·临床病理报告·

脑转移性混合性腺神经内分泌癌

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【摘要】 **目的** 报告首例脑转移性混合性腺神经内分泌癌的临床病理学特征，探讨诊断与鉴别诊断要点和预后影响因素。**方法与结果** 男性患者，35岁。临床表现为头痛、呕吐，CT显示右侧颞叶占位性病变。术中可见肿瘤直径约3 cm，边界欠清晰，质地软韧，血供丰富。肿瘤由大小较一致的小圆形细胞构成，局部肿瘤细胞围绕小血管形成"菊形团"样或乳头样结构，核分裂象活跃，与周围脑组织界限不清；肿瘤细胞弥漫性表达突触素和CD56，不表达胶质纤维酸性蛋白、广谱细胞角蛋白、CD3、CD20、波形蛋白、白细胞共同抗原、甲状腺转录因子-1、S-100蛋白、神经微丝蛋白、巢蛋白、细胞角蛋白（CK）5/6、CK8/18和CD99，Ki-67抗原标记指数约为62%。外院行乙状结肠肠镜检查发现肿物，组织学呈明显双相性，由大小一致的小圆形细胞和低至中度分化的腺癌细胞构成，二者界限清晰，无移行。小圆形肿瘤细胞弥漫性表达突触素和CD56，不表达广谱细胞角蛋白；腺癌细胞弥漫性表达广谱细胞角蛋白，不表达突触素和CD56。**结论** 混合性腺神经内分泌癌为2010年世界卫生组织命名和定义的肿瘤，发生脑转移者尚未见诸报道，明确诊断需依靠临床病史、组织形态学特征和免疫组织化学表型。

【关键词】 腺癌； 癌，神经内分泌； 中枢神经系统； 结肠，乙状； 肿瘤转移； 免疫组织化学； 病理学

Mixed adenoneuroendocrine carcinoma with brain metastasis

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【**Abstract**】 **Objective** To study clinicopathological features, diagnosis, differential diagnosis and prognosis of mixed adenoneuroendocrine carcinoma (MANEC). **Methods** One case of MANEC with brain metastasis was reported focusing on the following aspects: clinical manifestations, histopathological features and immunophenotypes, and the relevant literatures were reviewed. **Results** A 35-year-old male presented headache and vomiting, and his head CT scan showed a lesion located in the right temporal lobe. The tumor was detected after separating the cerebral cortex during the surgery. The tumor diameter was 3 cm. The tumor was soft and rubbery with ill-defined margins, and rich in blood supply. Under optical microscopy, the tumor was consisted of small round cells of the same size, with focal tumor cells arranged around blood vessels in a pseudorosette manner or papillary manner with brisk mitotic activity. The boundary between tumor and brain tissue was ill-defined. By using immunohistochemical staining, the tumor cells were diffusely positive for synaptophysin (Syn) and CD56, and negative for glial fibrillary acidic protein (GFAP), pan cytokeratin (PCK), CD3, CD20, vimentin (Vim), leukocyte common antigen (LCA), thyroid transcription factor-1 (TTF-1), S-100 protein (S-100), neurofilament (NF), nestin (Nes), CK5/6, CK8/18 and CD99. Ki-67 labeling index was about 62%. Sigmoidoscopy was performed later in another hospital and showed a mass in the patient's colon. The colon tumor was biphasic in appearance, and was consisted of two distinct components: isomorphic small round cells and low-middle differentiated adenocarcinoma cells. The small round tumor cells were diffusely positive for Syn and CD56, and negative for PCK. The adenocarcinoma cells showed opposite results. **Conclusions** MANEC is a rare tumor, which is defined in 2010 by WHO Classification of Digestive, and to the best of our knowledge, MANEC of the colon with brain metastasis has never been described. Therefore, this paper reports the first case of

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MANEC of the colon with brain metastasis. Definite diagnosis could be made by medical history, typical histopathological characteristics and immunohistochemical expressions.

【Key words】 Adenocarcinoma; Carcinoma, neuroendocrine; Central nervous system; Colon, sigmoid; Neoplasm metastasis; Immunohistochemistry; Pathology

混合性腺神经内分泌癌(MANEC)是一种临床罕见的神经内分泌肿瘤[1-2],2010年世界卫生组织(WHO)消化系统肿瘤分类提出该命名[3]。混合性腺神经内分泌癌是含上皮细胞和神经内分泌细胞两种成分的恶性肿瘤,其脑转移病例尚未见诸报道。本文首次报告1例发生于颞部的混合性腺神经内分泌癌脑转移患者,通过复习文献对其组织形态学特点、免疫组织化学表型、诊断与鉴别诊断、治疗及预后等临床病理学特征进行探讨。

病历摘要

患者 男性,35岁,因头痛1周于2013年11月4日入院。入院前1周夜间无明显诱因出现头痛,以额颞部明显,呈胀痛,影响睡眠,伴呕吐1次,休息后缓解,未予特殊处理。2 d后再次出现类似症状,亦未予特殊处理。1 d前外院头部CT显示右侧颞叶占位性病变。为求进一步诊断与治疗,遂至我院。患者自发病以来,精神、睡眠可,食欲欠佳,大小便正常,体重未见明显变化。

既往史、个人史及家族史 均无特殊。

入院后体格检查 体温37 ℃,脉搏75次/min,呼吸17次/min,血压124/77 mm Hg(1 mm Hg = 0.133 kPa)。神志清楚,高级神经功能正常;头部无畸形;双侧瞳孔等大、等圆,直径约3 mm,对光反射灵敏;伸舌居中,无口角歪斜;无颈项强直;其余脑神经未见异常。四肢肌力5级、肌张力正常,腱反射对称引出,浅感觉无明显减退,病理征阴性,脑膜刺激征阴性。共济运动无异常。

辅助检查 入院后完善各项实验室检查,血液一般检查和物理性质、肝肾功能试验均于正常值范围。头部CT检查显示,右侧颞叶占位性病变,大小约6 cm,周围可见水肿,中线结构稍移位。头部MRI检查显示,右侧颞叶占位性病变,胶质瘤可能性大(图1)。

诊断与治疗经过 临床诊断为右侧颞叶占位性病变,胶质瘤可能性大。于全身麻醉下行右侧颞顶叶占位性病变切除术。术中见肿瘤直径约3 cm,呈灰红色,边界欠清晰,质地较韧,血供丰富。行术中快速冰冻组织病理学检查提示小细胞恶性肿瘤。手术全切除肿瘤,行组织病理学检查。(1)大体标本观察:切除的肿瘤组织为灰白、灰红色不整形数块,大小约3 cm × 2 cm × 2 cm,切面呈灰白、灰红色,实性,质地较软,部分呈囊壁样,壁厚0.50 cm。经体积分数为3.7%的中性甲醛溶液固定,常规脱水、石蜡包埋,4 μm连续切片,分别行HE染色和免疫组织化学染色。(2)HE染色:光学显微镜观察,肿瘤组织由片状密集分布的小至中等大小细胞组成,形态较单一,大小较一致,胞核呈圆形或卵圆形,染色质稍粗,可见小核仁,胞质较少,部分区域肿瘤细胞围绕血管周围形成"菊形团"样结构或乳头样结构,核分裂象活跃(56/10个高倍视野);肿瘤组织无包膜,与周围脑组织界限不清(图2)。(3)免疫组织化学染色:采用EnVision二步法,免疫组织化学染色所用Ⅰ抗、Ⅱ抗、显色剂和染色系统参见表1。结果显示,肿瘤细胞弥漫性表达突触素(Syn)和CD56,不表达胶质纤维酸性蛋白(GFAP)、广谱细胞角蛋白(PCK)、CD3、CD20、波形蛋白(Vim)、白细胞共同抗原(LCA)、甲状腺转录因子-1(TTF-1)、神经微丝蛋白(NF)、S-100蛋白(S-100)、巢蛋白(Nes)、细胞角蛋白(CK)5/6、CK8/18和CD99,Ki-67抗原标记指数约为62%(图3)。最终病理诊断:(右侧颞叶)小细胞恶性肿瘤,考虑小细胞神经内分泌癌可能性大,不排除原始神经外胚层肿瘤(PNET)。

术后为明确病因进一步行PET-CT检查,考虑乙状结肠肿瘤。于2013年12月4日在外院行乙状结肠肠镜检查。乙状结肠活检大体标本观察,灰白色"米粒"样组织4块,直径0.20~0.30 cm,病理诊断为腺癌。于2013年12月13日手术切除乙状结肠肿瘤,行组织病理学检查。(1)大体标本观察:送检肠管一段,长度14 cm、周径4~4.50 cm,紧邻下切端可见隆起的溃疡型肿物,大小1.50 cm × 1.50 cm × (0.60~1) cm,侵犯肠壁1/3周。经3.7%中性甲醛溶液固定,常规脱水、石蜡包埋,4 μm连续切片,分别行HE染色和免疫组织化学染色。(2)HE染色:光学

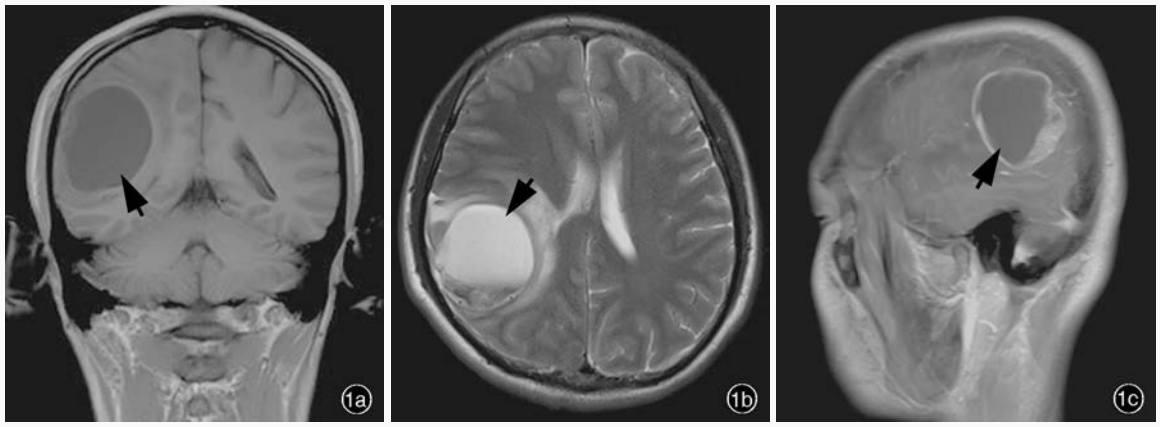

图1 头部MRI检查所见 1a 冠状位T_1WI显示，右侧颞叶囊性占位性病变（箭头所示） 1b 横断面T_2WI显示，右侧颞叶囊性占位性病变，囊液呈高信号，可见液液平面（箭头所示） 1c 矢状位增强T_1WI显示病灶呈环形强化（箭头所示）

Figure 1 Head MRI findings. Coronal T_1WI showed a cystic mass in the right temporal lobe (arrow indicates, Panel 1a). Axial T_2WI showed a cystic mass in the right temporal lobe, with hyperintensity cyst fluid, and fluid levels could be seen (arrow indicates, Panel 1b). Sagittal enhanced T_1WI demonstrated a ring enhancement of the lesion (arrow indicates, Panel 1c).

显微镜观察，肿瘤组织由两种成分构成，一种是呈片状密集分布的小至中等大小神经内分泌癌成分，形态较单一，大小较一致，胞核呈圆形或卵圆形，染色质稍粗，可见核仁，胞质较少，核质比为35%；另一种是低至中分化腺癌成分，以管状腺癌和低分化腺癌为主，细胞呈圆形或多角形，异型性明显，胞核呈多形性。两种成分界限清晰，无移行，核分裂象活跃（图4）。（3）免疫组织化学染色：采用EnVision二步法进行检测，免疫组织化学染色用Ⅰ抗、Ⅱ抗、显色剂和染色系统参见表2。结果显示，小圆形肿瘤细胞弥漫性表达Syn和CD56，不表达嗜铬素A（CgA）、PCK、黑色素细胞刺激素2（MSH2）、MSH6、MLH1和PMS2；腺癌细胞弥漫性表达PCK，部分表达MLH1和PMS2，不表达CgA、Syn、CD56、MSH2和MSH6（图5）。最终病理诊断为（乙状结肠）混合性腺神经内分泌癌，侵及肌层，肠断端未见肿瘤，送检的20个肠系膜淋巴结中3个可见转移癌。病理分期pT2N1M1 Dukes分期C期。术后予药物化疗，SOX＋替莫唑胺方案［奥沙利铂150 mg（d1）＋替吉奥50 mg（2次/d×14 d）＋替莫唑胺150 mg（1次/d×5 d）］，21 d为一疗程，共6个疗程；发生肺转移，遂改为单药XELODA＋替莫唑胺方案［希罗达150 mg（2次/d×14 d）＋替莫唑胺150 mg（1次/d×5 d）］，21 d为一疗程，维持1个疗程。随访至今近13个月，患者未再出现头痛等神经系统症状，肿瘤无复发，日常生活基本能够自理。最终我院修订病理诊断：脑转移性混合性腺神经内分泌癌，结合病史源自乙状结肠。

讨 论

混合性腺神经内分泌癌为临床罕见的神经内分泌肿瘤[1-2]，2010年由WHO正式命名[3]。混合性腺神经内分泌癌是一种形态学上形成可识别的腺上皮细胞和神经内分泌细胞两种成分的恶性肿瘤，故命名为癌，鳞状细胞癌成分罕见，两种成分的任意一种被人为定义为至少占30%[3]。免疫组织化学染色证实腺癌中含散在神经内分泌细胞不能归入此类[4]。其肿瘤生物学行为由侵袭性高的成分决定[5-6]。2010年WHO消化系统肿瘤分类未就其分级、核分裂程度和Ki-67抗原标记指数的意义予以明确说明。2011年《中国胃肠胰神经内分泌肿瘤病理学诊断共识》[4]指出，一旦确定肿瘤为神经内分泌性质，则根据肿瘤增殖活性进一步分类和分级，即Ki-67抗原标记指数≤2%为低级别、3%～20%为中级别、＞20%为高级别，但并未对Ki-67抗原标记指数在混合性腺神经内分泌癌中表达的意义予以明确说明。

由于混合性腺神经内分泌癌临床少见，缺乏足够的病例进行随机对照研究，其发病率和生存率尚未见明确报道，但近年研究发现，发病率有明显升高趋势。据文献报道，发病年龄16～81岁[7-21]，好发于胃、结肠、食管与胃结合部[12]、盲肠[14]、胆囊[15]、胆管[21]、壶腹[11]和子宫[13]。肿瘤发生部位不同，临床症状各异，表现为腹痛、腹胀、吞咽困难、便血，也

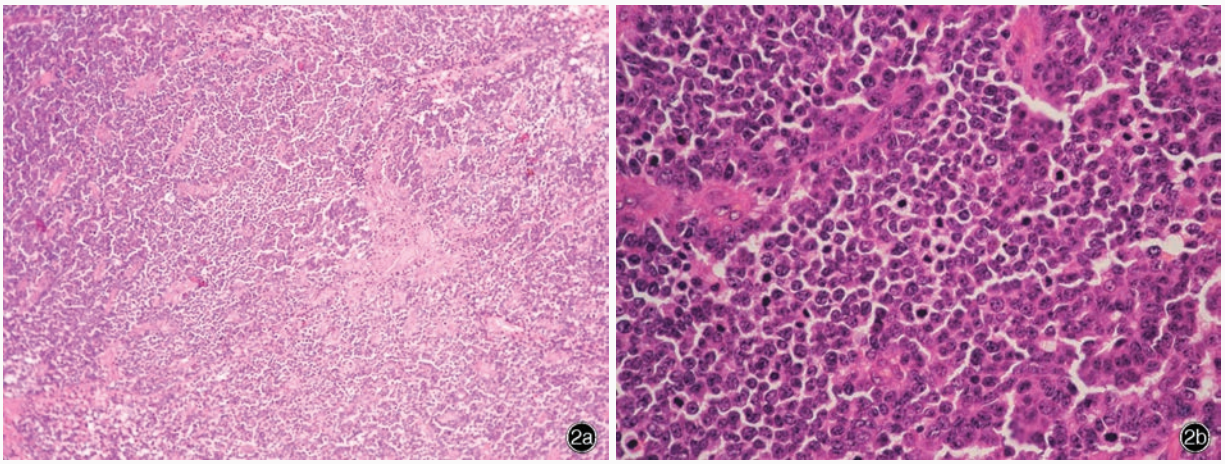

图2　光学显微镜观察所见　HE染色　2a　肿瘤细胞弥漫分布，大小较一致，胞质较少　低倍放大　2b　肿瘤细胞胞核呈圆形，染色质稍粗，可见核仁，核分裂象活跃　高倍放大

Figure 2　Optical microscopy findings.　HE staining　The tumor was composed of isomorphic small cells with scarce cytoplasm (Panel 2a).　low power magnified　Tumor cells presented round nuclei with dispersed chromatin, well-evident nucleoli and brisk mitotic activity (Panel 2b).　high power magnified

表1　中枢神经系统肿瘤免疫组织化学检测项目表

Table 1.　Antibodies used for immunohistochemical examination of CNS tumor

Antibody Ⅰ	Clone ID	Company	Restorative procedure	Dilution ratio	Antibody Ⅱ company	Dyeing system
Syn	SP11	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision
CD56	123C3	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision
GFAP	ASTR05/06	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision
PCK	AE1/AE3	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision
CD3	PS1	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision
CD20	L26	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision
Vim	V9	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision
LCA	RP2/18	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision
TTF-1	8G7G3/1	Zhongshan (China)	EDTA	Ready-to-use	Dako (Denmark)	EnVision
S-100	4C4.9	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision
NF	DA2/FNP7/RMdo20.11	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision
Nes	10C2	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision
CK5/6	H09	Zhongshan (China)	EDTA	Ready-to-use	Dako (Denmark)	EnVision
CK8/18	D33	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision
CD99	O13	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision
Ki-67	K2	Zhongshan (China)	Citric acid	Ready-to-use	Dako (Denmark)	EnVision

Syn，synaptophysin，突触素；GFAP，glial fibrillary acidic protein，胶质纤维酸性蛋白；PCK，pan cytokeratin，广谱细胞角蛋白；Vim，vimentin，波形蛋白；LCA，leukocyte common antigen，白细胞共同抗原；TTF-1，thyroid transcription factor-1，甲状腺转录因子-1；S-100，S-100 protein，S-100蛋白；NF，neurofilament protein，神经微丝蛋白；Nes，nestin，巢蛋白；CK，cytokeratin，细胞角蛋白；EDTA，ethylenediaminetetraacetic acid，乙二胺四乙酸

有少数病例无明显临床症状而在体检时发现，常伴淋巴结转移，亦可见肝脏[7,19-20]、骨骼[7]、胰腺转移的报道[13]。

大体标本观察，可为溃疡型、息肉型和浸润型，该例患者结肠组织标本呈溃疡型。光学显微镜观察，肿瘤组织由腺癌和神经内分泌癌两种成分构成，鳞癌成分罕见。腺癌区域以管状腺癌和低分化腺癌为主，部分可见黏液腺癌、印戒细胞癌、乳头状腺癌等组织学形态[8,20]；神经内分泌癌区域可见小细胞、大细胞、中间细胞成分单独或相互混杂存在。Shintaku等[15]报告1例神经内分泌癌成分呈嗜酸细胞分化。小细胞区域肿瘤细胞呈弥漫性或巢

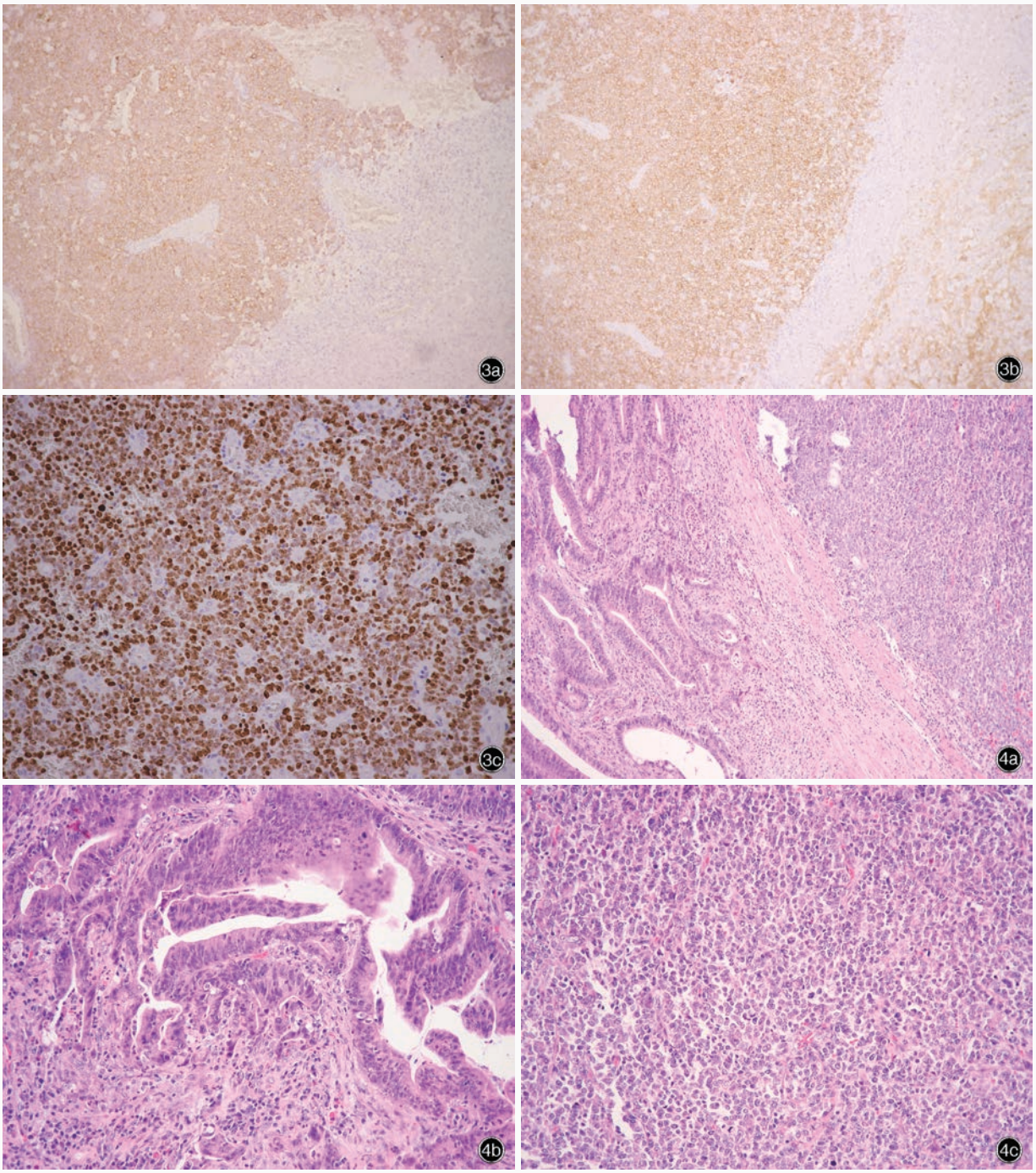

图3 光学显微镜观察所见 免疫组织化学染色(EnVision二步法) 3a 肿瘤细胞弥漫性表达Syn 低倍放大 3b 肿瘤细胞弥漫性表达CD56 低倍放大 3c 肿瘤细胞Ki-67抗原标记指数约为62% 中倍放大 **图4** 光学显微镜观察所见 HE染色 4a 肿瘤组织由两种成分构成,分别是神经内分泌癌(右上方区域)和管状腺癌(左下方区域),二者界限清晰,无移行 低倍放大 4b 神经内分泌癌区域肿瘤细胞呈巢片状分布,胞核呈圆形或卵圆形,染色质稍粗,可见核仁 中倍放大 4c 腺癌区域以管状腺癌和低分化腺癌为主 中倍放大

Figure 3 Optical microscopy findings. Immunohistochemical staining (EnVision) The tumor cells were diffusely immunopositive for Syn (Panel 3a) and CD56 (Panel 3b). low power magnified Ki-67 labeling index was about 62% (Panel 3c). medium power magnified **Figure 4** Optical microscopy findings. HE staining The tumor was composed of two separated and different features: neuroendocrine carcinoma (right top) and gland-forming adenocarcinoma (left bottom, Panel 4a). low power magnified An enlarged view of the neuroendocrine component was characterized by solid nests and sheets of tumor cells with round or oval nuclei, coarse chromatin and prominent nucleoli (Panel 4b), while the adenocarcinoma component was gland-forming and low-moderate differentiated adenocarcinoma (Panel 4c). medium power magnified

表2　乙状结肠肿瘤免疫组织化学检测项目表

Table 2.　Antibodies used for immunohistochemical examination of sigmoid flexure tumor

Antibody Ⅰ	Clone ID	Company	Restorative procedure	Dilution ratio	Antibody Ⅱ company	Dyeing system
Syn	SP11	Zhongshan (China)	Citric acid	Ready-to-use	Zhongshan (China)	EnVision
CD56	123C3	Zhongshan (China)	Citric acid	Ready-to-use	Zhongshan (China)	EnVision
PCK	AE1/AE3	Zhongshan (China)	Citric acid	Ready-to-use	Zhongshan (China)	EnVision
CgA	SP12	Zhongshan (China)	Citric acid	Ready-to-use	Zhongshan (China)	EnVision
MSH2	FE11	Zhongshan (China)	EDTA	Ready-to-use	Zhongshan (China)	EnVision
MSH6	BC/44	Zhongshan (China)	Citric acid	Ready-to-use	Zhongshan (China)	EnVision
MLH1	14	Zhongshan (China)	EDTA	Ready-to-use	Zhongshan (China)	EnVision
PMS2	EP51	Zhongshan (China)	EDTA	Ready-to-use	Zhongshan (China)	EnVision

Syn, synaptophysin, 突触素；PCK, pan cytokeratin, 广谱细胞角蛋白；CgA, chromogranin A, 嗜铬素A；MSH, melanocyte-stimulating hormone, 黑色素细胞刺激素；EDTA, ethylenediaminetetraacetic acid, 乙二胺四乙酸

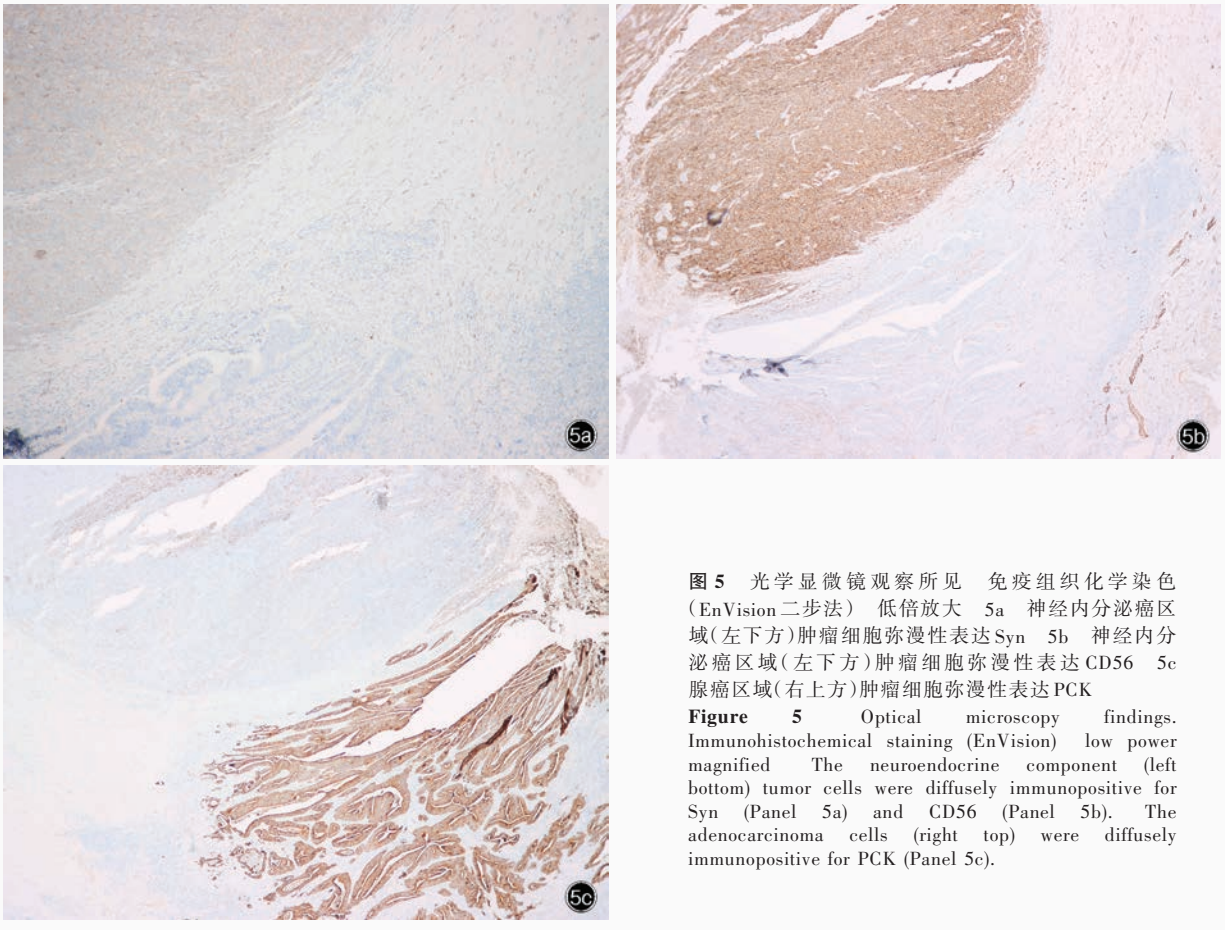

图5　光学显微镜观察所见　免疫组织化学染色（EnVision二步法）　低倍放大　5a　神经内分泌癌区域（左下方）肿瘤细胞弥漫性表达Syn　5b　神经内分泌癌区域（左下方）肿瘤细胞弥漫性表达CD56　5c　腺癌区域（右上方）肿瘤细胞弥漫性表达PCK

Figure 5　Optical microscopy findings. Immunohistochemical staining (EnVision) low power magnified The neuroendocrine component (left bottom) tumor cells were diffusely immunopositive for Syn (Panel 5a) and CD56 (Panel 5b). The adenocarcinoma cells (right top) were diffusely immunopositive for PCK (Panel 5c).

片状分布，胞质少，染色质呈颗粒状，核仁不明显；大细胞区域肿瘤细胞呈器官样、梁状和“栅栏”样排列，胞质丰富，胞核呈泡状、核仁明显。根据两种成分的相互关系分为两种类型：(1)交叉型。临床较为常见，两种成分相互交叉混合在一起。(2)碰撞型。临床少见，两种成分紧密相邻但互不混合，无或仅少量交叉。该例患者脑组织病变为单纯神经内分泌癌成分，乙状结肠病变为碰撞型，两种成分相邻但不混合。核分裂象活跃[(20～60)/10个高倍视野]，Ki-67抗原标记指数为40%～90%[20]，可见坏死。免疫组织化学染色，神经内分泌癌区域小细胞和大细胞均弥漫性表达Syn和CgA，但后者表达水平低于前者[1,7-8,20]。肿瘤细胞至少弥漫性表达Syn、CgA或CD56中的两种方可明确诊断为混合性腺神

经内分泌癌。生长激素抑制素(somatostatin)、促肾上腺皮质激素(ACTH)或血管活性肠肽(VIP)等激素肽在混合性腺神经内分泌癌中的表达也见诸文献报道[1]。尾型同源盒转录因子2抗体(CDX2)在结肠和直肠混合性腺神经内分泌癌两种成分中呈不同比例表达,尤其是在神经内分泌癌大细胞成分中[1]。也有文献报道,表达于肺神经内分泌癌的TTF-1和ASH1蛋白亦可在结肠和直肠混合性腺神经内分泌癌的两种成分中表达[20],提示结肠和直肠混合性腺神经内分泌癌表型具有异质性。值得注意的是,Penman等[22]发现,表达于结肠和直肠混合性腺神经内分泌癌细胞核的TTF-1克隆号为SPT24,克隆号为8G7G1的TTF-1则呈阴性,有助于鉴别诊断。P53蛋白在胃、壶腹以及结肠和直肠混合性腺神经内分泌癌中均呈阳性[20,23]。结肠和直肠混合性腺神经内分泌癌CD117阳性[1]和脉管侵犯常提示预后不良[1,20]。该例患者颅内病变肿瘤细胞弥漫性表达Syn和CD56,不表达GFAP、PCK、CD3、CD20、Vim、LCA、TTF-1、S-100、NF、Nes、CK5/6、CK8/18和CD99,Ki-67抗原标记指数约为62%;结肠小圆形肿瘤细胞弥漫性表达Syn和CD56,不表达CgA、CK、MSH2、MSH6、MLH1和PMS2。腺癌细胞弥漫性表达PCK,部分表达MLH1和PMS2,不表达CgA、Syn、CD56、MSH2、MSH6,与文献报道相一致。

关于混合性腺神经内分泌癌的组织起源尚不甚清楚,可能是腺癌和神经内分泌癌分别起源于不同细胞系;或腺癌和神经内分泌癌均来自干细胞,是肿瘤发展过程中多向分化的结果。最新基因研究结果显示,胃肠混合性腺神经内分泌癌的神经内分泌成分染色体异常发生率更高。多个腺癌和神经内分泌癌细胞一致的体细胞突变提示两种成分可能是同一病变进展而来,*SMARCA4*基因突变使腺癌成分转变为神经内分泌癌表型似乎更支持干细胞假说[1,6,24]。

典型神经内分泌癌(类癌和小细胞癌)具有独特的形态学表现,但未见混合性腺神经内分泌癌脑转移的报道,当肿瘤细胞数目较少、分化较差、病史不典型时,易出现诊断困难或误诊,应注意与下列疾病相鉴别:(1)中枢神经系统原始神经外胚层肿瘤。发生于幕上的原始神经外胚层肿瘤极为少见,平均发病年龄为5.50岁,男女比例约为1.20∶1。影像学表现为T_1W低信号,T_2WI可见囊性变或坏死。肿瘤细胞丰富,分化较差,胞核圆形、深染,胞质少,核分裂象不等,可见"菊形团"样结构。肿瘤细胞表达Syn、NF、S-100,偶灶性表达GFAP,Ki-67抗原标记指数较高。患者预后不良,肿瘤细胞可经脑脊液播散,属WHOⅣ级。(2)淋巴瘤。分为原发性中枢神经系统淋巴瘤(PCNSL)和继发于系统性淋巴瘤的中枢神经系统淋巴瘤,二者可发生于任何年龄阶段,高峰发病年龄为60~70岁,男性多见;原发性中枢神经系统淋巴瘤影像学表现为单发或多发性高或等信号影,鲜见囊性变,增强扫描病灶呈弥漫性强化、无钙化;肿瘤细胞因肿瘤类型不同而形态各异,但均呈弥漫性生长,肿瘤细胞似小淋巴细胞样或组织细胞样,核分裂象多见,细胞间连接不紧密,肿瘤细胞聚集于小血管周围形成以血管为中心的"袖套"样特征性生长方式,无"菊形团"样和器官样结构。淋巴瘤标志物如CD45、CD20和CD3等表达阳性,神经元标志物表达阴性。(3)Turcot综合征。Turcot综合征1型含有胶质母细胞瘤,不含家族性腺瘤性息肉病(FAP),部分患者可见*HNPCC*和*hMSH2*或*hMLH1*基因错配修复的胚系突变。Turcot综合征2型为髓母细胞瘤伴*FAP*和*APC*基因胚系突变。在文献报道的中枢神经系统肿瘤中,约95%的患者有髓母细胞瘤、胶质母细胞瘤和间变型星形细胞瘤。Turcot综合征胶质母细胞瘤患者年龄较散发性胶质母细胞瘤患者小。中枢神经系统以外的Turcot综合征1型表现为大息肉,约56%患者较早罹患结肠癌和直肠癌;2型表现为大量腺瘤性多发性息肉,约21%患者发生结肠癌和直肠癌。(4)其他转移性肿瘤。组织形态学、免疫组织化学染色和临床病史有助于诊断与鉴别诊断。

目前认为,在制定治疗方案时应考虑其恶性程度和侵袭力。混合性肿瘤包含高分化神经内分泌癌和腺癌成分时,按腺癌治疗;混合性肿瘤包含低分化神经内分泌癌成分时,考虑予以针对低分化神经内分泌癌的靶向治疗。关于混合性腺神经内分泌癌患者的预后尚存争议,平均生存期为16.60个月[20],一般认为,混合性腺神经内分泌癌预后较差,介于经典腺癌与神经内分泌癌之间,较单纯腺癌预后好[1,25]。有研究显示,混合性结肠腺癌-大细胞神经内分泌癌的预后优于小细胞-中间细胞型或大细胞-中间细胞型神经内分泌癌,但在胃混合性腺神经内分泌癌中未发现相似结果,提示其预后可能与病变部位相关[20]。

由于迄今报道的病例数较少,其组织形态学和

生物学行为均存在异质性，其治疗与预后尚待进一步探讨。该例患者神经内分泌癌区域以大细胞为主，术后行药物化疗，随访至今近13个月，未再出现头痛等神经系统症状，肿瘤无复发，一般状况良好。

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