doi: 10.3978/j.issn.2095-6959.2022.10.038
View this article at: https://dx.doi.org/10.3978/j.issn.2095-6959.2022.10.038

·临床病例讨论·

结肠肝样腺癌 1 例

王瀚[1,2]，尹书怡[2]，白辰光[2]

(1. 海军军医大学东方肝胆外科医院病理科，上海 200438；2. 海军军医大学长海医院病理科，上海 200433)

[摘　要] 肝样腺癌是一种罕见的腺癌组织病理学亚型，相对常见于胃，少见于肠道。海军军医大学长海医院收治了1例44岁男性乙状结肠原发性肝样腺癌病例。肿瘤组织主要呈梁索状、巢片状排列，细胞呈大多角形，细胞质丰富嗜酸性，核大深染，异型明显。免疫组织化学示AFP、Arginase-1、Glypican-3、CDX-2阳性，不表达CgA、Syn。患者手术后预后不佳。结肠肝样腺癌是一种独特的肠腺癌亚型，诊断高度依赖于病理，生物学行为恶性程度高，需予以重视。

[关键词] 肝样癌；肠道；甲胎蛋白

Hepatoid adenocarcinoma of colon: A case report

WANG Han[1,2], YIN Shuyi[2], BAI Chenguang[2]

*(1. Department of Pathology, Eastern Hepatobiliary Surgery Hospital, Naval Medical University, Shanghai 200438;
2. Department of Pathology, Changhai Hospital, Naval Medical University, Shanghai 200433, China)*

Abstract Hepatoid adenocarcinoma is a peculiar histopathological subtype of adenocarcinoma, which occurs commonly in the stomach and rarely in the intestine. A 44-year-old male patient with primary hepatoid adenocarcinoma located at the sigmoid colon was admitted to Changhai Hospital of Naval Medical University. The tumor tissue was mainly arranged in the shape of beam cord and nest, with large polygonal cells, abundant eosinophilic cytoplasm, large and hyperchromatic nuclei, and obvious atypia. AFP, Arginase-1, Glypican-3, and CDX-2 were positive, but CgA and Syn were negative by immunohistochemistry. The patient's prognosis after surgery was poor. Hepatoid adenocarcinoma of the colon is an independent subtype of adenocarcinoma of the intestine. The diagnosis is highly dependent on pathology, with high malignancy in biological behavior, which should be paid more attention to.

Keywords hepatoid carcinoma; intestine; alpha fetoprotein

肝样腺癌是一种伴随显著的肝细胞方向分化的罕见腺癌病理组织学亚型，可特征性地分泌甲胎蛋白(alpha fetoprotein，AFP)，病理形态上具有相似于肝细胞癌的梁索状排列方式以及大多角形的嗜酸性肿瘤细胞[1]。肝样腺癌生物学行为恶性程度高，预后差，因此需要引起重视，准确诊断。肝样腺癌可发生在身体各部位，相对好发于胃，罕见发生于结肠[2]。本文报道了1例发生于乙状结肠的肝样腺癌患者的临床病理特征及治疗预后情况，并复习相关文献，旨在提供临床诊治经验。

收稿日期 (Date of reception)：2022–04–28
通信作者 (Corresponding author)：白辰光，Email: bcg709@126.com
基金项目 (Foundation item)：国家自然科学基金 (81472276)。This work was supported by the National Natural Science Foundation of China (81472276).

1 临床资料

患者，男，44岁，无高血压、糖尿病、冠心病史，吸烟10余年，20支/d，平日少量饮酒。2017年12月正电子发射计算机断层显像(positron emission tomography-computed tomography，PET-CT)示乙状结肠局部肠壁增厚并氟代脱氧葡萄糖代谢增高，考虑肠癌伴浆膜面浸润，周围肠系膜多发淋巴结转移。行肠镜发现乙状结肠单发溃疡型肿物(图1A)，活体组织检查提示腺癌。下腹部增强CT显示乙状结肠癌伴周围淋巴结转移(图1B)，上腹部增强MRI显示肝脏无占位性病变。术前AFP>2 000 ng/mL，CEA 1.22 ng/mL，CA199 2.18 U/mL。无乙型肝炎和丙型肝炎。

患者于2017年12月遂行乙状结肠癌经腹前切除术(微创)+广泛肠粘连松解术。送检标本肉眼观：肠管一段，长11 cm，周径4.5~6.0 cm，距上切端4.5 cm、下切端3.5 cm，腹膜反折上见溃疡型肿物，大小3.0 cm×4.0 cm×0.8 cm，切面灰白色，实性，质硬。结肠系膜找到淋巴结29枚，直径0.1~1.5 cm。另送肠系膜下动脉根部淋巴结1枚，直径0.2 cm。吻合圈2个，共大小2 cm×2 cm×1 cm。镜下观：肿瘤组织主要呈梁索状、巢片状、筛孔状排列，少部分区域呈腺管状，大部分管腔内可见浆液，少部分管腔内见黏液。绝大部分肿瘤细胞呈大多角形，细胞质丰富嗜酸性，核大深染，异型明显(图2~4)，在分泌黏液的腺管状区域，肿瘤细胞呈柱状，细胞质内含黏液。肿瘤内可见灶性坏死，间质纤维组织较丰富，可见脉管癌栓和神经侵犯(图5、6)。肿瘤侵犯肠壁浆膜下层，结肠系膜淋巴结见肿瘤组织(19/29)，肠系膜下动脉根部淋巴结未见肿瘤组织(0/1)，标本两端切缘、环周切缘、吻合圈未见肿瘤组织。免疫组织化学示肿瘤组织AFP、Arginase-1、Glypican-3、CDX-2阳性(图7、8)，分泌黏液的腺管状区域只有CDX-2阳性。MLH-1、MSH-2、MSH-6、PMS-2阳性，CgA、Syn、NSE阴性，p53为野生型，Ki-67约为50%+。基因检测示*KRAS*、*NRAS*、*BRAF*、*PIK3CA*基因均为野生型。诊断为(乙状结肠)低分化肝样腺癌合并少量低分化管状腺癌，TNM分期为IIIC期(pT3N2bM0)。

患者手术切口愈合良好。于2018年1月行增强MRI发现右肝门静脉癌栓，于2018年2月始以mFOLFOX6方案行全身化疗，4个疗程后于2018年5月行右半肝+胆囊切除术，同时切除右肝门静脉癌栓。2018年6月行PET-CT发现肿瘤累及左肝门静脉，继续以mFOLFOX6方案行全身化疗，4个疗程后停止。2018年8月始注射爱必妥，口腔溃疡不良反应严重。2018年9月行PET-CT发现左肝门静脉癌栓合并肝脏多发转移性肿瘤，停用爱必妥。2018年10月起行肝局部放疗15次，效果不佳。2019年1月检查出现大量腹水，姑息处理后于2019年2月死亡。

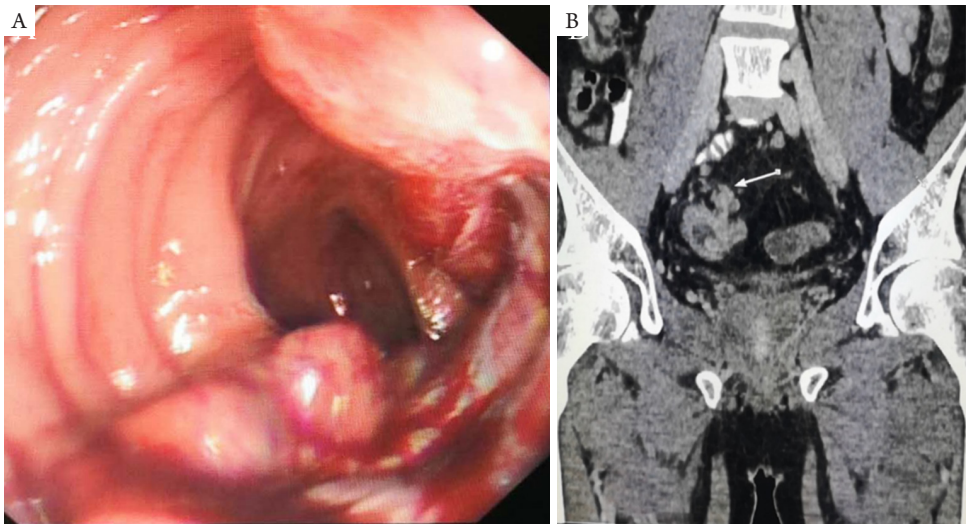

图1 内镜及影像表现

Figure 1 Endoscopic and imaging features

(A)内镜示溃疡型肿物；(B)下腹部CT示肠道肿物。

(A) An ulcerative mass was showed by endoscopy; (B) CT scan of the lower abdomen showed a mass in colon.

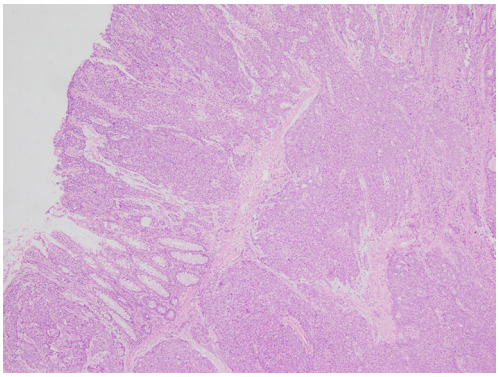

图2 肿瘤组织呈巢片状、梁索状排列，于肠壁浸润性生长(HE染色，×40)

Figure 2 The tumor tissues are arranged in a sheet and trabecular pattern, and infiltrated into the bowel wall (HE staining, ×40)

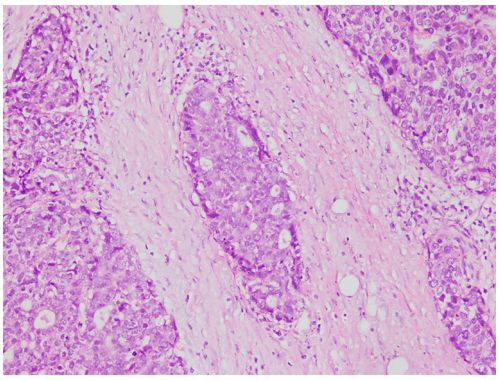

图5 肿瘤内见脉管癌栓(HE染色，×200)

Figure 5 Vessel carcinoma embolus is found in the tumor (HE staining, ×200)

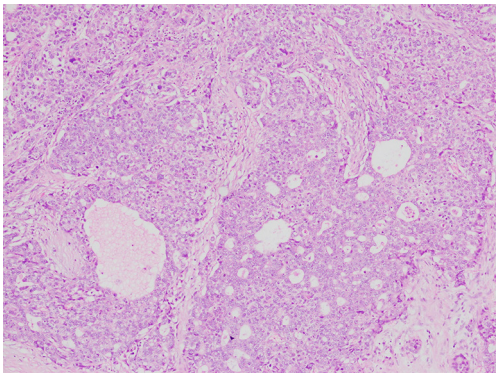

图3 肿瘤组织可见假腺样结构，腔内含浆液(HE染色，×100)

Figure 3 Pseudoglandular structure is formed in the tumor, and there is serous fluid in the lumen (HE staining, ×100)

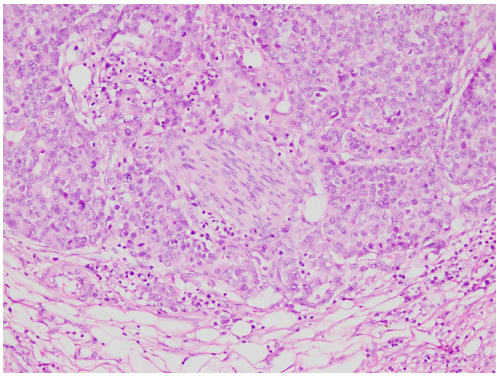

图6 肿瘤内见神经侵犯(HE染色，×200)

Figure 6 Perineural invasion is seen in the tumor (HE staining, ×200)

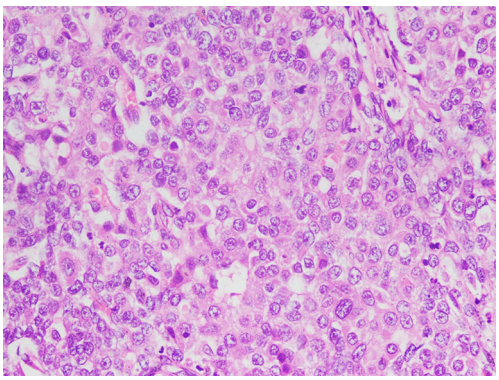

图4 肿瘤细胞呈大多角形，细胞质嗜酸性，核呈空泡状，可见核仁(HE染色，×400)

Figure 4 The tumor cells are large polygonal, with eosinophilic cytoplasm, and the nucleus is vacuolar with visible nucleoli (HE staining, ×400)

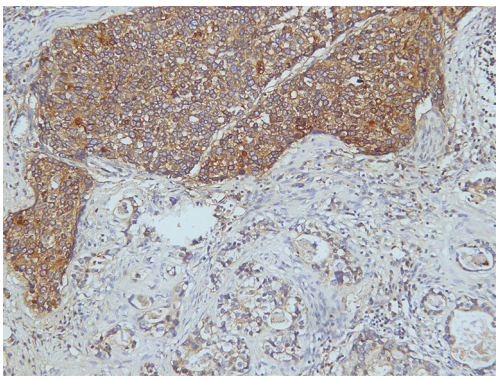

图7 肝样腺癌区域示AFP阳性，管状腺癌区域阴性(EnVision，×200)

Figure 7 AFP is positive in hepatoid adenocarcinoma but negative in tubular adenocarcinoma (EnVision, ×200)

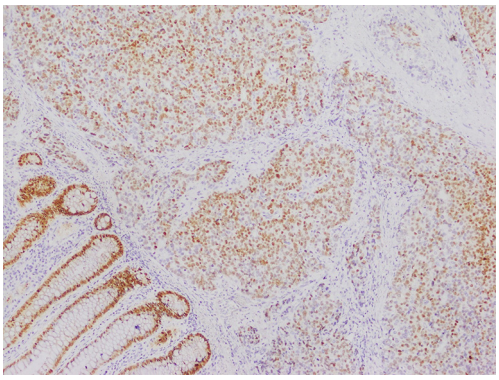

图8 CDX2在肝样腺癌区域阳性表达(EnVision，×100)

Figure 8 The expression of CDX2 is positive in the area of hepatoid adenocarcinoma (EnVision, ×100)

2 讨论

1985年，Ishikura等[3]首次报道了以产生AFP并出现肝样分化形态为特征的胃肝样腺癌。随后有研究[4-6]陆续发现肝样腺癌也可出现在其他器官。肠道是肝样腺癌的少见发病部位[7]，迄今仍未作为独立亚型写入第5版《世界卫生组织消化系统肿瘤分类》。本文报道了1例发生于乙状结肠的肝样腺癌患者，经过详细的影像学和病理学检查，证实肿瘤为肠道原发，提示了该类肿瘤发病部位的多样性，丰富了该疾病的认识。

在基本特征方面，一项纳入42例肠道肝样腺癌患者的研究[8]提示该病好发于60岁以下男性，与本例情况相同。此外，目前尚无肝样腺癌的环境相关风险因素，本例患者也没有肝炎病毒感染和大量酒精摄入等肝细胞癌常见风险因素[9]，因此病史有助于鉴别肠道原发性肝样腺癌与发生肠道转移的肝细胞癌。值得注意的是，已有多篇研究[10-12]报道了在炎症性肠病基础上发生的肝样腺癌，虽然尚不明确两者是否存在特殊的关联机制，但建议在诊断肠道肝样腺癌病例时关注周围肠黏膜改变。本例未发现炎症性肠病的证据。在实验室检查方面，有研究[13]报道AFP高值提示临床不良预后，本例AFP值极高，也与患者的临床转归相符合，因此，笔者建议一方面应对肠癌患者进行术前常规筛查AFP协助诊断，另一方面对伴AFP升高的肝样腺癌患者，可定期复查该指标以协助判断肿瘤复发和转移。该病影像学与内镜表现无显著特征，尚无法通过无创性检查与普通型结肠管状腺癌相鉴别[14]。此外，笔者认为上腹部影像学检查很有必要，可协助排除原发性肝细胞癌转移到肠道，本例术前影像学检查发现肝无占位性病变，可以较好地提示肿瘤非肝脏原发。

该病确诊高度依赖病理，组织形态联合免疫组织化学是有效的诊断方式。该病在组织形态上明显不同于普通的肠腺癌，肿瘤组织呈梁索状、巢片状排列，而非腺管状，本例患者肿瘤组织部分区域可见筛孔状或腺管状结构，但腺管内容物大部分为浆液，而非黏液，因此大部分腺管状结构为假腺管而非真腺管，此特点与肝细胞癌高度相似[15]。肿瘤细胞也非普通肠腺癌的高柱状富黏液细胞，而是具有嗜酸性颗粒状细胞质的大多角形细胞。不同于神经内分泌肿瘤，该病肿瘤细胞核不表现为胡椒盐样，而表现为空泡状，可伴显著的核仁。免疫组织化学在诊断和鉴别诊断中具有重要意义，一方面AFP、Arginase-1、Glypican-3等肝细胞癌标志物表达[16-17]，提示肿瘤与肝细胞高度相关，另一方面，肠癌标志物CDX-2的表达可协助排除肝细胞癌转移到肠道[18]。本例肿瘤生物学行为恶性程度高，出现脉管癌栓、神经侵犯、淋巴结转移。一项胃肝样腺癌的研究[19]也提示淋巴结转移和神经侵犯是不良预后的重要风险因素，说明病理学的全面评估在肝样腺癌诊断中具有重要价值。

在治疗方面，有学者[20]发现肝样腺癌的手术治疗预后显著优于非手术治疗，本例患者也对肠腺癌的传统放化疗手段反应不佳，相关方案并未取得良好的治疗反应。且该肿瘤具有嗜肝性，具体表现为术后短期内出现门静脉癌栓。因此该病在生物学行为上可能更类似于肝细胞癌而非肠腺癌。鉴于此，有研究[21]应用索拉菲尼治疗肝样腺癌，免疫检查点抑制剂的出现也拓宽了肝样腺癌的治疗思路[22-23]。上述治疗方式值得在未来进一步探索。

在发病机制方面，由于极低的发病率，目前还没有针对肠肝样腺癌的分子层面的探索。一项有关胃肝样腺癌的研究[24]认为肿瘤中的普通腺癌成分与肝样腺癌成分为同一克隆起源。另一项测序研究[25]也得出相同的结论，并认为这类肿瘤可能起源于多能前体细胞。该研究同时发现：与传统胃腺癌相比，肝样腺癌具有高度干细胞性和蛋氨酸循环高活性。蛋氨酸循环中的基因*MAT2A*和*AHCY*是肝样腺癌治疗的潜在靶点。结合本病例，形态学上管状腺癌区域与肝样腺癌区域分布关系密切，并且共同表达肠源性标记CDX2，因此笔者推测为单克隆起源。另一项关于肺肝样腺癌的基因组学研究[20]提示：肺肝样腺癌最常见的突变基因是*TP53*，突变率为100%。此外，*CDK8*、

CDKN2A、*EPHA5*、*SMARCA4*和*STK11*基因也为高频突变，突变率为50%。*TP53*基因突变在胃[26]、肾上腺[27]的肝样腺癌中也有报道。但是，2021年美国和加拿大病理学会年会的一篇摘要报道了20例不同器官的肝样腺癌的测序研究[28]显示：*TP53*基因突变虽然在各器官的肝样腺癌中都被检出，但其突变率仅为40%；此外，不同器官的肝样腺癌可能有截然不同的分子表达谱。本例p53为野生型表达，提示不同器官不同病例的肝样腺癌可能存在多样化的发病途径，仍需要更大规模的分子层面的研究去深入挖掘。

综上所述，结肠肝样腺癌是一种罕见且高度恶性的肿瘤。血清AFP高值提示不良预后。其确诊高度依赖病理，形态学上肿瘤排列呈巢片状、梁索状，肿瘤细胞呈大多角形，以及免疫组织化学表达肝源性标志具有较大提示作用，肠源性标志物的表达结合影像学检查能较好地与肝细胞癌肠道转移进行鉴别。肠肝样腺癌生物学行为恶性程度高，易产生脉管癌栓、神经侵犯、淋巴结转移等提示恶性行为的病理学现象。本例对肠癌的手术和非手术治疗均反应不佳，仍需进一步探索更好的治疗方案。

参考文献

1. Kishimoto T, Nagai Y, Kato K, et al. Hepatoid adenocarcinoma: a new clinicopathological entity and the hypotheses on carcinogenesis[J]. Med Electron Microsc, 2000, 33(2): 57-63.
2. 张继新, 崔力方, 周全, 等. 结肠肝样腺癌1例并文献复习[J]. 临床与实验病理学杂志, 2013, 29(12): 1366-1368.
   ZHANG Jixin, CUI Lifang, ZHOU Quan, et al. Hepatoid adenocarcinoma of colon: a case report and literature review[J]. Chinese Journal of Clinical and Experimental Pathology, 2013, 29(12): 1366-1368.
3. Ishikura H, Fukasawa Y, Ogasawara K, et al. An AFP-producing gastric carcinoma with features of hepatic differentiation. A case report[J]. Cancer, 1985, 56(4): 840-848.
4. Qian X, Zhou D, Gao B, et al. An alpha-fetoprotein-negative hepatoid adenocarcinoma of the gallbladder with squamous differentiation[J]. Hepatobiliary Surg Nutr, 2020, 9(1): 116-118.
5. Choi WK, Cho DH, Yim CY, et al. Primary hepatoid carcinoma of the ovary: a case report and review of the literature[J]. Medicine (Baltimore), 2020, 99(19): e20051.
6. 王瀚, 丛文铭, 郑建明, 等. 胰腺肝样腺癌3例临床病理学分析[J]. 诊断病理学杂志, 2021, 28(6): 452-455, 460.
   WANG Han, CONG Wenming, ZHENG Jianming, et al. Clinicopathological characteristics of pancreatic hepatoid adenocarcinoma: report of three cases[J]. Chinese Journal of Diagnostic Pathology, 2021, 28(6): 452-455, 460.
7. 胥子玮, 朱春燕, 封益飞, 等. 结肠肝样腺癌误诊为原发性肝癌一例并文献回顾[J]. 中华结直肠疾病电子杂志, 2019, 8(1): 80-84.
   XU Ziwei, ZHU Chunyan, FENG Yifei, et al. Colon hepatic adenocarcinoma misdiagnosed as primary liver cancer: case report and literature review[J]. Chinese Journal of Colorectal Diseases. Electronic Edition, 2019, 8(1): 80-84.
8. Zeng X, Zhang P, Xiao H, et al. Clinicopathological features and prognosis of intestinal hepatoid adenocarcinoma: evaluation of a pooled case series[J]. Oncotarget, 2018, 9(2): 2715-2725.
9. 国家卫生健康委办公厅. 原发性肝癌诊疗指南(2022年版)[J]. 临床肝胆病杂志, 2022, 38(2): 288-303.
   General Office of National Health Commission. Standard for diagnosis and treatment of primary liver cancer (2022 edition)[J]. Journal of Clinical Hepatology, 2022, 38(2): 288-303.
10. Lattes C, Carella R, Faggioli S, et al. Hepatoid adenocarcinoma of the rectum arising in ulcerative colitis: report of a case[J]. Dis Colon Rectum, 2000, 43(1): 105-108.
11. Borgonovo G, Razzetta F, Assalino M, et al. Rectal hepatoid carcinoma with liver metastases in a patient affected by ulcerative colitis[J]. Hepatobiliary Pancreat Dis Int, 2008, 7(5): 539-543.
12. Chen Y, Schaeffer DF, Yoshida EM. Hepatoid adenocarcinoma of the colon in a patient with inflammatory bowel disease[J]. World J Gastroenterol, 2014, 20(35): 12657-12661.
13. Zhou K, Wang A, Ao S, et al. The prognosis of hepatoid adenocarcinoma of the stomach: a propensity score-based analysis[J]. BMC Cancer, 2020, 20(1): 671.
14. Huang WP, Li LM, Li J, et al. Computed tomography features and clinical prognostic characteristics of hepatoid adenocarcinoma of the stomach[J]. Front Oncol, 2021, 11: 772636.
15. Torbenson MS. Hepatocellular carcinoma: making sense of morphological heterogeneity, growth patterns, and subtypes[J]. Hum Pathol, 2021, 112: 86-101.
16. Chandan VS, Shah SS, Torbenson MS, et al. Arginase-1 is frequently positive in hepatoid adenocarcinomas[J]. Hum Pathol, 2016, 55: 11-16.
17. 王瀚, 丛文铭, 郑建明, 等. 胃肝样腺癌17例临床病理分析[J]. 临床与实验病理学杂志, 2021, 37(1): 75-77.
   WANG Han, CONG Wenming, ZHENG Jianming, et al. Clinicopathological analysis of 17 cases of hepatoid adenocarcinoma of stomach[J]. Chinese Journal of Clinical and Experimental Pathology, 2021, 37(1): 75-77.
18. Mikaeel RR, Young JP, Tapia Rico G, et al. Immunohistochemistry features and molecular pathology of appendiceal neoplasms[J]. Crit

Rev Clin Lab Sci, 2021, 58(6): 369-384.

19. Lin JX, Wang ZK, Hong QQ, et al. Assessment of clinicopathological characteristics and development of an individualized prognostic model for patients with hepatoid adenocarcinoma of the stomach[J]. JAMA Netw Open, 2021, 4(10): e2128217.
20. Hou Z, Xie J, Zhang L, et al. Hepatoid adenocarcinoma of the lung: a systematic review of the literature from 1981 to 2020[J]. Front Oncol, 2021, 11: 702216.
21. Petrelli F, Ghilardi M, Colombo S, et al. A rare case of metastatic pancreatic hepatoid carcinoma treated with sorafenib[J]. J Gastrointest Cancer, 2012, 43(1): 97-102.
22. Li W, Li Q, Yu Y, et al. Effect of immune checkpoint inhibitors plus chemotherapy on advanced gastric cancer patients with elevated serum AFP or hepatoid adenocarcinoma[J]. Cancer Manag Res, 2020, 12: 11113-11119.
23. Sun Y, Chang W, Yao J, et al. Effect of immune checkpoint inhibitors in patients with gastric hepatoid adenocarcinoma: a case report and literature review[J]. J Int Med Res, 2022, 50(4): 3000605221091095.
24. Akiyama S, Tamura G, Endoh Y, et al. Histogenesis of hepatoid adenocarcinoma of the stomach: molecular evidence of identical origin with coexistent tubular adenocarcinoma[J]. Int J Cancer, 2003, 106(4): 510-515.
25. Liu Z, Wang A, Pu Y, et al. Genomic and transcriptomic profiling of hepatoid adenocarcinoma of the stomach[J]. Oncogene, 2021, 40(38): 5705-5717.
26. Kang M, Ma X, Shi J, et al. Distinct molecular phenotype and the potential prognostic value of immune prognostic index and tumor infiltrating lymphocytes in hepatoid adenocarcinoma of stomach[J]. Transl Oncol, 2022, 19: 101380.
27. Lin J, Cao Y, Yu L, et al. Non-α-fetoprotein-producing adrenal hepatoid adenocarcinoma: a case report and literature review[J]. Medicine (Baltimore), 2018, 97(39): e12336.
28. Abstracts from USCAP 2021: gastrointestinal pathology (311-404)[J]. Lab Invest, 2021, 101(1): 395-514.

本文引用： 王瀚, 尹书怡, 白辰光. 结肠肝样腺癌1例[J]. 临床与病理杂志, 2022, 42(10): 2587-2592. doi: 10.3978/j.issn.2095-6959.2022.10.038

Cite this article as: WANG Han, YIN Shuyi, BAI Chenguang. Hepatoid adenocarcinoma of colon: A case report[J]. Journal of Clinical and Pathological Research, 2022, 42(10): 2587-2592. doi: 10.3978/j.issn.2095-6959.2022.10.038