

[文章编号] 1671-587X(2026)02-0523-07

DOI:10.13481/j.1671-587X.20260225

SMARCB1/INI1 缺失型未分化胰腺癌 1 例报告及文献复习

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[摘 要] 酵母交配型转换/蔗糖不发酵 (SWI/SNF) 相关基质关联肌动蛋白依赖性染色质亚家族 B 成员 1 (SMARCB1) /整合酶相互作用分子 1 (INI1) (SMARCB1/INI1) 缺失型未分化胰腺癌 (UPC) 是一种极为罕见的胰腺癌特殊类型。本文作者报道 1 例 SMARCB1/INI1 缺失型 UPC 患者的临床表现、辅助检查和诊治经过, 并进行相关文献复习。患者, 女性, 65 岁, 因间断性上腹痛 1 个月余, 加重伴恶心、呕吐 9 d 入院。曾于外院行全腹部 CT 提示胰腺占位性病变。入院查体显示上腹部压痛, 无反跳痛或肌紧张。实验室检查, 糖类抗原 199 (CA199) 水平为 $50.58 \text{ U} \cdot \text{mL}^{-1}$, 空腹血糖为 $9.98 \text{ mmol} \cdot \text{L}^{-1}$ 。腹部 MRI 显示胰腺体尾部见囊实混合异常信号影, 呈不规则向胰腺外隆起; T1 加权成像 (T1WI) 呈稍低信号, 瘤体出血部分呈高信号; T2 加权成像 (T2WI) 呈高信号, 边界不清, 大小为 $2.0 \sim 5.6 \text{ cm}$, 致胃壁受压、受侵; 增强扫描示肿瘤囊壁呈明显环形强化, 脾动脉和静脉受侵, 门静脉栓子形成。胃镜见胃体大弯侧有 $4.0 \text{ cm} \times 5.0 \text{ cm}$ 的黏膜隆起, 考虑胰腺占位压迫所致。临床诊断为胰腺占位性病变, 恶性肿瘤可能性大, 手术切除为首选治疗方案。术后病理诊断为 SMARCB1/INI1 缺失型 UPC, 伴少量中分化鳞状细胞癌成分。患者术后接受化疗, 已随访 5 个月, 生活质量较术前改善, 无明显不适, 仍在密切随访中。SMARCB1/INI1 缺失型 UPC 较为罕见, 临床表现缺乏特异性, 通常进展迅速且预后不良, 临床中应争取尽早诊治。

[关键词] 胰腺肿瘤; SMARCB1/INI1 缺失型; 未分化肿瘤; 影像学表现; 病例报告

[中图分类号] R735.9 **[文献标志码]** B

SMARCB1/INI1-deficient undifferentiated pancreatic carcinoma: A case report and literature review

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ABSTRACT Switch/sucrose non-fermentable (SWI/SNF)-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1)/integrase interactor 1 (INI1) (SMARCB1/INI1)-deficient undifferentiated pancreatic carcinoma (UPC) is an extremely rare special type of pancreatic cancer. This article reported the clinical manifestations, auxiliary examinations, diagnosis, and treatment of a patient with

[收稿日期] 2025-06-12 [录用日期] 2025-07-29

[基金项目] 吉林省卫健委卫生健康技术创新项目 (2019J050)

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SMARCB1/INI1-deficient UPC, and reviewed the relevant literature. The patient, a 65-year-old female, was admitted due to intermittent upper abdominal pain for more than one month, aggravated with nausea and vomiting for 9 d. The abdominal CT scan performed at another hospital suggested a pancreatic space-occupying lesion. The physical examination results on admission revealed upper abdominal tenderness, without rebound tenderness or muscle guarding. The laboratory tests results showed a carbohydrate antigen 199 (CA199) level of $50.58 \text{ U}\cdot\text{mL}^{-1}$ and a fasting blood glucose level of $9.98 \text{ mmol}\cdot\text{L}^{-1}$. The abdominal MRI results revealed a mixed cystic and solid abnormal signal in the pancreatic body and tail, showing irregular extraluminal protrusion; it appeared as a slightly hypointense signal on T1-weighted imaging (T1WI), with the hemorrhagic part of the tumor appearing hyperintense; it appeared as a hyperintense signal on T2-weighted imaging (T2WI) with unclear boundaries, measuring 2.0—5.6 cm, causing compression and invasion of the gastric wall; enhanced scanning showed obvious rim enhancement of the tumor capsule, invasion of the splenic artery and vein, and portal vein thrombus formation. The gastroscopy results revealed a 4.0 cm×5.0 cm mucosal elevation on the greater curvature of the gastric body, considered to be caused by compression from the pancreatic mass. The clinical diagnosis was a pancreatic space-occupying lesion, highly suspected to be malignant, with surgical resection being the preferred treatment option. The postoperative pathological diagnosis was *SMARCB1/INI1*-deficient UPC with a small component of moderately differentiated squamous cell carcinoma. The patient received chemotherapy after surgery and has been followed up for 5 months, with an improved quality of life compared to before surgery, no significant discomfort, and remains under close follow-up. *SMARCB1/INI1*-deficient UPC is relatively rare, with non-specific clinical manifestations, usually progressing rapidly and associated with a poor prognosis; therefore, early diagnosis and treatment should be pursued in clinical practice.

KEYWORDS Pancreatic neoplasm; *SMARCB1/INI1* deficiency; Undifferentiated carcinoma; Imaging manifestation; Case report

未分化胰腺癌(undifferentiated pancreatic carcinoma, UPC)是一种罕见的胰腺肿瘤组织学亚型,由NISHIHARA等^[1]于1997年首次报道,其占胰腺肿瘤的2%~3%^[2],与传统胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)比较,UPC预后通常较差。国内外相关研究^[3-5]表明:UPC常具有更强的侵袭性和不良预后,临床表现缺乏特异性,血清学及影像学诊断困难,多数患者确诊时已进展至中晚期,转移率更高;不可切除病例的中位生存期约为4个月。作为酵母交配型转换/蔗糖不发酵(switch/sucrose non-fermentable, SWI/SNF)染色质重塑复合物的核心亚基,SWI/SNF相关基质关联肌动蛋白依赖性染色质亚家族B成员1(SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1, *SMARCB1*),亦称整合酶相互作用分子1(integrase interactor-1, *INI1*),广泛表达于机体所有组织的细胞核中,参与细胞发育和分化,并具有肿瘤抑制作用^[6]。该基因缺失可通过多种机制促进肿瘤发生发展。目前,国内外关于*SMARCB1/*

*INI1*缺失型UPC的报道较为罕见,全球仅10余例^[7-12],国内仅见1例报道^[13]。本文报道的患者病理类型尤为特殊,包含具有多形性瘤巨细胞和横纹肌样细胞形态的未分化癌成分及鳞状细胞癌成分,该混合表型在国内外均尚未见报道。本文作者通过分析该患者的临床表现、影像学特征、病理学特点和诊治过程,结合文献复习,旨在提高临床医生对该罕见疾病的认识,为UPC的诊断和治疗提供参考。

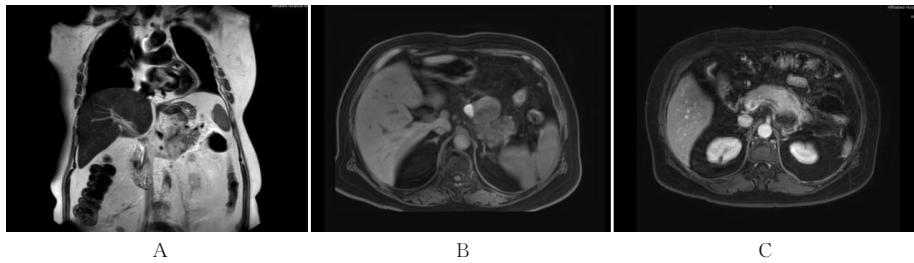
1 临床资料

1.1 一般资料 患者,女性,65岁,因间断性上腹痛1个月余,加重伴恶心和呕吐9 d,于2025年1月入住本院普通外科。患者入院1周前于外院行全腹CT检查提示胰腺占位性病变。入院后患者神志清楚,食欲欠佳,大小便无异常。专科查体:腹部平坦,上腹部有压痛,无反跳痛或肌紧张,肝脾肋下未触及,墨菲氏征阴性,移动性浊音阴性。

1.2 辅助检查 血常规、凝血功能、肝功能、肾功能及电解质等相关检查结果均正常。肿瘤标志物糖类抗原199(carbohydrate antigen 199, CA199)

水平为 $50.58 \text{ U}\cdot\text{mL}^{-1}$, 空腹血糖为 $9.98 \text{ mmol}\cdot\text{L}^{-1}$ 。心电图、心脏彩超和胸部CT均未见明显异常。腹部MRI: 胰腺体和尾部见囊实混合异常信号影, 呈不规则向胰腺外隆起; T1加权成像(T1-weighted imaging, T1WI)呈稍低信号, 瘤体出血部分呈高信号; T2加权成像(T2-weighted imaging, T2WI)呈高信号, 边界不清, 大小为 $2.0\sim 5.6 \text{ cm}$, 与胃

壁分界不清, 胃壁受压、受侵。增强扫描: 肿瘤囊壁呈明显环形强化, 脾动脉和静脉受侵, 门静脉内可见栓子形成。影像学诊断胰腺占位性病变, 考虑为胰腺癌伴胃壁和脾动、静脉受侵。见图1。胃镜检查: 胃体大弯侧可见1枚大小为 $4.0 \text{ cm}\times 5.0 \text{ cm}$ 的黏膜隆起病变(图2), 考虑为胰腺肿瘤压迫胃壁所致。



A: T2WI coronal; B: T1WI axial pressure-lipid sequence; C: T1WI axial enhancement scan delay period.

图1 *SMARCB1/INI1* 缺失型UPC患者MRI图像

Fig. 1 MRI images of *SMARCB1/INI1*-deficient UPC patient

1.3 治疗 结合患者临床表现和辅助检查结果, 临床诊断为胰腺占位性病变(胰腺癌可能性大)。完善术前评估后, 决定行全身麻醉下经腹腔镜剖腹探查术。术中探查肝、胆、网膜、胃十二指肠和结肠等腹腔脏器, 可见胰体尾部一肿瘤, 大小为 $5.0 \text{ cm}\times 2.5 \text{ cm}\times 2.0 \text{ cm}$; 胃后壁局部受侵, 考虑为局部晚期病变, 可考虑进行根治性切除。由于游离胰体尾过程中渗血较多, 遂中转开腹。取左上腹旁正中切口, 逐层切开, 进一步探查见胰体尾肿瘤侵犯胃体大弯侧后方, 与胃壁及脾动静脉黏连无法分离, 决定行胰体尾切除、脾切除和胃部分切除术。术中见瘤体张力较大, 切开后部分脓血性液体溢出, 肿瘤为囊实性, 伴有出血、坏死和脓腔形成, 经手术操作完整取出肿瘤。见图3。患者术后经对症治疗, 逐渐恢复出院。术后第4周, 患者开始接受辅助化疗, 第1周期化疗采用FOLFIRINOX方案, 但患者出现严重腹泻等消化道症状, 故第2、3、4和5周期采用了较为缓和的AG方案, 即白蛋白紫杉醇联合吉西他滨。调整后, 患者不良反应明显减轻, 仅出现轻微恶心。现患者术后5个月, 日常活动正常, 生活可自理, 卡氏功能状态(Karnofsky performance status, KPS)评分为90分。

1.4 术后病理 大体检查: 送检标本为胰体尾和脾脏。胰腺大小为 $10.0 \text{ cm}\times 3.5 \text{ cm}\times 3.0 \text{ cm}$, 表面灰红, 黏连; 距胰腺断端 5.5 cm 处(尾部)表面见1枚肿物, 大小为 $4.0 \text{ cm}\times 1.8 \text{ cm}\times 1.5 \text{ cm}$,



图2 *SMARCB1/INI1* 缺失型UPC患者胃镜图像

Fig. 2 Gastroscope image of UPC patient with *SMARCB1/INI1*-deficient

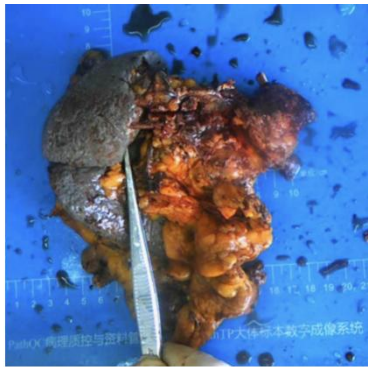
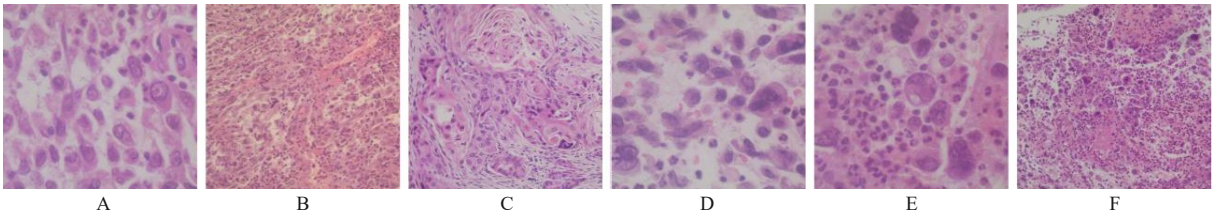


图3 *SMARCB1/INI1* 缺失型UPC患者肿瘤切除标本照片

Fig. 3 Photograph of tumor resection specimen from *SMARCB1/INI1*-deficient UPC patient

大部分呈囊性,内壁灰红、粗糙;少部分实性,实性区大小为1.5 cm×1.3 cm×1.2 cm,灰黄,质略韧,实性区距脾脏最近处约0.5 cm;其余胰腺切面呈灰白、灰黄色,分叶状。脾脏大小为11.5 cm×5.0 cm×4.5 cm,表面灰红、光滑,切面灰红;胰腺周围粘连网膜一块,大小为14.5 cm×7.5 cm×4.5 cm,未触及明显质硬区,其内见一灰红区,大小为1.0 cm×1.5 cm×0.6 cm。另见灰红色组织一块,大小为2.5 cm×1.0 cm×0.5 cm。镜下检查:肿瘤细胞大部分呈弥漫片状分布,间质可见黏液;细胞核大,呈圆形或多角形,明显异型,可见较大的明显嗜酸性核仁及核分裂;胞浆丰富,嗜酸性,并见多形性瘤巨细胞,灶状区域伴变性、坏死;少部分区呈巢团状分布,伴明显鳞状分化,可见角化珠形成。胰周及网膜淋巴结未见肿瘤转移(0/6)。见图4。免疫组织化学:弥漫片状区细胞角蛋白

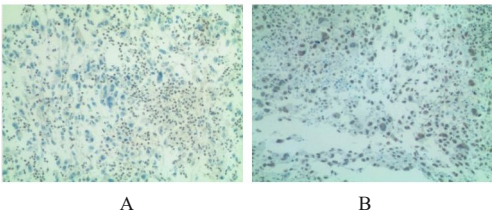
(cytokeratin, CK)(+),波形蛋白(vimentin, VIM)(+),CD68(部分+),上皮膜抗原(epithelial membrane antigen, EMA)(+),平滑肌肌动蛋白(smooth muscle actin, SMA)(部分+),INI1(-),Brahma相关基因1(brahma-related gene 1, BRG1)(+),Myogenin(-),生肌分化因子1(myogenic differentiation 1, MyoD1)(-),Desmin(-),ETS相关基因(ETS-related gene, ERG)(-),S100(-),P53(80%+),Ki67(50%+);鳞状分化区P40、P63和CK5/6(+)。见图5。病理诊断:SMARCB1/INI1缺失型UPC,并见少量中分化鳞状细胞癌(约占10%),胰腺断端(-),脉管侵犯(+),神经侵犯(+),脾脏及大网膜未见肿瘤累及,淋巴结未见肿瘤转移。



A: Tumor cells with prominent nucleoli (HE, ×400); B: Diffuse distribution of tumor cells(HE, ×100); C: Squamous cell carcinoma (HE, ×100); D: Tumor cells with poor adhesion and rhabdoid features(HE, ×400); E: Binucleated and multinucleated tumor giant cells(HE, ×400); F: Multinucleated tumor giant cells(HE, ×100).

图4 SMARCB1/INI1缺失型UPC患者肿瘤组织病理形态表现

Fig. 4 Pathomorphology of tumor tissue of UPC patient with SMARCB1/INI1-deficient



A: INI1(-); B: BRG1(+).

图5 SMARCB1/INI1缺失型UPC患者肿瘤组织中INI1和BRG1蛋白表达情况(免疫组织化学,×100)

Fig. 5 Expressions of INI1 and BRG1 proteins in tumor tissue of SMARCB1/INI1-deficient UPC patient (Immunohistochemistry, ×100)

2 讨论

UPC细胞一般呈多形性、卵圆形或梭形,细胞核偏位、呈空泡状,细胞黏附性差,缺乏纤维间质,侵袭性强。根据世界卫生组织2019年消化系

统肿瘤分类,UPC可分为以多形性为主的间变性未分化癌和以梭形细胞为主的肉瘤样未分化癌。伴有横纹肌样改变的未分化癌被列入肉瘤样未分化癌中,并可伴有SMARCB1/INI1表达缺失^[13]。

本例患者的病理类型较为独特,其肿瘤主体为黏附性差、形态多样的未分化癌,伴有少部分鳞状细胞癌(约占10%)。此类胰腺双相癌在既往报道中非常罕见。CHO等^[14]研究显示:UPC包括具有横纹肌样特征的未分化癌和黏液癌2种成分,且二者均检测出SMARCB1/INI1错义突变。KAN等^[15]报道了1例UPC伴鳞状分化患者,研究显示:肿瘤中未分化癌占70%,镜下以间变性巨细胞癌成分为主,鳞癌占30%;基因组分析确定了2种成分存在共同基因突变,提示其可能同源,且鳞状细胞癌成分携带更多基因突变,包括SMARCA4和SMARCB1突变。与上述病例不同的是,本例患者

鳞癌成分未伴有 *SMARCB1/INI1* 缺失, 其具体来源及其与未分化癌的关系尚不明确。然而, 一项胰腺原发性鳞状细胞癌的研究^[16]认为其可能源于因持续炎症而发生鳞状化生的胰管。研究^[17]指出: 该现象可能是混合性腺鳞状细胞癌中的腺体成分消失后的表现, 或从已存在的腺癌伴鳞状化生发展而来, 抑或是来自具有生物潜能的原始干细胞发展和演变为鳞癌。

SMARCB1/INI1 基因缺失最初在肾和肾外的恶性横纹肌样肿瘤 (malignant rhabdoid tumor, MRT) 及非典型畸胎样/横纹肌样肿瘤 (atypical teratoid/rhabdoid tumor, AT/RT) 中被识别并成为其诊断标志物^[18]。随着 *SMARCB1* 免疫组织化学法和分子病理技术的普及, 更多 *SMARCB1* 缺陷型肿瘤被发现, 如上皮样肉瘤 (epithelioid sarcoma, ES)、低分化脊索瘤 (poorly differentiated chordoma, PDC) 和滑膜肉瘤 (synovial sarcoma, SS) 等。研究^[19-20]表明: 该基因失活可促进肿瘤发生与转移, 而恢复其表达则可抑制肿瘤细胞增殖和迁移。此外, *SMARCB1/INI1* 基因还与无翅型 MMTV 整合位点家族蛋白 (wingless-type MMTV integration site family, Wnt) 信号通路、音猬因子 (sonic Hedgehog, SHH) 信号通路及多梳蛋白家族 (polycomb group, PcG) 通路等相关, 其异常表达可能通过干扰这些通路的正常功能, 促进肿瘤发生发展^[21]。*SMARCB1/INI1* 缺失还可能影响肿瘤微环境, 如改变细胞外基质和细胞黏附功能相关基因的表达, 进而促进肿瘤细胞的存活与增殖^[22]。同时, *SMARCB1/INI1* 缺失型胰腺癌与 Kirsten 大鼠肉瘤病毒癌基因同源物 (Kirsten rat sarcoma viral oncogene homolog, *KRAS*) 基因状态有关联。AGAIMY 等^[10]研究显示: 根据 *SMARCB1/INI1* 的表达和 *KRAS* 是否突变, 胰腺横纹肌样癌可分为 2 种亚型, 即多形性巨细胞亚型和单形间变性细胞亚型; 多形性巨细胞亚型伴 *KRAS* 突变和 *SMARCB1* 表达完整, 单形间变性细胞亚型则有 *SMARCB1* 缺失且不伴有 *KRAS* 突变。

UPC 通常起病隐匿, 症状不典型, 患者可能出现黄疸、皮肤瘙痒、体质量减轻、恶心呕吐和发热等症状, 或主诉腹痛、胃胀及背痛, 部分患者可能无症状^[23]。本例患者以腹痛和恶心为首发症状, 就诊时已存在胃壁受侵, 符合该疾病侵袭性强及早期症状隐匿的特点。实验室检测应关注直接胆

红素 (direct bilirubin, DB)、间接胆红素 (indirect bilirubin, IB)、总胆红素 (total bilirubin, TB) 和天冬氨酸氨基转移酶 (aspartate aminotransferase, AST)、碱性磷酸酶 (alkaline phosphatase, ALP) 及丙氨酸氨基转移酶 (alanine aminotransferase, ALT) 等肝酶是否升高, 以及肿瘤标志物 CA125、CA199 和癌胚抗原 (carcinoembryonic antigen, CEA) 是否异常。MUGAANYI 等^[9]研究显示: *SMARCB1* 缺失型胰腺癌患者伴 TB、AST、ALP 及 CA125 水平升高, 但 CA199 和 CEA 水平正常。HUA 等^[11]研究显示: *SMARCB1* 缺失型胰腺癌初诊时伴有 ALP 和 AST 水平升高。影像学诊断需结合 CT、MRI 及超声内镜 (endoscopic ultrasound, EUS) 检查的综合评估。ISHIGAMI 等^[24]研究表明: UPC 多表现为低血管性, 伴有上游主胰管扩张, 部分可见坏死、囊性变及钙化; MRI 检查中部分病例可观察到出血和含铁血黄素沉积; 对于胆总管受压迫的患者, 磁共振胰胆管成像 (magnetic resonance cholangiopancreatography, MRCP) 可清晰显示出胆道树的扩张。本例患者 MRI 表现为囊实性肿物, 侵袭性强, 内部可见囊变及出血坏死, 与既往研究的影像表现一致; 可见门静脉内栓子形成, 考虑为癌栓。EUS 引导下细针穿刺 (EUS-guided fine needle aspiration, EUS-FNA) 可在超声实时引导下获取胰腺病变组织, 通过组织学、细胞学和分子生物学检测, 有效明确胰腺病变性质^[25]。因此, 对疑似 UPC 的术前诊断应结合患者临床信息综合评估, 并应尽早行 EUS-FNA 以明确病理诊断。

SMARCB1/INI1 缺失型 UPC 应与以下疾病鉴别: ①恶性黑色素瘤 (malignant melanoma, MM)。肿瘤细胞形态多样, 可呈肉瘤样、癌样、腺样、腺泡状或腺泡状软组织肉瘤样等, 间质反应各异, 常见为纤维间质反应, 局灶可出现横纹肌样特征, 免疫组织化学显示 S-100、SOX-10、黑色素瘤相关抗原 45 (human melanoma black-45, HMB-45) 和黑色素瘤抗原 A 等阳性; ②转移性横纹肌肉瘤 (rhabdomyosarcoma, RMS)。肿瘤细胞呈多边形或梭形, 核深染, 胞质红染, 局部有瘤巨细胞, 可见横纹肌母细胞分化和病理性核分裂, 免疫组织化学显示 Myogenin、MyoD1 和 Desmin 表达阳性; ③血管平滑肌脂肪瘤 (angiomyolipoma, AML)。一种少见的间叶源性肿瘤, 由不同分化程度的平滑肌样细胞和脂肪细胞组成, 好发于肾脏、肝和胰

腺,某些肝脏AML中可罕见出现横纹肌样特征,与多形性脂肪肉瘤(pleomorphic liposarcoma, PLPS)类似,易误诊;肿瘤细胞表达HMB-45、Melan A和VIM阳性,嗜铬粒蛋白A(chromogranin A, CgA)和突触素(synaptophysin, Syn)阴性。

由于*SMARCB1/INI1*缺失型UPC较为罕见,目前尚未形成规范的诊疗指南。对于本例患者,手术切除联合术后化疗是首选治疗方案。对于发现时已属晚期且无法手术切除的患者,应给予化疗。在不可手术切除的UPC患者中,已有报道^[26]使用FOLFIRINOX方案,但疗效似乎并不理想。KING等^[27]研究显示:当患者从FOLFIRINOX方案转换为AG方案后,疗效显著且长期有效。LAND等^[12]研究显示:局部晚期*SMARCB1/INI1*缺失型UPC的患者行根治性切除术和AG方案辅助化疗,在术后长达18个月的随访中无复发迹象。本例患者在接受1周期FOLFIRINOX方案治疗后,出现了明显的恶心、腹泻和脱发等不良反应。因此,第2~5周期调整为较为缓和的AG方案,患者不良反应明显减轻,食欲也有所改善。患者术后第1、3和5月复查CA199水平分别为27.40、22.82及24.79 U·mL⁻¹,较术前明显降低;腹部CT提示胰腺周围无进展征象;生活质量改善,目前仍在持续化疗中。然而,考虑到该肿瘤侵袭性强且预后不良,需高度警惕复发风险,密切随访并动态评估疗效。上述结果表明AG方案可能是一种潜在有效的替代化疗方案。研究^[28]表明:*SMARCB1/INI1*缺失会导致多种软组织肉瘤(soft tissue sarcoma, STS)中果蝇*Zeste*基因增强子同源蛋白2(enhancer of *Zeste* homolog 2, EZH2)的异常表达和活性增强,从而促进肿瘤发生发展,使得EZH2成为抗肿瘤治疗中的新靶点。他泽司他是一种选择性EZH2抑制剂,已被批准用于治疗晚期ES,未来有望用于其他*SMARCB1/INI1*缺失型肿瘤的治疗。研究^[29]发现:氯喹和他莫昔芬等自噬抑制药物联合硼替佐米及伊沙佐米等蛋白酶抑制剂,对*SMARCB1/INI1*缺失型肿瘤具有明显抑制作用。

综上所述,*SMARCB1/INI1*缺失型UPC是一种罕见的侵袭性强、恶性程度高且预后差的胰腺肿瘤,目前尚缺乏成熟的诊疗规范。尽管如此,本例患者仍得益于早期且及时的外科干预及术后辅助化疗。延误治疗可严重影响患者疗效和生存质量。临床工作中应提高对该疾病的认识,力求早诊断、早

治疗。未来随着研究的深入和循证医学证据的积累,该疾病的诊疗方案将日趋完善。

利益冲突声明:

所有作者声明不存在利益冲突。

作者贡献声明:

周中伟参与临床资料收集和论文撰写,杜伟和宁宇参与研究设计,于晶和郭峰有参与临床资料及文献整理,杨学良参与论文选题、审阅和修改。

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