

doi: 10.13241/j.cnki.pmb.2019.07.023

阑尾杯状细胞类癌合并回盲部混合型腺神经内分泌癌 1 例病例报道并文献复习*

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摘要 目的:报道 1 例极为罕见的阑尾杯状细胞类癌(goblet cell carcinoid, GCC)合并回盲部混合型腺神经内分泌癌(mixed adenoneuroendocrine carcinoma, MANEC),以提高临床医师对本病的认识。**方法:**回顾性分析 1 例阑尾 GCC 合并回盲部 MANEC 患者的临床、病理特征、免疫组化及术后情况并进行文献复习。**结果:**该病例经病理切片会诊明确诊断为 GCC,行右半结肠切除术后进一步诊断为回盲部 MANEC,行 1 次 FOLFOX 化疗后,一般情况良好。**结论:**阑尾 GCC 合并回盲部 MANEC 是具有高度侵袭性的异质性恶性肿瘤,免疫组化局部 CgA 和局部 Syn 阳性、Tang 分类 C 组、临床分期 IV 期和非根治性手术为不良预后的危险因素。

关键词:阑尾;杯状细胞类癌;混合性腺神经内分泌癌

中图分类号:735.3+6 **文献标识码:**A **文章编号:**1673-6273(2019)07-1306-03

Goblet Cell Carcinoid of the Appendix with Hysteretic Mixed Adenoneuroendocrine Carcinoma: a Case Report and Literature Review*

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ABSTRACT Objective: To report an extremely rare case of appendiceal GCC with hysteretic MANEC that in order to improve clinicians' understanding of this disease. **Methods:** The clinical manifestations, pathology, expression of immunohistochemistry and the post-operative conditions in a case of appendiceal GCC patients with hysteretic MANEC was retrospectively analyzed and the related literature was reviewed. **Results:** The case was diagnosed as GCC by pathological section consultation, and further diagnosed as hysteretic MANEC after right hemicolectomy. After one cycle of FOLFOX chemotherapy, the general condition was good. **Conclusion:** The appendiceal GCC with hysteretic MANEC is a highly invasive heterogeneous malignant tumor. Focally positive staining pattern for CgA and Syn, Tang group C, clinical stage IV and non-radical surgery are risk factors for the poor prognosis.

Key words: Appendix; Goblet cell carcinoid; Mixed adenoneuroendocrine carcinoma

Chinese Library Classification(CLC): 735.3+6 **Document code:** A

Article ID: 1673-6273(2019)07-1306-03

前言

杯状细胞类癌(goblet cell carcinoid, GCC)是具有神经内分泌特征的罕见的侵袭性阑尾异质性肿瘤,占所有阑尾肿瘤的比例低于 14%^[1,2]。1974 年,Subbuswamy 等^[3]首先将其命名为杯状细胞类癌。在 GCC 上发展的腺癌构成混合型腺神经内分泌癌(mixed adenoneuroendocrine carcinoma, MANEC)的重要部分,腺癌组分是印戒细胞癌或低分化癌的形式^[4]。本文主要回顾性分析 1 例阑尾 GCC 合并回盲部 MANEC 患者的病例资料并进行相关文献复习,具体报道如下。

1 临床资料

患者男性,43 岁,因阑尾术后 18 天,病理诊断阑尾类癌 1

天入院。患者于 2018 年 06 月 22 日因右下腹疼痛不适在当地医院行阑尾切除手术,术后患者腹部持续性胀痛不适,伴有血便。2018 年 07 月 09 日携病理切片就诊于我院行病理切片会诊(2 名优秀病理科医师)提示(见图 1):杯状细胞类癌。参阅当地医院病例资料及询问病史:术中见阑尾充血肿胀,病变组织位于阑尾尖端,术后病理诊断示:阑尾腺癌,内分泌癌不排除,癌组织位于粘膜下层侵透肌层,大小约 1.5 cm,系膜、切缘及阑尾根部均未见癌组织。2018 年 07 月 10 日行腹部 CT 平扫示(见图 2):回盲部肠壁增厚,考虑肿瘤侵犯,周围见多发肿大淋巴结。2018 年 07 月 17 日行电子肠镜示(见图 3):回盲部见一不规则肿物突出官腔,考虑回盲部肿瘤。病理活检提示(见图 4):低分化腺癌,部分区域呈印戒细胞癌之分化;免疫组化:Villin(+),CDX2(+),CKp(+),ki67 为 50%,CgA(-),Syn(-);特殊染色:

* 基金项目:甘肃省自然科学基金项目(1506RJZA309)

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(收稿日期:2018-09-20 接受日期:2018-10-15)

AB/PAS(-)。2018年07月24日行右半结肠切除术。病理学特点(见图5:A,B,C,D):回盲瓣处见一溃疡型肿物,大小 3×2.5 cm,占据管腔 $1/3$ 。镜下见癌组织呈小巢状结构或弥漫呈片状,部分癌细胞形似印戒样,间质内纤维组织增生,炎细胞浸润;免疫组化:GST π (+),TP53为10%,CDX2(+),CgA(局部+),Syn

(局部+),Ki67为40%。病理诊断:(回盲部)溃疡型混合型腺神经内分泌癌,肿瘤由低分化腺癌(50%)和杯状细胞类癌(50%)构成,肿瘤大小 3×2.5 cm,癌组织侵及肠壁全层,未侵及浆膜,脉管内可见癌栓,标本阑尾残端、上下切缘、系膜侧切缘及吻合口切缘未见癌组织,淋巴结转移(0/17)。

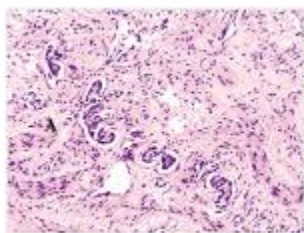


图1 阑尾 GCC 病理检查结果
(HE:×100)

Fig.1 Pathological results of
appendiceal GCC(HE:×100)



图2 CT 结果示:回盲部肠壁增
厚,周围见多发肿大淋巴结

Fig.2 CT results show: intestinal
wall of ileocecus was thickened and
multiple enlarged lymph nodes were
seen around



图3 肠镜示:回盲部突出一不规则
肿物,管腔狭窄

Fig.3 Colonoscopy results show:
ileocecus protrudes from an irregular
mass and lumen is narrow

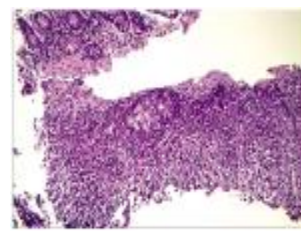


图4 回盲部低分化腺癌病理检查
结果(HE:×100)

Fig.4 Pathological results of the
ileocecal poorly differentiated
adenocarcinoma(HE:×100)

2 讨论

根据2010年WHO对阑尾神经内分泌肿瘤分类标准,除了阑尾经典类癌外,GCC和MANEC两个独立的实体肿瘤被确立。MANEC被认为由预先存在的GCC进展而来,具有更强的侵袭力和更差的预后^[2,5-7]。典型的GCC病理特征较为特异,

表现为黏膜下生长,肿瘤细胞呈杯状或印戒细胞样,由小而一致的细胞巢构成;MANEC包括GCC伴印戒细胞癌和GCC伴低分化腺癌两种病理类型。GCC是一种罕见的具有独特组织学特点的异质性肿瘤,几乎只发生于阑尾,约占阑尾类癌的6%^[8],目前认为GCC起源于黏膜下隐窝细胞的多能干细胞,具有神经内分泌及腺样分化的特征^[9]。

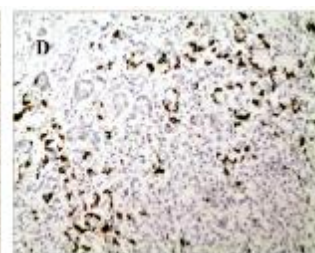
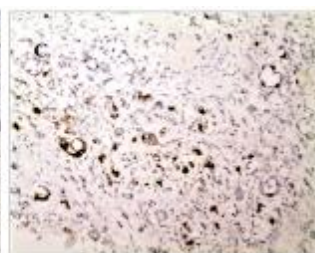
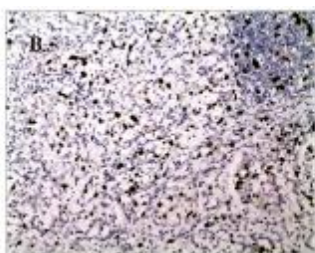
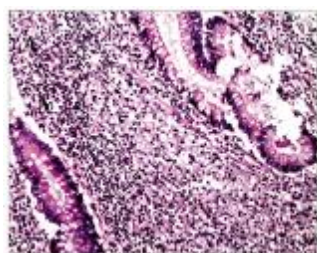


图5(A,B,C,D)右半结肠切除术后回盲部MANEC病理检查结果。A 癌巢由低分化腺癌和杯状细胞类癌构成,可见促纤维组织增生,炎细胞浸润(HE:×100);B 多数肿瘤细胞Ki-67免疫组化显著阳性(Ki-67:×100);C、D分别为CgA、Syn免疫组化结果:CgA和Syn呈明显的局灶性阳性(IHC:×100)

Fig.5(A,B,C,D) Pathological results of ileocecal MANEC, after right hemicolectomy: A The cancer nest consists of poorly differentiated adenocarcinoma and GCC, hyperplasia and inflammatory cell infiltration(HE:×100). B Immunohistological reaction with the Ki-67, Significant positivity of most tumor cells(Ki-67:×100). C, D are CgA, Syn immunohistochemistry results: Clearly focally positive of CgA and Syn(IHC:×100)

GCC最常累及阑尾尖端,其次是体部和基底部,常沿阑尾纵轴呈圆状弥漫浸润性生长,常因阑尾壁增厚导致管腔狭窄诱发阑尾炎症状而就诊,而以阑尾切除术后病理检查和免疫组化偶然发现,发病平均年龄为58岁,高于普通阑尾类癌发病年龄42岁,低于腺癌发病平均年龄62岁^[10-12]。典型的GCC中肿瘤细胞为三重表达:神经内分泌标记物CgA、Syn、CD56、NSE阳性,结肠上皮细胞标记物CK7、CK20、CEA、MUC2和CDX-2阳性,潘氏细胞Math-1和HD5阳性^[13],如果GCC伴有腺癌,则p53、MUC1和MUC2阳性^[14]。本例患者因阑尾炎症状行阑尾切除术,病变组织位于阑尾尖端,而回盲部为GCC伴有腺癌。

Tang等^[15]根据病理形态学特征将GCC患者分为三组(A、B、C)。典型的GCC(A组)被定义为分化好的杯状细胞,呈簇状

或条索状排列,细胞学异型性、阑尾壁破坏及促纤维增生不明显,可存在细胞外黏液变性;GCC伴腺癌,印戒细胞类型(B组)被定义为杯状细胞或印戒细胞排列成不规则的大簇,缺乏融合的单层细胞或单细胞浸润模式片状结构,细胞学异型性、阑尾壁破坏及促纤维增生明显;GCC伴腺癌,低分化癌类型(C组)定义为存在局灶性杯状细胞,同时可见难与未分化或低分化腺癌相区别的区域(>1个低倍镜视野或1 mm²),Tang分类已被证明可用于预测临床行为和预后^[5-7,10,16]。ENETS-2007病理TNM分期中,肿瘤大小<1 cm为T1,肿瘤大小≤2 cm伴有浆膜下或阑尾系膜入侵<3 mm为T2,肿瘤大小>2 cm伴有浆膜下或阑尾系膜入侵>3 mm为T3,肿瘤伴有腹膜或其他器官入侵是T4。本病例肿瘤位于阑尾尖端及回盲部,阑尾尖端肿瘤为

典型的GCC,符合Tang分类A组,回盲部为MANEC,由低分化腺癌细胞和杯状细胞类癌细胞相互浸润,符合Tang分类C组。病理分期为T4期,无淋巴结及腹膜转移。

由于GCC的罕见性及人们对其生物学行为认识不足,GCC患者的管理仍面临巨大挑战,因为缺乏特异的生物学标记物及临床特征,其通常在阑尾切除术后偶然诊断。虽然限于阑尾的疾病的五年生存率在50%-80%,但在远处转移的情况下,却不到20%^[16]。近年来一项大样本量荟萃分析期显示GCC、MANEC生存期(OS)分别为13.8年、6.5年,而若为临床IV期,OS却只有1.9年和1.5年^[11]。由于GCC、MANEC的不良预后,Olsen及其同事^[10]报告的一项由83名患者组成的覆盖了约75%的丹麦人群的队列研究,结果显示GCC中局部CgA和局部Syn阳性、临床分期IV期和非根治性手术为不良预后的危险因素。Tang分类C组患者的Ki67中位数显著高于Tang分类A组和B组患者,确认Tang分类是一个重要的预后因素,而Ki67指数与总体生存率无关,但Ki67指数与Tang分类相关。

本案例患者肿瘤位于阑尾尖端,癌组织位于粘膜下层侵袭肌层,大小约1.5cm,系膜、切缘及阑尾根部均未见癌组织。根据中国胃肠胰神经内分泌肿瘤专家共识(2016版)^[17],该患者属于低度恶性,具有较好的预后,单纯行阑尾切除术即可。其特殊之处在于患者行阑尾切除术后腹部持续性胀痛不适,伴有血便,进一步检查及手术发现合并回盲部混合型腺神经内分泌癌,虽未见腹腔及淋巴结转移,但合并了Tang分类C组、临床分期IV期、高Ki67指数、脉管癌栓、局部CgA和局部Syn阳性等不良预后危险因素,若无术后持续腹部胀痛不适及血便,行右半结肠切除术,患者将会有更差的预后。该患者已根据2012年ENETS指南^[18]行FOLFOX化疗方案化疗一次,现未见任何临床症状,仍在进一步随访中。

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