·论 著·

11例卵巢高钙血症型小细胞癌临床分析并文献复习

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［摘要］ **背景与目的：**卵巢高钙血症型小细胞癌（small cell carcinoma of the ovary, hypercalcemic type，SCCOHT）是一种罕见的恶性程度极高的妇科肿瘤，好发于年轻女性。分析SCCOHT的临床特征及诊疗情况，并通过文献复习梳理其临床表现、治疗模式及预后因素等特征。**方法：**对复旦大学附属肿瘤医院2000年1月—2019年12月收治的11例SCCOHT患者的病例资料进行回顾性分析。**结果：**11例患者中位发病年龄为31岁（22~40岁），临床主要表现为腹痛（63.7%）及盆腔占位性病变（36.4%）。根据原发性卵巢癌2019年国际妇产科联合会（International Federation of Gynecology and Obstetrics，FIGO）分期，11例患者中Ⅰ期有4例，Ⅲ期1例，Ⅳ期6例。4例（36.4%）患者表现为血钙升高。11例患者均接受了手术治疗及术后辅助化疗，9例（81.8%）患者出现盆腔复发，在确诊后1年内死亡，中位生存时间为6个月，6个月生存率为45.5%，10个月生存率为13.6%。**结论：**SCCOHT的发病年龄较轻，恶性程度极高，预后较差。手术治疗联合辅助化疗是一线治疗手段。盆腔及腹腔是最常见的复发转移部位。靶向治疗及免疫治疗可能有一定的应用前景。

［关键词］ 卵巢小细胞癌；高钙血症型；临床表现；治疗；预后

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Clinical characteristics of 11 patients with small cell carcinoma of the ovary, hypercalcemic type and literature review

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［**Abstract**］ **Background and purpose:** Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare gynecological malignancy with poor prognosis, which mostly occurs in young women. This study analyzed clinical characteristics and treatment of 11 patients with SCCOHT, then clinical manifestations, treatment patterns and prognostic factors were summarized through literature review. **Methods:** A retrospective study was conducted on clinical data of 11 cases diagnosed with SCCOHT from Jan. 2000 to Dec. 2019 in Fudan University Shanghai Cancer Center. **Results:** The median age of 11 patients was 31 years (from 22 to 40 years). The main clinical presentations were abdominal pain (63.7%) and pelvic mass (36.4%). According to 2019 International Federation of Gynecology and Obstetrics (FIGO) staging system for ovarian cancer, stage Ⅰ included 4 cases, stage Ⅲ consisted of 1 case and stage Ⅳ had 6 cases. Four (36.4%) patients had elevated serum calcium. All patients were administered with surgery followed by adjuvant chemotherapy. Nine (81.8%) cases died within 1 year from initial diagnosis, and the median survival time was 6 months. In this cohort, 6-month survival rate was 45.5%, and 10-month survival rate was 13.6%. **Conclusion:** SCCOHT occurs in younger patients and is difficult to deal with due to its significantly aggressive behavior. Surgery combined with adjuvant chemotherapy is

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first-line treatment strategy. Pelvis and abdomen are the most common recurrence sites. Targeted therapy and immunotherapy are promising for SCCOHT.

［**Key words**］ Ovary small cell carcinoma; Hypercalcemic type; Clinical manifestations; Treatment; Prognosis

卵巢高钙血症型小细胞癌（small cell carcinoma of the ovary, hypercalcemic type，SCCOHT）是一种罕见的高度恶性的妇科肿瘤。1979年被Robert等[1]首次提出，并将其主要特征概括为：① 小而深染的分裂活跃的细胞；② 发病年龄较早（通常在40岁以下）；③ 常伴有高钙血症。迄今为止，全球报道的病例不足400例[2]。该疾病发病年龄较轻，恶性程度极高，预后差。本文将通过回顾性分析11例复旦大学附属肿瘤医院收治的SCCOHT患者的临床资料、治疗方式及预后，结合文献复习梳理其临床特征及诊疗模式。

1 资料和方法

1.1 一般资料

2000年1月—2019年12月复旦大学附属肿瘤医院共收治11例SCCOHT患者，其中外院治疗后转诊7例，复旦大学附属肿瘤医院初诊4例。病例资料及随访信息完整，病理切片由复旦大学附属肿瘤医院资深妇科肿瘤病理学专家复核确认符合SCCOHT病理学诊断标准。11例患者中位发病年龄为31岁（22岁~40岁），7例（63.6%）患者以腹痛为主要症状，4例（36.4%）患者以盆腔占位性病变首发。3例患者仅表现为血钙升高（血钙浓度≥2.75 mmol/L）而无高钙血症临床表现，1例患者血钙升高伴有高钙血症临床表现（惊厥、厌食、疲劳等），4例患者血钙在正常范围内（血钙浓度为2.25~2.75 mmol/L）。7例患者CA12-5升高，2例患者CA12-5在正常范围内。根据2019年原发性卵巢癌国际妇产科联合会（International Federation of Gynecology and Obstetrics，FIGO）分期系统，Ⅰ期患者有4例（36.4%），Ⅲ期患者1例（9.1%），Ⅳ期患者6例（54.5%）。9例（81.8%）患者为单侧肿瘤，2例（18.2%）患者表现为双侧肿瘤（表1）。

表 1 11例SCCOHT患者临床资料

Tab. 1 Clinical characteristics of 11 SCCOHT patients

n (%)

Clinical characteristics	Number
Age at diagnosis/year	31
Median age/year	22-40
Clinical presentation	
Abdominal pain	7 (63.6)
Pelvic mass	4 (36.4)
Serum CA12-5	
Elevated	7 (63.6)
Normal	2 (18.2)
Not available	2 (18.2)
Serum calcium	
Normal	4 (36.4)
Elevated	4 (36.4)
Not available	3 (27.2)
Tumor site	
Unilateral	9 (81.8)
Bilateral	2 (18.2)
FIGO stage	
Ⅰ	4 (36.4)
Ⅲ	1 (9.1)
Ⅳ	6 (54.5)
Survival state	
Dead	9 (81.8)
Alive	2 (18.2)

1.2 手术情况

6例患者接受了单侧附件切除术。其中2例患者外院误诊为卵巢成熟型/幼年型颗粒细胞肿瘤，术后未进行辅助治疗，分别于术后1、6个月出现盆腔复发转诊至复旦大学附属肿瘤医院行复发手术，经复旦大学附属肿瘤医院病理学会诊后证实原病理学诊断结果符合SCCOHT。其中1例患者在外院接受单侧附件切除术后转诊至复旦大学附属肿瘤医院补充手术。其中1例患者在接受保育手术后2个月出现盆腔及腹腔多发转移后行复发手术。5例患者接受了卵巢癌根治手术，其中2例患者因盆腔及腹腔复发行复发手术。

1.3 术后辅助治疗

11例患者均接受了以铂类药物为基础的化疗。4例患者采用顺铂/卡铂和依托泊苷（cisplatin/carboplatin and etoposide，CE）方案化疗，3例患者接受顺铂、依托泊苷和异环磷酰胺（cisplatin, etoposide and ifosfamide，PEI）方案化疗，2例患者接受紫杉醇/多西他赛+铂类药物化疗，1例患者采用博莱霉素、依托泊苷和顺铂（bleomycin, etoposide and cisplatin，BEP）方案化疗。1例患者经过多线化疗后复发转移（表2）。

表 2 11例SCCOHT患者治疗策略及预后情况

Tab. 2 Treatment strategies and outcomes for 11 SCCOHT patients

Case number	FIGO stage	Serum calcium	Chemotherapy regimen	Recurrence site	Survival time *t*/month	Outcome
1	Ⅰ	Normal	CE × 6	Pelvis and abdomen	6	Dead
2	Ⅰ	-	BEP × 3	Pelvis and abdomen	7	Dead
3	Ⅰ	Normal	PEI × 3	-	8	Alive
4	Ⅰ	Elevated	CE × 6	-	24	Alive
5	Ⅲ	Normal	TC × 6; VAP × 3; GEMOX × 2; TIP × 2	Pelvis and liver	10	Dead
6	Ⅳ	-	DP × 6	Pelvis and abdomen	2	Dead
7	Ⅳ	Elevated	TC × 6	Pelvis and abdomen	4	Dead
8	Ⅳ	Elevated	PEI × 6	Pelvis and peritoneum	5	Dead
9	Ⅳ	Elevated	CE × 6	Pelvis and abdomen	5	Dead
10	Ⅳ	-	PEI × 6	Pelvis and abdomen	6	Dead
11	Ⅳ	Normal	CE × 6	Pelvis and abdomen	7	Dead

CE: Cisplatin/carboplatin and etoposide; BEP: Bleomycin, etoposide and cisplatin; PEI: Cisplatin, etoposide and ifosfamide; DP: Docetaxel and cisplatin; TC: Carboplatin and paclitaxel; GEMOX: Gemcitabine and oxaliplatin; VAP: Etoposide, cisplatin and pirarubicin; TIP: Paclitaxel, ifosfamide and cisplatin

2 结 果

2.1 术后病理学诊断概况

根据原发性卵巢癌2019年FIGO分期，Ⅰ期4例，Ⅲ期1例，Ⅳ期6例。其中2例患者经外院诊断为卵巢幼年型/成熟型颗粒细胞肿瘤，经病理会诊后确认原片符合SCCOHT。11例患者肿块平均大小为16.0 cm（0.6 cm~32.0 cm），9例患者为单发肿瘤，2例患者为双侧肿瘤。6例Ⅳ期患者均可见盆腔及腹腔多发转移病灶。11例患者中有4例患者出现淋巴结转移，其中3例患者肿瘤累及腹主动脉旁淋巴结，另1例患者伴肠周淋巴结转移。仅1例患者可见脉管癌栓。

2.2 复发转移情况及预后

9例（81.8%）患者出现盆腔及腹腔复发，其中Ⅳ期患者6例，Ⅲ期患者1例，Ⅰ期患者2例。9例复发患者均在确诊后1年内死亡，中位生存时间为6个月（2~10个月）。2例存活患者均为Ⅰ期，无瘤生存期分别为24个月和8个月。本研究中该病6个月生存率为45.5%，10个月生存率为13.6%。

3 讨 论

SCCOHT较为罕见，发病率在妇科恶性肿瘤中<1%，发病年龄较轻，通常在40岁以下[2]。1994年Yong等[3]报道的150例SCCOHT大规模回顾性研究患者的平均发病年龄为23.9岁[3]，美国MD Anderson癌症中心报道的47例SCCOHT患者平均发病年龄为30.0岁[4]。复旦大学附属肿瘤医院收治的11例患者平均年龄为30.5岁，中位年龄为31岁。

目前，*SMARCA4*基因突变被认为是导致SCCOHT发病的有害突变。*SMARCA4*基因定位于19号染色体，负责编码SWI/SNF重构复合物的亚基单元，在恶性横纹肌样瘤（malignant rhabdoid tumor，MRT）或非典型畸胎样横纹肌样瘤（atypical teratoid/rhabdoid tumor，ATRT）领域研究较多[5]。在一项129例大型基因外显子测序研究中，*SMARCA4*双等位基因突变率达100%[6]。Ramos等[7]通过外显子测序发现

SCCOHT患者中，*SMARCA*4基因体系/胚系突变率为69%（9/13），其中SMARCA4蛋白表达缺失者14例（82%），而在其他原发性卵巢癌中仅有0.4%（2/485）检测到该蛋白的缺失。SMARCA2蛋白与SMARCA4蛋白表达双重缺失在SCCOHT诊断中具有较高的敏感性和特异性[8-9]。

该病多以腹痛或盆腔肿块首发[4, 10]。大约有1/3患者表现为高钙血症，而2/3患者仅表现为血钙升高[4,11]。部分患者肿瘤标志物CA12-5升高[12]。肿瘤常为单侧，好发于右侧，家族性病例可为双侧[4]。约74.5%的患者（35/47）可出现肿瘤复发，盆腔和腹部是两个较为常见的复发部位[4]。复旦大学附属肿瘤医院收治的11例患者中，晚期（Ⅲ、Ⅳ期）患者7例，早期（Ⅰ期）患者4例。4例患者血钙升高，4例患者血钙在正常范围内。因此，笔者认为血钙水平对SCCOHT诊断有一定参考价值，但病理学诊断才是金标准。大多数患者诊断时已是晚期，化疗药物的敏感性较差，患者的存活率较低。

SMARCA4蛋白表达缺失是SCCOHT诊断的特异性指标，可伴有SMARCA2蛋白共缺失。上皮膜抗原、角蛋白、钙结合蛋白、细胞黏附分子10等表面分子可辅助诊断。神经元特异烯醇化酶和P53蛋白阳性也有一定的诊断价值[13]。该病的组织起源尚不明确，可能起源于上皮细胞、性索细胞、生殖细胞，也可能来源于神经内分泌分化。该病需与其他卵巢肿瘤如性索间质细胞肿瘤、颗粒细胞瘤、卵巢小细胞癌（肺型）等鉴别[14]。

该病的患者群主要为年轻女性患者，是否采取保留生育手术尚无定论。在本研究中，6例患者接受了保留生育手术，其中1例无瘤生存期达24个月，而其中4例在术后半年内出现盆腔复发转诊至复旦大学附属肿瘤医院行复发手术。结合文献，Young等[15]报道的57%（8/14）ⅠA期患者接受了根治性手术与23%（5/21）接受了保留生育手术的ⅠA期患者相比复发转移较少（*P*=0.075）。美国MD Anderson癌症中心诊疗的26例患者接受了保留生育手术后无一妊娠，且对生存获益无明显影响[4]。北京协和医院报道的7例SCCOHT患者，其中3例接受了保留生育手术后均出现了复发[16]。结合文献报道，我们发现与高级别浆液性卵巢癌不同，该病的患者群更加年轻化，就国内外现有的研究数据来看，保育手术对生存获益无明显影响，但考虑到该疾病恶性程度较高，根治性手术或能降低复发转移。

目前尚无标准化疗方案，以铂类药物为主的化疗方案在SCCOHT中获益远低于小细胞肺癌。有研究提出，患者对铂类药物的敏感性与疾病的分期有关，早期患者或能获益。在我们的研究中，5例Ⅰ期患者均接受了以铂类药物为基础的化疗，2例死亡，3例存活。晚期（Ⅳ、Ⅲ期）患者在铂类药物化疗后无一例存活。但考虑到本研究样本量较小，疾病分期与铂类药物敏感性的关系尚待进一步研究证实。BEP方案以及多药联合化疗［长春花碱、顺铂、环磷酰胺、博莱霉素、多柔比星和依托泊苷（vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin and etoposide，VPCBAE）］方案研究及高剂量化疗（high-dose chemotherapy，HDCT）联合造血干细胞移植（stem cell transplantation，SCT）治疗也有应用。结合文献，笔者对国外相关病例治疗模式进行了回顾总结（表3）。对于原发性上皮性卵巢癌，美国国立综合癌症网络（National Comprehensive Cancer Network，NCCN）指南推荐除了早期低级别恶性肿瘤外，其余上皮性卵巢恶性肿瘤术后均需要接受辅助治疗。鉴于该疾病恶性程度较高，预后极差，笔者认为早期患者也应接受术后辅助化疗。通过回顾小样本病例报道结合本研究中的11例患者资料，我们发现Ⅰ期患者采用EC方案化疗总生存率约为6/8（75%），BEP方案化疗总生存率约为2/4（50%）。而晚期（Ⅲ、Ⅳ期）患者总体预后较差，个案报道提示VPCBAE方案或HDCT联合SCT可能获益。

放疗能否提高SCCOHT患者的生存获益缺乏有效证据。有限的小样本研究及个案报道表明放疗有使SCCOHT患者潜在获益的可能[20, 33-34]。

EZH2抑制剂是SCCOHT靶向治疗的研究热点。在临床前研究中，组蛋白甲基转移

表 3 SCCOHT文献回顾及治疗总结

Tab. 3 Treatment modality in SCCOHT through literature review

Author	Year	Number	Serum calcium	Chemotherapy regimen	Recurrence site	OS *t*/month	Outcome
Kascak, et al [17]	2016	1	-	CE (1)	Pelvis	10	Dead
McCormick, et al [18]	2009	1	Elevated	Stage ⅡB: CE (1)	Pelvis and Peritoneum	10	Dead
Montalto, et al [19]	2011	1	Elevated	Stage ⅠC: CE (1)	-	49	Alive
McDonald, et al [20]	2012	1	Elevated	Stage ⅡC: CE+ radiotherapy	Pelvis	11	Dead
Isonishi, et al [21]	2008	3	Normal	Stage ⅡC: PTE (1); Stage ⅢC: TC (1) and CEP (1)	Abdomen	>48 (ⅡC); 4 and 9 (ⅢC)	1 alive; 2 dead (2 stage ⅢC)
Bailey, et al [22]	2014	1	Elevated	Stage IC: EC followed by PIA (1)	-	9	Alive
Wallbillich, et al [23]	2012	3	-	VPCBAE (3)	-	33, 16 and 1	Alive
Pressey, et al [24]	2013	2	Elevated (1); Normal (1)	Stage ⅢC: VPCBAE; Stage ⅢB: HDCT+ radiotherapy	-	84 and 33	Alive
David, et al [25]	2018	1	Normal	TC+ beva followed by SCT	-	5	Died of transplantation complications
Khosla, et al [26]	2018	1	Normal	Stage Ⅳ: BEP followed by TC	Pelvis and abdomen	24	Dead
Zaied, et al [27]	2012	1	Normal	Stage ⅠC: BEP	-	2	Died of sepsis
Qin, et al [28]	2018	1	Elevated	Stage ⅢC: HDCT+SCT (1)	-	8	Alive
Nelsen, et al [29]	2010	1	Elevated	Stage ⅢC: HDCT+SCT (1)	-	17	Alive
Yoshida, et al [30]	2018	2	Elevated (1)	Stage ⅢC: TC followed by doxorubicin, followed by nedaplatin+ irinotecan+ beva (1); stage ⅢA1:TC (1)	Vaginal cuff (ⅢA1)	7 and 72	Alive
Woopen, et al [31]	2012	4	Elevated (2); Normal (1)	TC (2); IAP (1); CE followed by topotecan, followed by paclitaxel+ beva (1)	Peritoneum	8, 29, 47, 15	3 alive; 1 dead
Pautier, et al [32]	2007	27	-	PAVEP+HDCT (10)	-	-	7 CR; 3 relapse (2 ⅡC and 1 ⅢC)
Callegaro-Filho, et al [4]	2016	39	-	CE (15); VPCBAE (10); TC(7); TP+ beva (1); BEP (3); CPAE (1); CE followed by TC (1); HDCT+SCT (1)	-	-	28 (87.5%) relapse

CE: Cisplatin/carboplatin and etoposide; TC: Carboplatin and paclitaxel; VPCBAE: Vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin and etoposide; BEP: Bleomycin, etoposide and cisplatin; PAVEP: Cisplatin, adriamycin, vepeside, cyclophosphamide; PTE: Docetaxel, etoposide, cisplatin; PIA: Cisplatin, ifosfamide, doxorubicin; CPAE: Cisplatin, cyclophosphamide, doxorubicin and etoposide; HDCT: High-dose chemotherapy; SCT: Stem cell transplantation; Beva: Bevacizumab

酶EZH2抑制剂在SCCOHT细胞系和小鼠移植瘤模型中有一定抑制效果[35-37]。一项EZH2抑制剂tazemetostat针对SCCOHT和其他*SWI/SNF*突变肿瘤的Ⅱ期临床试验结果尚未发布。CDK4/6抑制剂在临床前研究中也有一定作用[38]。其他靶向抑制剂如PARP抑制剂等尚需进一步研究。

程序性死亡［蛋白］-1（programmed death-1，PD-1）/程序性死亡［蛋白］配体-1（programmed death ligand-1，PD-L1）单抗免疫治疗已在肿瘤治疗领域广泛应用。Lin等[39]通过18例SCCOHT患者高通量测序研究发现，

95%（15/16）典型的SCCOHT患者肿瘤突变负荷（tumor mutation burden，TMB）较低，而在2例大细胞突变类型的SCCOHT患者中TMB较高，低TMB预示着免疫治疗的反应性可能较差。但Jelinic等[40]通过研究4例SCCOHT患者的肿瘤微环境，发现虽然其TMB较低，但在肿瘤细胞、间质细胞及肿瘤相关巨噬细胞中均能检测到PD-L1的阳性表达。该研究结果提出SCCOHT患者对PD-L1单抗免疫治疗可能有一定的反应性。

SCCOHT发病年龄较轻，预后极差。33%ⅠA期患者在术后随访1~13年（中位随访时间5.7年）内没有复发，而只有10%的ⅠC期患者和6.5%Ⅱ期及以上患者术后没有复发（*P*=0.000 9）[3]。在我们的研究中，2例Ⅰ期患者存活，2例Ⅰ期患者手术后仍出现盆腔复发。Ⅲ期及Ⅳ期患者术后2年内均死亡。血钙升高患者的总生存率为12.5%（1/8），血钙正常患者的总生存率也是12.5%（1/8），因而血钙水平能否作为预后指标在本研究中尚不能得出肯定结论，需大样本研究证实。笔者认为，FIGO分期及术后治疗模式是该病预后的重要指标。综合国内外的研究数据可知，年龄增加、诊断时血钙正常、无大细胞成分，肿瘤<10 cm可能是预后良好的重要因素[12, 14-15, 41]。

综上所述，SCCOHT临床治疗难度较大，手术治疗联合辅助化疗是首选。保留生育手术对生存获益的影响不明确，最佳辅助化疗方案仍需进一步探索。FIGO分期是疾病预后的重要因素，根据分期选择不同化疗方案的思路有一定价值。靶向治疗及免疫治疗有望成为最新治疗手段，相关临床试验结果令人期待。

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