doi: 10.3978/j.issn.2095-6959.2018.08.037
View this article at: http://dx.doi.org/10.3978/j.issn.2095-6959.2018.08.037

原发性子宫内膜小细胞神经内分泌癌 1 例并文献复习

肖川，王晨晨，沈铭红，吕京澴

(南京医科大学附属苏州医院，苏州市立医院病理科，江苏 苏州 215002)

[摘　要] 子宫内膜小细胞神经内分泌癌(small cell neuroendocrine carcinoma，SCNEC)是一种罕见的具有侵袭性的疾病，预后极差。本文报道的1例54岁绝经后妇女，因阴道出血、腹痛入院，超声提示子宫肌瘤多发，子宫增大。患者行全子宫切除术，双侧输卵管、卵巢切除术和膀胱前病灶切除术。病理结果为原发性子宫内膜SCNEC，妇产科联盟(Federation of Gynecology and Obstetrics，FIGO)2008分期至少为IIIA期。患者未进行淋巴结清扫，在接受7个周期的化学治疗(以下简称化疗)后无病生存8个月。目前临床上针对这种罕见的侵袭性疾病的最佳治疗方案尚未建立，需要个体化的多学科综合治疗。

[关键词] 小细胞神经内分泌癌；子宫内膜；超声；免疫组织化学染色

Primary small cell neuroendocrine carcinoma of endometrium: a case report and review of literature

XIAO Chuan, WANG Chenchen, SHEN Minghong, LÜ Jinghuan

(Department of Pathology, Suzhou Hospital Affiliated to Nanjing Medical University, Suzhou Municipal Hospital, Suzhou Jiangsu 215002, China)

Abstract Primary small cell neuroendocrine carcinoma (SCNEC) of the endometrium is a rare disease with an aggressive behavior and has a very poor prognosis. We presented a case of a 54-year-old postmenopausal woman with vaginal bleeding and abdominal pain. She underwent a radical abdominal hysterectomy with bilateral salpingo-oophorectomy and the lesionectomy on the front of the bladder. The pathological diagnosis was SCNEC and the Federation of Gynecology and Obstetrics (FIGO 2008) stage was at least IIIA. The patient is currently healthy without evidence of disease for 8 months after received chemotherapy for 7 cycles without lymphadenectomy. To date, the optimal treatment for this rare and aggressive disease has not been established and requires an individualized multidisciplinary management.

Keywords small cell neuroendocrine carcinoma; endometrium; ultrasound; immunohistochemical staining

收稿日期 (Date of reception)：2018–05–15

通信作者 (Corresponding author)：吕京澴，Email: jhlv@njmu.edu.cn

小细胞神经内分泌癌(small cell neuroendocrine carcinoma，SCNEC)主要发生于肺，肺外小细胞癌非常罕见，但几乎可以出现于任何器官，其最常见的来源为胃肠道(33%)，其次是生殖系统(20%)，头颈部(11%)及乳房(10%)[1]。在女性生殖道中，宫颈是最常见的部位，占宫颈癌的2%。子宫内膜是最少见的部位，仅占所有子宫内膜癌的0.8%[2]。类似于小细胞肺癌(small cell lung cancer，SCLC)，子宫内膜SCNEC表现出侵袭性的生物行为，预后差[2-5]。自1979年Albores-Saavedra等[6]第1次描述了子宫内膜小细胞癌后，至今约有90例病例见诸于文献[7]中。其中，60%为晚期[妇产科联盟(Federation of Gynecology and Obstetrics，FIGO) III期或IV期]，中位生存期仅5个月[8]。然而，对于组织病理学的诊断及治疗方案，目前尚无明确的共识。

1 临床资料

患者，女，54岁(孕3，产1)，因“绝经3年，腹胀伴阴道出血半月余”入院。B超示：子宫大小约100 mm×86 mm×110 mm，左右卵巢未探及，子宫内膜厚约2 mm，子宫前壁肌层回声增粗不均匀，前壁见一75 mm×50 mm不均质中等回声，边界不清，彩色多普勒血流成像(color Doppler flow imaging，CDFI)未见明显彩色血流信号。子宫前壁另见32 mm×24 mm，26 mm×21 mm等低回声区，外突，CDFI示未见明显彩色血流信号。超声提示：子宫前壁不均质中等回声，子宫肌瘤多发，子宫增大(图1A)。患者行全子宫及双侧附件切除术。

术中探查见：子宫中位，增大如孕3个月余，质脆，子宫前壁下段及膀胱腹膜折返处见数枚鱼肉样组织，与膀胱返折腹膜界限欠清，子宫后壁与肠管粘连，肠管增厚，水肿，直肠表面见数枚米粒样凸起。双侧附件未见明显异常。术中冰冻结果诊断为恶性肿瘤。手术标本的肉眼检查示：宫底破碎的全子宫，15 cm×12 cm×8 cm，切面见子宫前壁弥漫结节状，灰黄暗红色，质嫩，坏死明显(图1B)。组织病理诊断为原发性SCNEC伴有广泛的坏死，侵及肌壁全层，多血管和淋巴管浸润，左右宫旁见癌累及，膀胱前病灶见癌组织累及，双卵巢见癌累及，双输卵管未见癌累及。镜下肿瘤由小细胞构成，排列成巢状或条索状，细胞异型性显著，核浆比增高(图2)。免疫组织化学结果示：肿瘤细胞嗜铬素A(CgA)，突触素(Syn)，神经元特异性烯醇化酶(neuron-specific enolase，NSE)，SCLC，CD56阳性，广谱细胞角蛋白(CKpan)局部弱阳性，CD10，抑制素(inhinbin)局灶弱阳性，Ki-67 80%阳性，上皮膜抗原(epithelial membrane antigen，EMA)，CD99，Bc12，钙视网膜蛋白(CR)，雌激素受体(ER)，孕激素受体(PR)，CD117，DoG1，结蛋白(Desmin)，平滑肌动蛋白(smooth muscle actin，SMA)，肾母细胞瘤(WT1)，波形蛋白(Vimentin)，周期素D1(CyclinD1)，甲状腺转录因子1(thyroid transcription factor-1，TTF-1)均阴性，D2-40淋巴管阳性，CD31血管壁阳性(图3)。

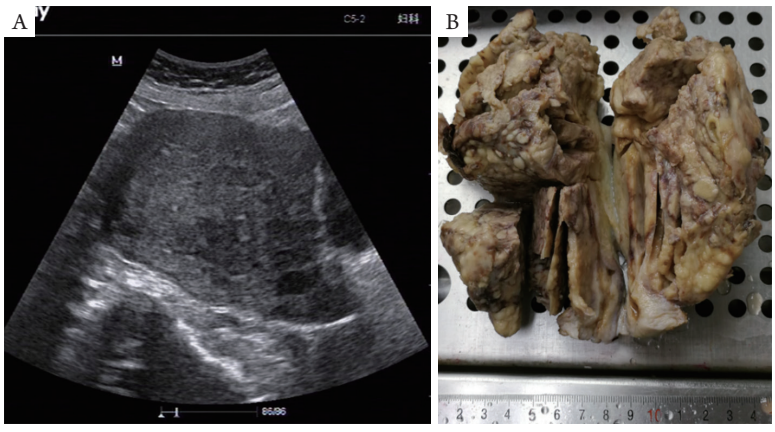

图1 肿瘤超声表现及大体形态

Figure 1 Ultrasound manifestations and gross morphology of tumor

(A)盆腔超声检查显示子宫增大，子宫前壁充满结节；(B)肉眼观肿瘤浸润子宫肌壁超过50%，到达子宫浆膜。

(A) Pelvic ultrasound shows that the anterior wall of the uterus is filled with nodules; (B) More than 50% of the myometrium of the uterus is infiltrated by the naked eye, reaching the uterine serosa.

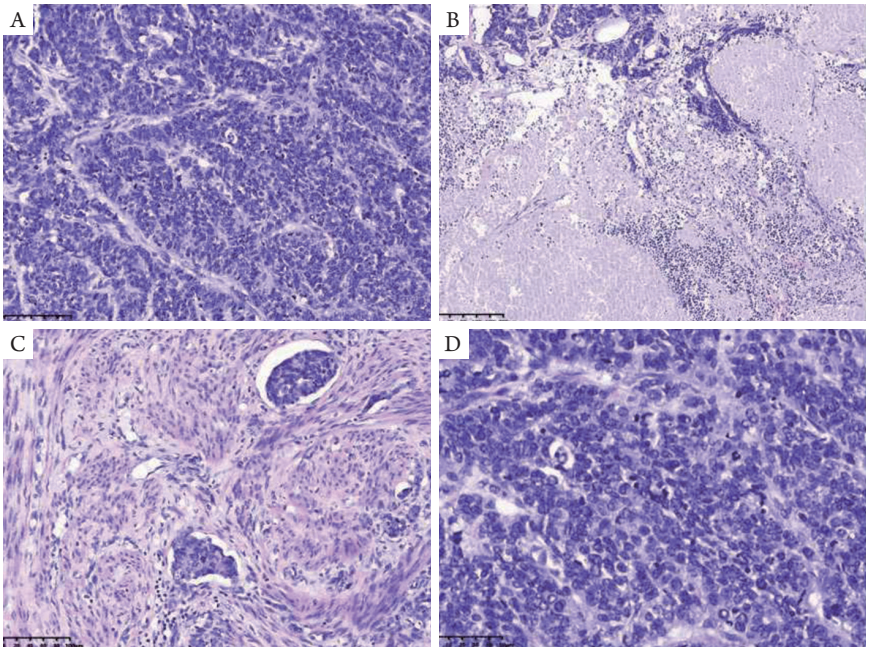

图2 肿瘤组织学形态(HE染色)

Figure 2 Histologic morphology of tumor (HE staining)

(A)组织病理显示肿瘤细胞由弥漫一致的小细胞构成，生长方式呈器官样结构、梭形、巢状岛状或小梁状(×200)；(B)坏死显著(×100)；(C)脉管侵犯(×200)；(D)一致的小细胞群，核深染，核分裂象易见；核卵圆形或成角，相互嵌合，胞质稀少(×400)。

(A) Histological examination showed a prevalent solid pattern with organ like structure, nests or cords composed of diffuse small cells (×200); (B) Tumor necrosis was evident (×100); (C) Vascular invasion was present (×200); (D) Tumor was composed of consistent small cells with scanty cytoplasm, hyperchromatic nuclei, and high mitotic rate, nuclear oval or angled, chimeric (×400).

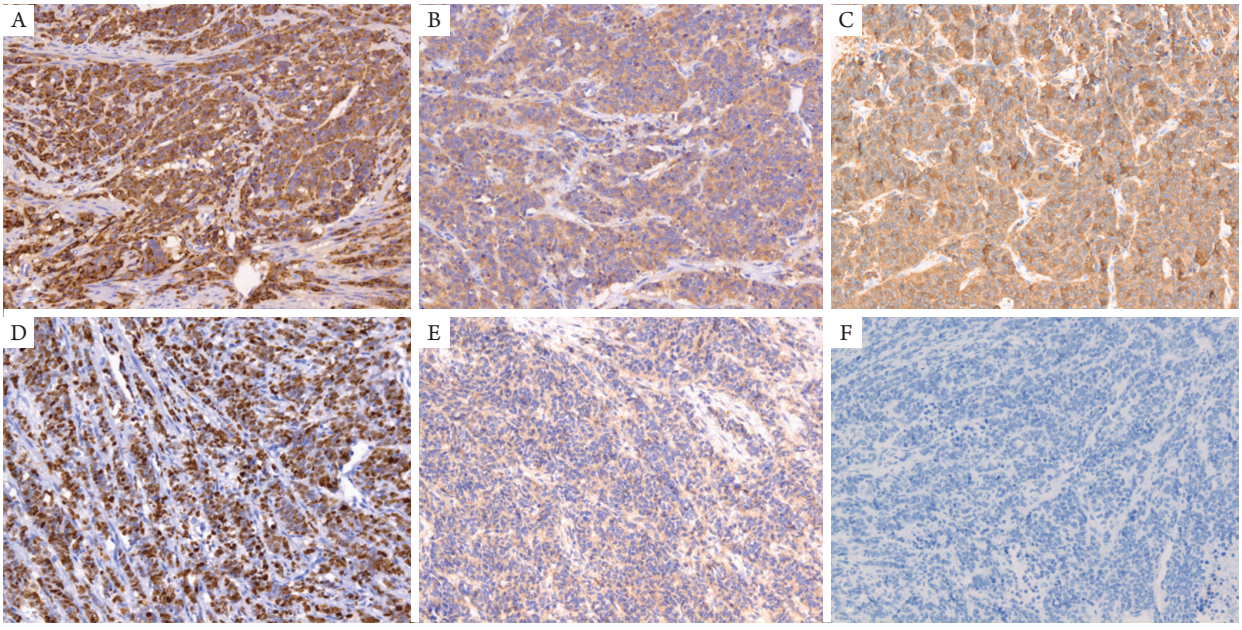

图3 免疫组织化学染色(×200)

Figure 3 Immunohistochemistry staining (×200)

(A) CgA阳性；(B)Syn阳性；(C)NSE阳性；(D)Ki-67 80%阳性；(E)CD117阴性；(F)TTF-1阴性。

(A) CgA positive; (B) Syn positive; (C) NSE positive; (D) Ki-67 80% positive; (E) CD117 negative; (F) TTF-1 negative.

显微镜下未见其他肿瘤分化成分，电镜下肿瘤细胞由细胞桥粒连接，胞质内可见有致密核心的分泌颗粒。术后CT示：右肺下叶底部小结节影，后腹膜多发肿大淋巴结，脾脏增大。MRI示：子宫神经内分泌癌术后改变，盆腔内髂血管旁淋巴结肿大，两侧腹股沟区多发小淋巴结。正电子发射计算机断层显像(positron emission tomography-computed tomography，PET-CT)示：全子宫+双侧附件切除术后，全身^{F}18-FDG葡萄糖代谢未见明显异常增高，右下肺近胸膜小结节，脾大，肝内小钙化灶，两侧颌下，后腹膜及腹股沟小淋巴结，考虑炎性淋巴结。肿瘤指标未见明显异常。

SCNEC是一种恶性肿瘤，预后较差，患者因临床分期较晚，未进行第2次手术淋巴结清扫。经过7个周期化疗，化疗方案为顺铂+依托泊苷，每21 d为1个周期，该患者至截稿无病存活8个月。

2 讨论

根据世界卫生组织(WHO)对子宫体肿瘤的分类，子宫内膜神经内分泌肿瘤包括低级别的类癌和高级别的大细胞神经内分泌癌(large cell neuroendocrine carcinoma，LCNEC)和SCNEC[9]。尽管“纯”SCNEC的病例并不少见，但多数情况下，子宫内膜的SCNEC是一种混合实体，存在其他肿瘤表型，如腺癌。既往研究[10]表明：混合型和单纯型神经内分泌癌之间的预后没有差异，在子宫内膜的SCNEC中，分期是决定患者预后的关键因素。SCNEC的发病年龄为23~87(平均60)岁，高于子宫内膜腺癌患者。异常或绝经后阴道出血是最常见的症状，本例患者还出现腹泻、尿频、尿急、尿不尽，畏寒发热。此外，患者还可以出现不同的副肿瘤症状和综合征，如视网膜病变、库欣综合征或膜性肾小球肾炎等[11-12]。van Hoeven等[3]总结SCNEC诊断标准如下：1)有明确的原发于子宫内膜的证据；2)肿瘤由单一的小至中等大的肿瘤细胞组成，致密、成片生长，可合并或不合并其他肿瘤亚型成分；3)免疫组织化学神经内分泌标志物至少有1种阳性。鉴别诊断包括转移性SCLC、胚胎型横纹肌肉瘤、恶性淋巴瘤、白血病、间质肉瘤、原始性神经外胚层肿瘤和恶性混合的苗勒氏肿瘤。显然，除仔细的组织病理学观察外，免疫组织化学染色是最有效的鉴别方法。值得注意的是，虽然TTF-1在甲状腺和肺癌的诊断中被广泛使用[13-14]，但在鉴别转移性SCLC与原发性肺外SCNEC时应谨慎使用。因为TTF-1在肺外SCNEC中也可以表达，比如妇科腺癌[15]。CD117(c-KIT)是参与肿瘤发生的跨膜性癌基因蛋白，特别是在胃肠道间质瘤中表达。超过60%的SCLCs以磷酸化形式表达CD117(c-KIT)[16-17]，但与患者存活率[18]或者靶向治疗[19]没有显著的相关性。在SCNEC中，尽管KIT的表达是膜阳性，但使用PCR测序等分子遗传学分析没有发现KIT的突变(外显子9，11，13和17)[20]。一项包含6例SCNEC的临床病理研究[21]显示：在所有复发病例中，患者首先出现复发症状，而不是影像学上的异常发现或升高的肿瘤指标；只有1名患者在疾病复发时出现CA125升高(50.5 U/mL)。因此，监测血清CA125水平对子宫内膜SCNEC的随访意义不大。在本例中，TTF-1，CD117均阴性，CA125水平也正常。SCLC的细胞来源与呼吸道上皮细胞相同的内胚层来源，且细胞来自于小鼠模型所示的多能前体细胞[22-23]。SCNEC的组织起源尚不明确，目前有2种假设：一种为SCNEC来源于子宫内膜的神经内分泌细胞，由子宫内膜多能干细胞分化；另一种为SCNEC来源于子宫内膜腺癌中癌细胞的突变。本文病例倾向于前者，因为不存在其他肿瘤的分化。类似于SCLC，子宫内膜的SCNEC是侵袭性肿瘤，具有系统性传播的倾向且预后不良，到目前为止，这种罕见的肿瘤还未建立统一的治疗方案[24]。虽然没有证据表明原发性根治性手术对该病的病程有影响，但手术切除通常是该肿瘤治疗的第一步[25]。其手术治疗包括全子宫切除术、双侧输卵管卵巢切除术、网膜切除术和盆腔/腹主动脉淋巴结清扫术等，其次是基于铂的化疗和放疗[3,25-26]。本病例只进行了腹部全子宫切除和双侧附件切除术，PET-CT扫描未见明确肿瘤转移迹象，患者未进行淋巴结清扫，选择了先进行化疗，因此笔者无法在目前的研究中评估确切的FIGO分期，但即使没有淋巴结转移，也至少是IIIA期。通过参考SCLC在肺肿瘤中使用的辅助化疗方法，一般采用顺铂和依托泊苷的联合化疗方案。也有其他的治疗方案可供使用，如多西紫杉醇+顺铂，紫杉醇+卡铂，顺铂+伊立替康等。患者目前尚无复发或转移的迹象，提示淋巴结清扫和手术切除也可以不作为首选的治疗方案。当然这需要更多的病例验证和探索更多的个性化、多学科治疗方案[27-28]。此外，也有研究[29]使用与生长抑素相似的化疗和奥曲肽进行联合治疗。也有研究[30]显示用奥曲肽治疗可观察到局部效应，但其他病例显示出肿瘤增大和反复高血糖等不良反应[29]。

综上所述，子宫内膜的SCNECs迅速发展，预后极差，对诊断、治疗和可能的分子机制仍需要更深入的研究。

参考文献

1. Howard S, O'Regan K, Jagannathan J, et al. Extrapulmonary small cell carcinoma: a pictorial review[J]. AJR Am J Roentgenol, 2011, 197(3): W392-W398.
2. Huntsman DG, Clement PB, Gilks CB, et al. Small-cell carcinoma of the endometrium. A clinicopathological study of sixteen cases[J]. Am J Surg Pathol, 1994, 18(4): 364-375.
3. van Hoeven KH, Hudock JA, Woodruff JM, et al. Small cell neuroendocrine carcinoma of the endometrium[J]. Int J Gynecol Pathol, 1995, 14(1): 21-29.
4. Varras M, Akrivis C, Demou A, et al. Primary small-cell carcinoma of the endometrium: clinicopathological study of a case and review of the literature[J]. Eur J Gynaecol Oncol, 2002, 23(6): 577-581.
5. Albores-Saavedra J, Martinez-Benitez B, Luevano E. Small cell carcinomas and large cell neuroendocrine carcinomas of the endometrium and cervix: polypoid tumors and those arising in polyps may have a favorable prognosis[J]. Int J Gynecol Pathol, 2008, 27(3): 333-339.
6. Albores-Saavedra J, Rodríguez-Martínez HA, Larraza-Hernández O. Carcinoid tumors of the cervix[J]. Pathol Annu, 1979, 14(Pt 1): 273-291.
7. Matsumoto H, Nasu K, Kai K, et al. Combined large-cell neuroendocrine carcinoma and endometrioid adenocarcinoma of the endometrium: a case report and survey of related literature[J]. J Obstet Gynaecol Res, 2016, 42(2): 206-210.
8. Matsumoto H, Takai N, Nasu K, et al. Small cell carcinoma of the endometrium: a report of two cases[J]. J Obstet Gynaecol Res, 2011, 37(11): 1739-1743.
9. 卢朝辉, 陈杰. WHO女性生殖器官肿瘤学分类(第4版)解读[J]. 中华病理学杂志, 2014, 43(10): 649-650.
   LU Zhaohui, CHEN Jie. Introduction of WHO classification of tumours of female reproductive organs (4th edition)[J]. Chinese Journal of Pathology, 2014, 43(10): 649-650.
10. Bahig H, Portelance L, Legler C, et al. Small cell carcinoma of the endometrium: report of a case and review of the literature[J]. Minerva Ginecol, 2009, 61(4): 365-369.
11. Doukhopelnikoff A, Debrock G, Steelandt T, et al. The importance of recognizing paraneoplastic symptoms: a case report of neuroendocrine small cell carcinoma of the endometrium presenting as paraneoplastic Cushing's syndrome[J]. Facts Views Vis Obgyn, 2017, 9(2): 121-126.
12. Sato H, Kanai G, Kajiwara H, et al. Small-cell carcinoma of the endometrium presenting as Cushing's syndrome[J]. Endocr J, 2010, 57(1): 31-38.
13. Fabbro D, Di Loreto C, Beltrami CA, et al. Expression of thyroid-specific transcription factors TTF-1 and PAX-8 in human thyroid neoplasms[J]. Cancer Res, 1994, 54(17): 4744-4749.
14. Folpe AL, Gown AM, Lamps LW, et al. Thyroid transcription factor-1: immunohistochemical evaluation in pulmonary neuroendocrine tumors[J]. Mod Pathol, 1999, 12(1): 5-8.
15. D'Antonio A, Addesso M, Caleo A, et al. Small cell neuroendocrine carcinoma of the endometrium with pulmonary metastasis: a clinicopathologic study of a case and a brief review of the literature[J]. Ann Med Surg (Lond), 2015, 5: 114-117.
16. Camps C, Sirera R, Bremnes RM, et al. Analysis of c-kit expression in small cell lung cancer: prevalence and prognostic implications[J]. Lung Cancer, 2006, 52(3): 343-347.
17. Pelosi G, Masullo M, Leon ME, et al. CD117 immunoreactivity in high-grade neuroendocrine tumors of the lung: a comparative study of 39 large-cell neuroendocrine carcinomas and 27 surgically resected small-cell carcinomas[J]. Virchows Arch, 2004, 445(5): 449-455.
18. López-Martin A, Ballestín C, Garcia-Carbonero R, et al. Prognostic value of KIT expression in small cell lung cancer[J]. Lung Cancer, 2007, 56(3): 405-413.
19. Dy GK, Miller AA, Mandrekar SJ, et al. A phase II trial of imatinib (ST1571) in patients with c-kit expressing relapsed small-cell lung cancer: a CALGB and NCCTG study[J]. Ann Oncol, 2005, 16(11): 1811-1816.
20. Lasota J, Miettinen M. KIT and PDGFRA mutations in gastrointestinal stromal tumors (GISTs)[J]. Semin Diagn Pathol, 2006, 23(2): 91-102.
21. Koo YJ, Kim DY, Kim KR, et al. Small cell neuroendocrine carcinoma of the endometrium: a clinicopathologic study of six cases[J]. Taiwan J Obstet Gynecol, 2014, 53(3): 355-359.
22. Park KS, Liang MC, Raiser DM, et al. Characterization of the cell of origin for small cell lung cancer[J]. Cell Cycle, 2011, 10(16): 2806-2815.
23. Sutherland KD, Proost N, Brouns I, et al. Cell of origin of small cell lung cancer: inactivation of Trp53 and Rb1 in distinct cell types of adult mouse lung[J]. Cancer Cell, 2011, 19(6): 754-764.
24. Brennan SM, Gregory DL, Stillie A, et al. Should extrapulmonary small cell cancer be managed like small cell lung cancer?[J]. Cancer, 2010, 116(4): 888-895.
25. Atienza-Amores M, Guerini-Rocco E, Soslow RA, et al. Small cell carcinoma of the gynecologic tract: a multifaceted spectrum of lesions[J]. Gynecol Oncol, 2014, 134(2): 410-418.
26. Gardner GJ, Reidy-Lagunes D, Gehrig PA. Neuroendocrine tumors of the gynecologic tract: a Society of Gynecologic Oncology (SGO) clinical document[J]. Gynecol Oncol, 2011, 122(1): 190-198.

27. Bige O, Saatli B, Secil M, et al. Small cell neuroendocrine carcinoma of the endometrium and laparoscopic staging: a clinicopathologic study of a case and a brief review of the literature[J]. Int J Gynecol Cancer, 2008, 18(4): 838-843.
28. Tsujioka H, Eguchi F, Emoto M, et al. Small-cell carcinoma of the endometrium: an immunohistochemical and ultrastructural analysis[J]. J Obstet Gynaecol Res, 1997, 23(1): 9-16.
29. Shahabi S, Pellicciotta I, Hou J, et al. Clinical utility of chromogranin A and octreotide in large cell neuro endocrine carcinoma of the uterine corpus[J]. Rare Tumors, 2011, 3(4): e41.
30. Verschraegen CF, Matei C, Loyer E, et al. Octreotide induced remission of a refractory small cell carcinoma of the endometrium[J]. Int J Gynecol Cancer, 1999, 9(1): 80-85.

本文引用：肖川, 王晨晨, 沈铭红, 吕京澴. 原发性子宫内膜小细胞神经内分泌癌1例并文献复习[J]. 临床与病理杂志, 2018, 38(8): 1812-1817. doi: 10.3978/j.issn.2095-6959.2018.08.037

Cite this article as: XIAO Chuan, WANG Chenchen, SHEN Minghong, LÜ Jinghuan. Primary small cell neuroendocrine carcinoma of endometrium: a case report and review of literature[J]. Journal of Clinical and Pathological Research, 2018, 38(8): 1812-1817. doi: 10.3978/j.issn.2095-6959.2018.08.037