade Ia	Yes	Cisplatin / Etoposide	no	6 years

disorders of consciousness, confusion, and sometimes polyuria and polydypsia. However, this type of non-parathyroid hypercalcemia is largely asymptomatic and will only be detected on blood analysis. The pathophysiological mechanism is not fully understood but it could result from the secretion by the tumour cells of a protein closely related to parathyroid hormone (PTH) namely parathyroid hormone-related protein (PTHrp). The protein can be detected in tumour cells by immunohistochemistry [10] and its mRNA by in situ hybridization [11]. Several studies suggested that the serum level of PTHrp and calcium could be a biological tumour marker [1,10,11]. In our case, immunostaining of PTH in very few tumour cells is consistent with this hypothesis [Figure 3H]. Normalization of serum calcium level is frequently found after surgical resection of the tumour, as in our clinical case, suggesting secretion of PTHrp by the tumour cells. Medical therapies, such as hyperhydration, can also be used before surgery to reduce hypercalcemia, with addition of diuretics like furosemide or administration of calcitonin and pamidronate in severe cases [6]. In our patient, the calcium level was high at diagnosis and normalized after surgery. Since then, her serum calcium level remained normal.

Macroscopically, the tumour is usually large, unilateral, solid or mixed, and can show signs of necrosis and areas of bleeding. Microscopically, the histology is specific, revealing small round cells with sparse cytoplasm and a hyperchromatic nucleus containing a small nucleolus. The mitotic index is very high. Fluid containing spaces can form between cells and create a follicle-like pattern in 80% of cases [1]. In some cases, large cells with an eosinophilic cytoplasm can be seen in a histological variant of this carcinoma. Large, typically pale eosinophilic intracytoplasmic hyaline globules are present in 60% of the tumours, usually associated with eccentric displacement of the nucleus. The nuclei are larger and less chromatic than in the small cells. This parameter is considered detrimental to patient survival [1].

The histological origin of this tumor is still controversial. In their initial report, Young et al. described the tumour as of epithelial origin. Further immunohistochemical studies showed that SCCOHT express several epithelial markers such as cytokeratins AE1/AE3 and epithelial membrane antigen, neuroendocrine markers such as synaptophysin and several other markers such as vimentin, calretinin, Wilm's Tumour-1, CD10 and p53 [1,13]. More recent genetic studies showed a consistent mutation of the SMARC-A4 gene coding for the Brg-1 transcription factor. Mutation in the related SMARC-B1 gene is found in malignant rhabdoid tumours, and the terminology ovarian rhabdoid tumour has been proposed for SSCOHT [4].

Peritoneal small cell carcinoma, hypercalcemic type (SCC-HT) with healthy ovaries has been described by Popiołek et al. in 2005 [12]. They reported a case of a 35-year old patient who underwent exploratory laparotomy for a mass suggestive of uterine myoma. Peritoneal carcinomatosis was found and the patient had a debulking surgery. Histological analysis showed a SSC-HT with a large cell component. This is the only case reported in the literature of peritoneal SCC-HT with healthy ovaries [12]. Because of the small number of reported cases, there are presently no specific guidelines for the treatment and follow-up of patients with SCCOHT, but it is likely that such aggressive tumour requires equally aggressive treatment. In this context, three complementary treatments may be discussed: surgery, chemotherapy and pelvic radiation.

Surgery is crucial to obtain the diagnosis and to treat the disease. It is often performed in multiple steps as suggested by the study of Young et al. [1] and the present study. Indeed, most patients initially underwent unilateral salpingo-oophorectomy, sometimes with hysterectomy. Rarely, a cystectomy is first carried out [1]. In many cases, more radical surgery (with omentectomy, lymphadenectomy) is conducted in a second step, after histological confirmation of the disease. Because patients are generally young, conservative treatment is applied first but once the diagnosis is known, a second, more aggressive, surgical treatment is proposed because of the aggressiveness of the disease. The risk linked to preservation of the uterus and/or the other adnexa is not known, and there is presently no consensus regarding the safety of conservative surgery. In patients who have received conservative surgical treatment, no pregnancy has been reported after treatment. This may be explained by the chemotherapy and pelvic radiotherapy administered after the surgery as well as the low life expectancy after diagnosis.

Chemotherapy is given after surgery in the majority of patients. In Table 2 collecting all the cases described in the literature, a 99% rate of chemotherapy administration was observed. The treatment is often multidrug therapy, combining agents like cisplatin, doxorubicin, etoposide, vincristine, vinblastine and cyclophosphamide, given the aggressiveness of the tumour and the low survival rate of these patients. Several associations of cytotoxic drugs are reported in the literature such as VPCBAE (vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin and etoposide) [14,15] and PAVEP (cisplatin, doxorubicine, etoposide, cyclophophamide) [15]. Significant toxicity of these associations has been described such as myelosuppression, nausea and vomiting, and severe gastric disorders [16].

Table 2 shows that the most commonly used cytotoxic agents are platinum, taxol, etoposide and the previously described protocols (PAVEP and VPCBAE). Indeed, 90% of patients benefit from these agents (274 patients out of 299). The remaining 10 percent either did not receive chemotherapy (4 out of 299 patients), or the products were unknown, or they received other molecules.Chemotherapy treatments are also used for recurrence, mostly found in the pelvis and abdomen.

Pelvic radiotherapy can also be used as adjuvant therapy for patients with SCCOHT. Indeed, a prospective study conducted by Pautier et al. showed a trend in decreasing recurrence in the patients who had received radiotherapy [17]. This is the only prospective study conducted in SCCOHT, with 27 patients included. All patients received six courses of chemotherapy after the surgery. At the end of chemotherapy, those still alive without recurrence (18/27) were randomly distributed to one of two study arms: 10 patients received pelvic radiotherapy at high dose and 8 patients did not undergo any adjuvant radiotherapy. When radiotherapy was administered, only the pelvis was treated with doses between 40 Gy and 50 Gy [17]. Outcomes showed 3 recurrences among the 10 patients treated by radiotherapy but 5 recurrences among the 8 patients in the observational arm. This treatment may therefore be discussed but data are insufficient to systematically propose pelvic radiotherapy, especially to

patients with early stage disease. In Table 2, 10% of patients received radiation therapy (always after chemotherapy).In the present case, no adjuvant radiotherapy was given and the patient did not experience recurrence. In case of recurrence, radiotherapy may be a treatment option if not previously used [18].

From our review of the literature, a number of disease-related and patient-related factors emerged that could influence the prognosis:

1. **Tumour stage:** This is a crucial element in the prognosis of the patient. In the study by Young et al. 14 out of 42 patients (33%) with stage 1A disease were still alive without recurrence after 1 to 13 years of follow-up. Conversely, only 2 out of 20 patients (10%) with stage 1C and 4 out of 62 patients (6.5%) with stage II, III and IV disease were alive at the end of the follow-up period.

2. **Age at the time of diagnosis:** Age below 30 years is considered to be unfavorable for patient survival.

3. **Tumour size:** An ovarian mass greater than 10 cm is a pejorative factor for patient survival.

4. **Hypercalcemia:** This represents another pejorative factor for the prognosis of the patient, especially if the calcium level is significantly elevated. Calcemia can be used as a tumour marker if it is initially raised.

5. **Presence of large cells at pathologic analysis:** This is considered to be unfavorable for the evolution of the disease.

6. **Completeness of surgery:** The more complete surgery, better the evolution of the disease.

7. **The use of pelvic radiotherapy:** As described in the prospective study of Pautier et al. this adjuvant therapy may bring an increase of recurrence-free survival.

In the present case report, although our patient had multiple negative factors related to the disease (age, tumour size, hypercalcemia, no radiotherapy), she is still alive and disease-free 9 years after treatment. Secondary SCCOHT lesions have also been described. The most frequent sites of metastasis are the liver, lungs, brain or bones [1], with lymph nodes involvement in some cases. One case of breast metastasis has also been reported [19]. All cases of SCCOHT with metastases show very poor survival of only a few months according to our review [1,19].

A genetic risk factor has been hypothesized to play a role in SCCOHT. Indeed, multiple cases of SCOOHT have been described within families, and often with first degree relatives [1,19]. In addition, it was observed that the age at which the disease occurred decreased in the next generation. This suggests a dominant autosomal transmission and a mutation in a gene (or a family of genes) could explain these different family cases. It has now been demonstrated that SMARC-A4 mutation is found in the majority of SCCOHT. In this context, a mutation of SMARCA4 may be a therapeutic target. Indeed, ponatinib has shown its effectiveness (inhibitor tyrosines kynases) [20].

Other previous theories suggested that p53, crucial in the genesis of many tumour diseases [18,21,22], may be impaired in these patients. Similarly, a Ras gene mutation, found in 27% of ovarian cancers, has also been described in SCCOHT [23-25]. Even if there is no clear evidence of genetic abnormality in most cases, the aggressiveness of the disease, the young age of occurrence of the disease and the tendency toward family recurrence are all arguments in favor of a genetic component in the origin of the disease [26]. In this context, McDonald and al. proposed that genetic counseling may be appropriate for the other family members [18].

Conclusion

SCCOHT is a rarely encountered tumour with only a few hundred cases reported in the medical literature. It is affecting mainly young women and has a very poor prognosis in the short term. We report a case of SCCOHT with a 9-year recurrence-free interval, which is exceptional for this pathology, and review all cases described in the literature.

Histologically, SCCOHT is composed of small cells with a hyperchromatic nucleus harbouring a nucleolus. A follicle-like pattern of tumour cells is found in 80% of cases. Immunohistochemistry is helpful to clarify the diagnosis. Hypercalcemia is found in 2/3 of cases, although it is rarely symptomatic. The main hypothesis is that the tumour secretes PTHrp, a substance closely related to PTH. Calcium levels usually normalize after tumour excision. In case of hypercalcemia identified at diagnosis, serum calcium level may be used as a tumour marker. A number of criteria influencing the prognosis of the disease have been highlighted. Treatment involves surgical removal of the tumour with total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and omentectomy followed in most cases by multi-drug chemotherapy. Adjuvant radiotherapy can also be discussed. Despite intensive treatment, the mortality rate of this disease is very high, with average survival of a few months after diagnosis.

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