论　著

基于子宫内膜异位的直肠-乙状结肠透明细胞癌合并子宫内膜样腺癌：病例报告

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【摘要】报告1例基于子宫内膜异位的直肠-乙状结肠透明细胞癌合并子宫内膜样腺癌，并对病例特点及治疗进行分析。患者，女，66岁，因腹胀10 d为主诉于本院就诊，临床表现为右下腹肿块，无明显压痛，肛查无明显异常。影像学检查：盆腔右侧-乙状结肠右旁见不规则软组织肿块影，病灶左侧缘与乙状结肠分界不清，致肠腔偏心性狭窄；阴道残端上方见形状不规则肿块，病灶与肠管分界不清。患者20年前因双侧卵巢子宫内膜异位行全子宫切除术＋右侧附件切除术＋左侧卵巢囊肿剔除术。此次手术切除直肠与乙状结肠肿物与右侧髂窝肿物，病理显示子宫内膜样腺癌与透明细胞癌混合。术后化疗：力朴素240 mg/卡铂500 mg。化疗期间肿瘤复发且进行性增大，肿瘤标记物持续增加，换用多美素50 mg后依旧持续性进展。子宫内膜异位至肠道并恶变病例罕见，且本例对化疗耐受，与卵巢癌变相同的治疗方法是否值得推广有待进一步探究。

【关键词】子宫内膜异位　直肠-乙状结肠　透明细胞癌
【中图分类号】R473.71　文献标志码　A　doi：10.3969/j.issn.2096-3351.2021.04.011

The rectal-sigmoid colon clear cell carcinoma mixed with endometrial adenocarcinoma based on endometriosis: A case report

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【**Abstract**】This article reports a case of rectal-Sigmoid colon clear cell carcinoma with endometrial adenocarcinoma based on endometriosis and analyzes its features and treatment. The female patient, aged 66 years, attended our hospital with the chief complaint of abdominal distension for 10 days, and clinical manifestation included a mass in the right lower abdomen, with no obvious tenderness or abnormalities in anal examination. Imaging examination showed an irregular soft tissue mass on the right side of the pelvic cavity, located at the right side of the sigmoid colon, with unclear boundaries between the left side of the lesion and the sigmoid colon, which led to the eccentric stenosis of the intestinal cavity, and irregular masses were observed above the vaginal stump, with unclear boundaries between the lesion and the intestinal canal. The patient underwent total hysterectomy+right adnexectomy+left ovarian cyst removal due to ovarian endometriosis at both sides 20 years ago. The masses in the rectum, the sigmoid colon, and the right iliac fossa were surgically removed, and pathological examination showed endometrial adenocarcinoma with clear cell carcinoma. Lipusu 240 mg and carboplatin 500 mg were given as postoperative chemotherapy. Recurrence and progressive enlargement of tumor were observed during chemotherapy, with continuous increases in tumor markers, and progression was still observed after the drug was switched to Domesil 50 mg. The case of endometriosis involving the intestine with malignant transformation is rare, and this case is resistant to chemotherapy. Further studies are needed to explore the promotion of the same treatment method as ovarian cancer.

【**Key words**】Endometriosis　Rectal-sigmoid colon　Clear cell carcinoma

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子宫内膜异位是一种常见的女性增殖性疾病，育龄期女性的发病率为4%～15%[1]。该疾病可累及各种生殖器官，也可累及非生殖系统，包括胃肠道、膀胱、肺部、中枢神经系统甚至皮肤。临床实践中不难看出，子宫内膜异位症虽然属于良性疾病，但其仍有恶变的风险。胃肠道的子宫内膜异位较罕见，多数发生在直肠与乙状结肠（50%～90%）[2-3]。其中，卵巢的子宫内膜恶变较常见，但肠道的子宫内膜异位恶变比较罕见，且70%为子宫内膜样腺癌，透明细胞癌仅占4.5%[4-6]。因此，我们报道了1例直肠-乙状结肠恶变的子宫内膜异位病例，并对其特点及治疗进行分析

1 临床资料

患者，女，66岁，因腹胀10 d于2018年12月来本院就诊。10 d前患者无明显诱因出现腹胀，不伴发热、恶心、呕吐、腹泻。既往有子宫内膜异位症病史，无家族史。于1999年（47岁）时行“全子宫切除术＋右侧附件切除术＋左侧卵巢囊肿剔除术”。组织学检查示卵巢良性子宫内膜异位症。子宫切除术后患者未接受任何激素治疗。

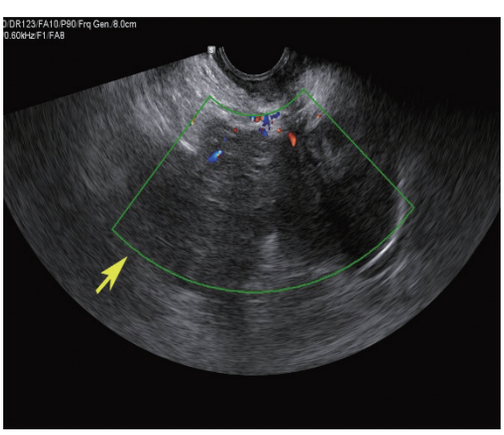
专科情况：右下腹可扪及肿块，无明显压痛，肛查无明显异常。

影像学检查：术前最后一次B超（图1）、MRI（图2）可见肿块，示“大小约90 mm×50 mm×49 mm，病灶左侧缘与乙状结肠分界不清，致肠腔偏心性狭窄，肠粘膜尚完整。肿块向外至右侧盆壁，推压右侧髂动静脉。右侧髂外静脉受压。右侧髂动脉管腔未见狭窄。右侧输尿管下段与肿块分界欠清。左侧髂臼内侧见一大小约11×6 mm的类椭圆形T2W1高信号，T1W1低信号，增强扫描边缘强化”。

实验室检查：术前：CEA 41.09 ug/L，CA125 546.4 U/mL，SCC 45.4 ug/L，CA19-9 82.6 U/mL；术后：CEA 1.9 ug/L，CA125 32.9 U/mL，SCC 5.6 ug/L，CA19-9 5.8 U/mL。

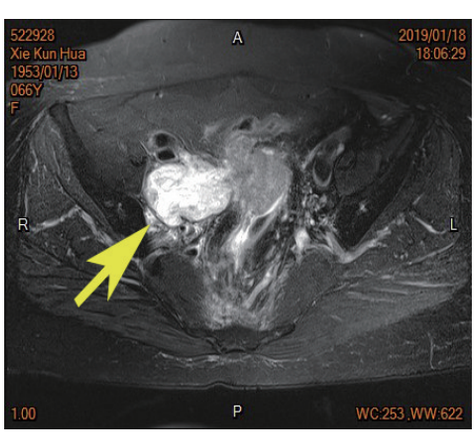
入院诊断：子宫内膜异位症待排恶变。

病理检查：病理示（图3）盆腔腹膜后肿物符合交界性子宫内膜样肿瘤，局灶呈高分化子宫内膜样腺癌及透明细胞癌；（图4）直肠乙状结肠肿物符合透明细胞癌，局部见高分化子宫内膜样腺癌及非典型子宫内膜样腺体。免疫组化子宫内膜样腺体：ER（+），PR（+），P40（-），P63（-），透明细胞：ER（-），PR（-），P40（-），P63（-）。诊断为子宫内膜异位症恶变，混合型子宫内膜样腺癌和透明细胞癌。



注：B超示阴道残端上方可见肿块91 mm×55 mm×72 mm，形状不规则，病灶与肠管分界不清，内部为不均匀实性回声

图1　阴道B超图



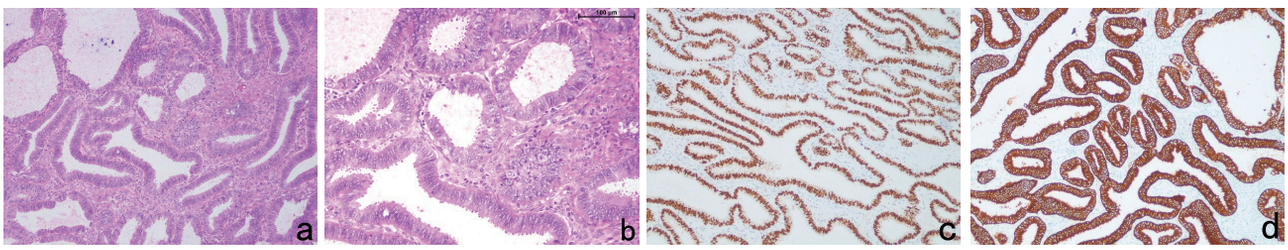
注：MRI示盆腔右侧-乙状结肠右旁见哑铃状软组织肿块影

图2　腹部MRI图

2　治疗

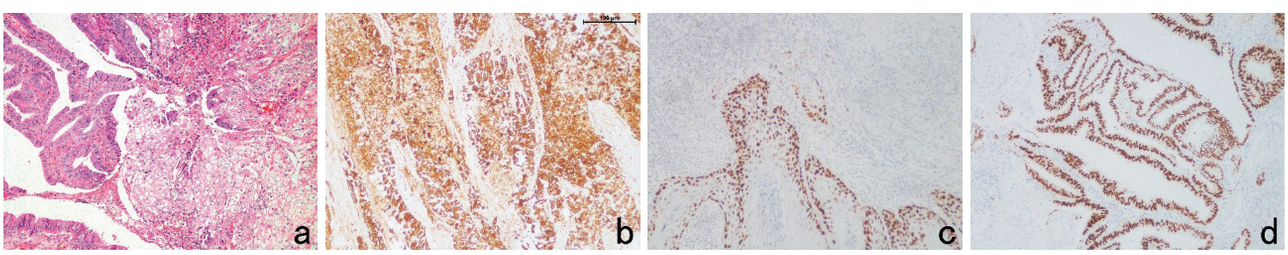
肿瘤细胞减灭术：右侧盆腔腹膜后肿物切除＋直肠乙状结肠肿物切除＋左侧附件切除＋左侧卵巢血管高位结扎＋直肠乙状结肠端端吻合。盆腔腹膜后肿物质硬，与右侧髂窝处致密粘连；直肠乙状结肠肿物质软，糟烂，血供丰富，右侧输尿管受肿物压迫，已变形移位。按照上皮性卵巢癌行后续化疗，采用6周期间隔3周的铂类-紫杉醇联合化疗方案。患者于术后2^{+}月完成3次TC方案化疗（D1力朴素240 mg.iv.drip，D2卡铂500 mg.iv.drip）。

随访：化疗期间B超发现阴道肿物增大（图5），妇科肿瘤指标进行性增加（图6）。考虑子宫内膜样腺



注:HE染色-a(×40),b(×100);免疫组化:c(×100)PR(+),d(×100)CK(+)

图3 右侧盆腔腹膜后肿物图



注:HE染色-a(×100);免疫组化:b(×100)CK(+),c(×100)P53(+),d(×100)PR(+)

图4 直肠乙状结肠肿物图

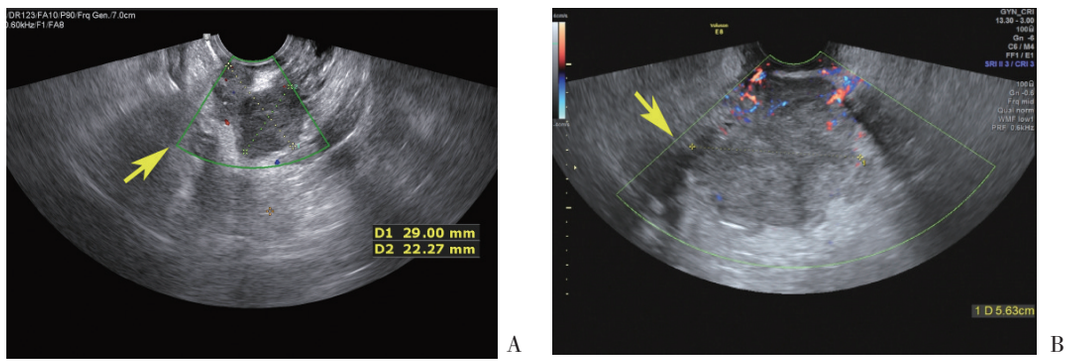
癌及透明细胞癌复发,于2019年5月27日行细胞减灭术。术中自回盲部上端约40 cm空肠及肠系膜见大小不等肿瘤侵犯,膀胱表面及阴道残端均见肿瘤侵犯、边界不清,大小7 cm,质软,糟烂,血供丰富。因肿物与膀胱致密粘连,切除膀胱肿物后见4 cm裂口,未能切除全部肿块。术后肿瘤指标继续上升,阴道残端也持续增大。因患者出现反复高热,未能按时进行化疗。入院行抗感染治疗,住院期间患者出现急性左心衰于ICU治疗。第3疗程后80 d开始多柔比星化疗,多美素50 mg.iv.drip。症状仍无明显好转。患者化疗不敏感,无法放疗,肿瘤持续性进展,与家属沟通后放弃治疗。

3 讨论

关于由卵巢子宫内膜异位症引起的癌症的发病率已有若干报道[7-11]。在日本的一项前瞻性研究中,平均12.8年的随访期间发现6 398名卵巢子宫内膜异位症女性中46例(0.72%)发生癌变,且随年龄的增长而增加,诊断为卵巢癌的平均年龄为51.4岁[12]。Heidemann等[13]报道上皮性卵巢癌在子宫内膜异位症女性中的患病率为2.0%~17.0%。据报道,瑞典子宫内膜异位症女性一生中被诊断为卵巢癌的风险为1.5%[14]。对于有长期卵巢子宫内膜异位症病史的患者,卵巢癌发生的相对风险进一步增加[15-19]。同样,Siufi等[20]报道子宫内膜异位症患者患卵巢癌的风险升高(95%*CI*:1.19~1.71)。

大约18.3%~25%的子宫内膜异位症相关恶性肿瘤发生在卵巢外[21]。这些肿瘤通常是子宫内膜样或透明细胞癌,而非上皮性肿瘤非常罕见,包括子宫内膜间质肉瘤、腺肉瘤和癌肉瘤[22-25]。就病理诊断而言,只有36%~42%的病例可检出子宫内膜异位症良、恶性之间的过渡区,肿瘤与子宫内膜异位组织共存足以证明病变来自子宫内膜[26-27]。卵巢外恶性肿瘤可累及结肠和直肠-阴道隔、小肠、外阴、阴道、输卵管、泌尿道,胸膜和盆腔淋巴结较少见,并与良性卵巢外子宫内膜异位症平行分布。这类女性更可能是绝经后、肥胖和雌激素替代疗法(ERT)的使用者[28]。肠道、泌尿道、脐部子宫内膜异位症的恶变发生率与子宫内膜异位症的恶变发生率相似,约为1%[29-31]。相比之下,文献中没有关于肺子宫内膜异位症引起的恶性肿瘤的报道。可能是由于肺部子宫内膜异位组织的性质差异[32-33]。另外,腹腔和胸腔的炎症和免疫状态等微环境的差异可能会影响恶性转化[24]。

遗传异常,如染色体5q的杂合性缺失也被视为可能的因素。Pearce等[34]在一项对保存的组织标本的回顾性研究中发现,40例手术疤痕子宫内膜异位症患者中11例(27.5%)和36例深度浸润性子宫内膜异位症患者中13例(36.1%)存在体细胞癌驱动事件,包括KRAS、ERBB2、PIK3CA和CTNNB1的hotspot突变。在两种类型的子宫内膜异位症中,PTEN缺失的发生率相似(分别为17.5%和13.9%),而ARID1A缺失仅在1例深度浸润性子宫内膜异位症中发生[35]。这些改变可能对异位组织在这些部位的着床和生长很重要,但它们在癌变发生中的作用仍不清楚[36-39]。一项免疫组织化学研究显示,与增生性子宫内膜相比,



注：A. 2019-03-11 阴道残端上方可见肿块29 mm × 22 mm；B. 2019-05-21 盆腔肿块54 mm × 60 mm × 56 mm

图5 腹部B超图

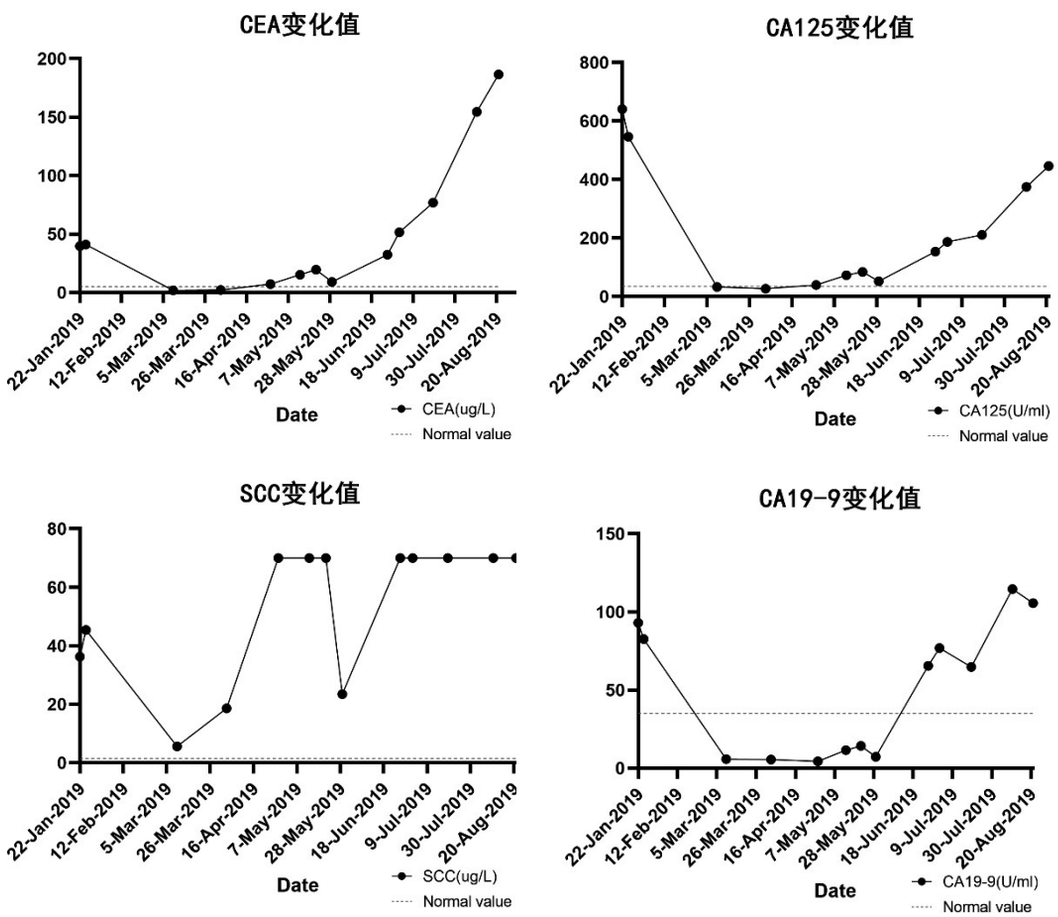


图6　肿瘤标志物变化趋势

腹膜和胃肠道子宫内膜异位症患者N-cadherin的表达显著降低，而在子宫内膜异位症相关的肠癌中，N-cadherin和连环蛋白的表达完全缺失[40-43]。因此，N-cadherin表达的改变可能参与了胃肠道子宫内膜异位症的发病机制，甚至参与了恶性肿瘤的发展。

目前，临床医生能否预测哪些患者会发生恶变，以及如何治疗这些患者仍是未知的。虽然对这些肿瘤的治疗方法尚无共识，但只要有可能，都应进行原发性减容手术，切除所有肉眼可见病变[44-46]。术后化疗通常包括卡铂＋紫杉醇，但与卵巢癌相比，其反应较差[47-48]。晚期病例中新辅助化疗的应用以及ER+/PR+肿瘤患者的内分泌治疗的应用还在进一步研究中[49]。辅助放射治疗有时被给予，特别是对盆腔受累有限的患者，但其真正的疗效仍未知[50-51]。Nezhat等[52]认为需要持续随访的子宫内膜异位症患者包括有长期子宫内膜异位症病史的女性、患有与子宫内膜异位症相关的不孕症或不孕症治疗，或有卵巢子宫内膜瘤的女性。良性子宫内膜异位症的治疗包括观察、

激素治疗或手术切除。Nezhat等[53]主张手术治疗的妇女应完全切除所有子宫内膜异位病灶,并对卵巢子宫内膜进行组织评估,以排除恶性肿瘤。一系列切除可见病变的手术获益需要与术后并发症的风险相平衡。此外,没有明确的数据表明早期手术治疗与降低疾病进展和恶性肿瘤的风险相关。Nezhat等[54]还建议进行激素治疗,旨在减少复发子宫内膜异位和子宫腺肌瘤的风险。化疗的作用还不太清楚。在Benoit等[55]的研究中,他们得出的结论是:考虑到化疗对子宫内膜癌的有限疗效,对此类疾病化疗的效果是最不显著的。

恶性卵巢外子宫内膜异位症的预后取决于肿瘤的分期,肿瘤局限于起源部位的患者5年生存率为82%~100%,弥散性腹膜内疾病的患者5年生存率为0%~12%[56]。根据距首次化疗后复发的时间,可以将病例分为难治性、铂类耐药型、铂类部分敏感型、铂类敏感型[57-58]。本例患者在全面分期手术后2月内复发,接受铂类化疗期间肿瘤持续性进展,为难治型。原因考虑为本例病例病理类型为子宫内膜腺癌与透明细胞癌混合,病理类型特殊,且透明细胞癌对铂类化疗有强耐药性,故没有有效的治疗方案。异位于肠道的子宫内膜组织发生癌变较少见。有研究表明异位的子宫内膜囊肿会形成更倾向于恶变的微环境:①子宫内膜异位囊肿中有高浓度的游离铁,而游离铁通过在肝脏和肺等几个器官中诱导持续的氧化应激而与癌症发展相关。子宫内膜异位囊肿内的上皮细胞暴露于广泛的氧化应激中,可能会受到更多DNA损伤导致恶变;②Mandai等[59]使用微阵列数据集,识别出区分透明细胞癌与其他类型卵巢癌的基因特征,并命名为"透明细胞癌特征"。此基因特征在异位子宫内膜团块中的短暂表达影响了异位的子宫内膜囊肿的微环境,可能会导致后天修饰的透明细胞癌突变。虽然此为卵巢癌的透明细胞癌的相关研究,但机制上可能也可以用于探讨肠道子宫内膜异位恶变的形成机制。卵巢癌的透明细胞癌类型为子宫内膜异位恶变所致,故本例肠道的子宫内膜异位恶变采用的和卵巢癌化疗相同的方案。但因为肠道子宫内膜异位相关恶变病例目前仍然很少,恶变机制与治疗方案是否可参考卵巢子宫内膜异位相关透明细胞癌还需要探讨。HNF-1β的过度表达在子宫内膜异位的恶变、化疗耐药、细胞凋亡调节上有比较重要的意义,而本例病例病理免疫组化有显示HNF-1β强阳性[60]。

4 结论

透明细胞癌的病理类型对化疗的耐药性导致本病例疗效及预后不佳。同样是子宫内膜异位相关组织恶变,卵巢癌变与肠道癌变是否适用相同的治疗方案还有待进一步探讨。

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