·脑静脉系统疾病·

恶性颅内高压诊治思考:一例报告

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【摘要】 **目的**　报告1例恶性颅内高压病例,回顾其诊断与治疗经过,并分析病因,以提高临床医师对恶性颅内高压的认知。**方法与结果**　男性患者,19岁,亚急性发病,呈慢性病程,以黑蒙、头痛、颈肩痛、视物模糊及耳鸣发病,影像学检查提示脑静脉窦狭窄且狭窄两端存在明显压力差,但脑静脉窦支架植入术无效,经视神经鞘减压术后头痛及视物模糊等症状无明显改善,最终经脑组织活检术确诊为胶质母细胞瘤(WHOⅣ级),手术切除肿瘤灶,术后8个月死亡。**结论**　恶性颅内高压伴脑静脉窦狭窄两端存在压力差的患者不宜行支架植入术,明确狭窄原因及类型对正确诊断及指导治疗至关重要。

【关键词】 胶质母细胞瘤;　颅内高压;　支架;　脑静脉

Diagnosis and treatment of malignant intracranial hypertension: one case report

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【**Abstract**】 **Objective**　This paper reports a case of malignant intracranial hypertension, reviews his diagnosis and treatment, and analyzes his etiology, in order to improve the clinicians′ cognition of this disease. **Methods and Results**　The patient was a 19-year-old male with subacute onset and chronic course of disease, presenting with amaurosis, headache, neck and shoulder pain, blurred vision and tinnitus disease. Imaging findings showed cerebral venous sinus stenosis (VSS) with obvious pressure difference at both ends of stenosis. However, venous sinus stenting was ineffective. After optic nerve sheath decompression, the symptoms of headache and blurred vision were not significantly improved. Finally, the patient was diagnosed as glioblastoma (WHO Ⅳ), and died 8 months after removal of the tumor foci. **Conclusions**　Patients with the pressure difference at both ends of malignant intracranial hypertension with VSS should not take stenting. Clarifying the cause and type of stenosis is very important for correct diagnosis and guide treatment.

【**Key words**】 Glioblastoma;　Intracranial hypertension;　Stents;　Cerebral veins

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颅内高压系指在各种病理状态下出现颅内压力超过200 mm H_2O,临床表现为头痛、呕吐或视乳头水肿等症状与体征,诱发因素多为颅腔内容物体积增加并超出颅内压调节代偿范围所致,是颅内多种疾病所共有的临床综合征[1]。恶性颅内高压系指短时间内形成颅内高压,患者可在4周内视力进行性减退,并于数日内完全失明[2],由于其病因复杂多样,临床上极易误诊或漏诊,患者大多预后不良。恶性颅内高压患者多伴有脑静脉窦狭窄(VSS),而后者并非其唯一病因,因此并非所有伴脑静脉窦狭窄的颅内高压患者均适宜行静脉窦支架植入术,需根据狭窄类型确定手术适应证。首都医科大学宣武医院于2019年收治1例因多形性胶质母细胞瘤伴脑静脉窦狭窄所诱发的恶性颅内高压病例,鉴于该患者诊断与治疗经过曲折,特此报告以为神经内外科医师诊断与治疗此类病例提供参考。

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病例资料

患者 男性，19岁。因黑蒙4个月，颈肩痛3个月，视物模糊、耳鸣2个月，于2019年5月16日入院。患者4个月前无明显诱因出现由蹲位变直立位时黑蒙，数秒后自行缓解；3个月前出现持续性颈肩痛，伴间歇性恶心、呕吐；2个月前双眼视物不清、左侧耳鸣，症状呈持续性。当地医院以“颅内高压待排”收入院（3月24日），入院后头部MRI（3月26日）显示左侧侧脑室枕角旁可疑高信号，增强后未见明显强化（图1a，1b），FLAIR成像显示左侧侧脑室枕角旁高信号（图1c）；头部MRV（4月3日）显示左侧横窦、乙状窦纤细（图1d）。腰椎穿刺脑脊液检查，压力＞330 mm H_2O（1 mm H_2O = 9.81 × 10^{-3} kPa，80～180 mm H_2O），常规、生化均于正常值范围。根据临床表现及辅助检查，并排除颅脑创伤、炎症、寄生虫感染、先天性脑病以及脑组织缺氧等原因引起的颅内高压，且无明显肿瘤证据，诊断为特发性高颅压（IIH）。予以甲泼尼龙1000 mg/d静脉滴注冲击治疗5天无效，DSA＋脑静脉窦测压术（4月16日）显示，上矢状窦前部至右侧横窦近端压力差为26 mm Hg（1 mm Hg = 0.133 kPa），上矢状窦后部狭窄两端的压力差为14.10 mm Hg，右侧横窦狭窄两端压力差为21.50 mm Hg，右颈内静脉狭窄两端压力差为5.10 mm Hg（图2a），修正诊断为特发性高颅压；脑静脉窦狭窄。经患者及家属同意，行脑静脉窦支架植入术（4月17日），于上矢状窦、右侧横窦、右颈内静脉分别植入2、3和1枚支架，术后即刻DSA＋脑静脉窦测压术显示，所有支架两端均无明显压力差（图2b）。术后第2和5天脑脊液压力＞330 mm H_2O，MRV显示上矢状窦、右侧横窦再次出现明显狭窄；DSA＋脑静脉窦测压术（4月29日）显示，上矢状窦前部至右侧横窦狭窄两端的压力差为44 mm Hg，上矢状窦前后部狭窄两端压力差为33.30 mm Hg，右侧横窦狭窄两端的压力差为11.10 mm Hg（图2c），再次行脑静脉窦支架植入术，于上矢状窦和右侧横窦分别再植入5和2枚支架，术后DSA＋脑静脉窦测压术显示所有支架两端均无明显压力差（图2d）；脑脊液压力＞330 mm H_2O，蛋白定量657 mg/L（150～450 mg/L），葡萄糖2 mmol/L（2.50～4.40 mmol/L），氯化物118 mmol/L（118～128 mmol/L）。经上述治疗，患者症状与体征并无明显改善，为求进一步诊断与治疗于2019年5月16日至我院急诊，以“颅内高压原因待查”收入院。既往有红细胞葡萄糖-6-磷酸脱氢酶缺乏症病史19年，其余无可述及。

二次入院诊断与治疗过程 体格检查：体温为36.5 ℃，心率为70次/min，呼吸12次/min，血压120/80 mm Hg，心、肺、腹部检查无异常。神志清楚，语言流利；双侧瞳孔等大、等圆，直径约5 mm，对光反射迟钝，双眼呈水平眼震；双侧额纹、鼻唇沟对称，伸舌居中，颈部抵抗；四肢肌力、肌张力、腱反射正常；Kernig征阳性，双侧病理征未引出。实验室检查：血尿便常规未见异常；腰椎穿刺脑脊液检查压力＞330 mm H_2O，白细胞计数8 × 10^6/L［（0～5）× 10^6/L］，蛋白定量540 mg/L，葡萄糖2.09 mmol/L，氯化物122 mmol/L，入院后多次脑脊液检查外观均为无色、透明，蛋白定量、葡萄糖水平低于正常值范围（表1）。脑脊液第二代测序技术（NGS）未检出致病菌。眼底检查提示双侧视乳头明显水肿，视力减退。MRI显示，左侧侧脑室枕角旁异常信号（图3a，3b），增强后未见明显强化；磁共振黑血血栓成像（MRBTI）增强扫描显示静脉窦、脑深静脉、皮质静脉管壁均无明显增厚强化，仅上矢状窦局部硬脑膜强化（图3c）；增强MRV显示上矢状窦显影断续，右侧横窦未见异常（图3d），提示支架植入术后再狭窄。临床诊断为颅内高压原因待查；脑静脉窦狭窄；视乳头明显水肿。经患者及家属同意，行右眼视神经鞘减压术（5月27日），于术中显露视神经，释放少量脑脊液（具体不详），球侧注射地塞米松2.50 mg＋妥布霉素20 × 10^3 U，术后予以左氧氟沙星0.488 mg/次（6次/d）及复方妥布霉素0.30 mg/次（6次/d）滴眼，共住院21天，于6月6日出院。出院时头痛症状有所缓解，右眼视力无明显改善，遵医嘱口服醋甲唑胺50 mg/次（2次/d）、维生素B_1 10 mg/次（3次/d）、甲钴胺0.50 mg/次（3次/d）、阿司匹林100 mg/d、氯吡格雷75 mg/d。出院后约3个月因头痛、视物模糊加重再次入我院（8月29日），头部MRI显示左侧侧脑室枕角旁异常信号较前明显（图4a，4b），增强后未见明显强化（图4c，4d）。结合多次脑脊液检查结果，拟诊胶质瘤。经脑脊液脱落细胞检查发现核大、深染的异形细胞（图5），考虑癌性脑膜炎。继续采取抗凝、抗血小板、脱水及改善循环治疗，皮下注射低分子量肝素0.60 ml/12 h，静脉滴注前列地尔10 μg/d、甘露醇125 ml/8 h，同时口服氯吡格雷75 mg/d。头痛和视物模糊等仍无改善，遂建议行脑组织活检术。外院行脑组织活检术，组织标本为左侧顶叶组

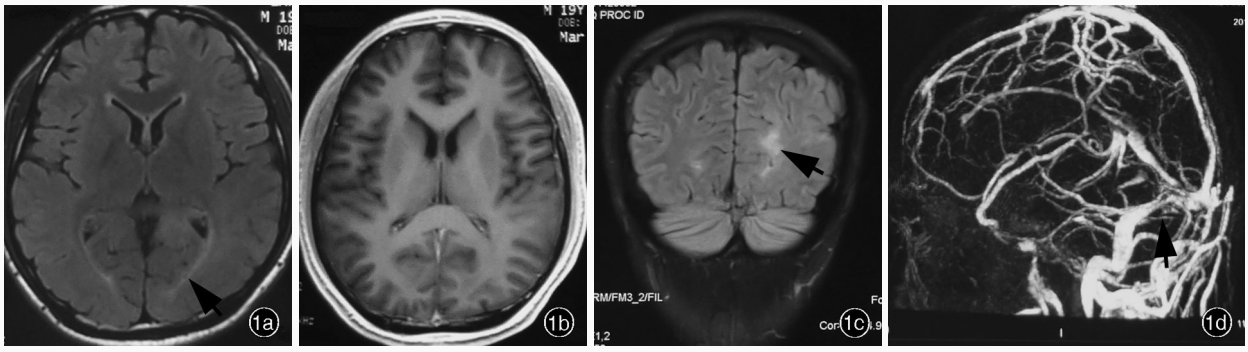


图1　首次入院时头部影像学所见　1a　横断面FLAIR成像左侧侧脑室枕角旁异常高信号(箭头所示)　1b　横断面增强T_1WI未见强化　1c　冠状位抑脂FLAIR成像左侧侧脑室枕角旁不规则高信号(箭头所示)　1d　侧位MRV左侧横窦、乙状窦纤细(箭头所示)

Figure 1　Head imaging findings on first admission　Axial FLAIR showed suspiciously hyperintensity in the inferior horn of left lateral ventricle (arrow indicates, Panel 1a). Axial enhanced T_1WI showed no obvious enhancement (Panel 1b). Coronal fat suppression FLAIR showed irregular hyperintensity in the inferior horn of left lateral ventricle (arrow indicates, Panel 1c). Lateral view of MRV showed slenderness in the left transverse sinus and sigmoid sinus (arrow indicates, Panel 1d).

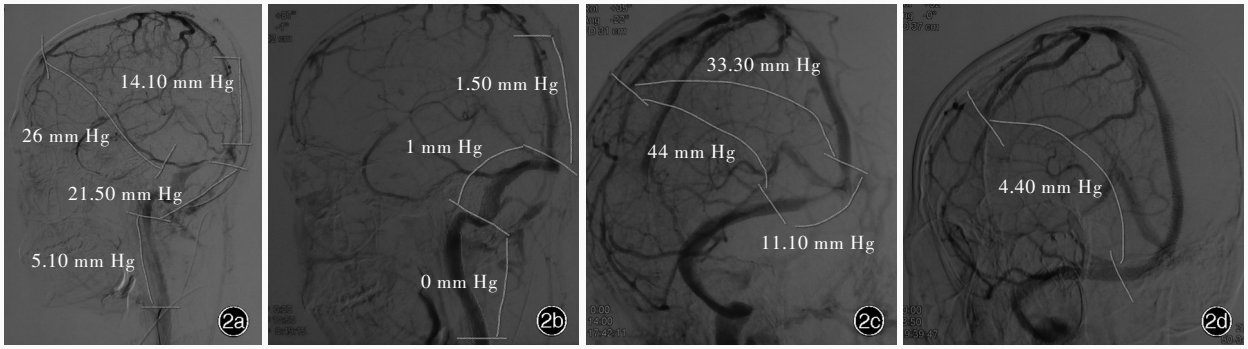


图2　首次入院两次支架植入术前后侧位DSA脑静脉窦测压结果　2a　首次术前测压,上矢状窦前部至右侧横窦近端、上矢状窦后部狭窄两端、右侧横窦狭窄两端、右颈内静脉狭窄两端压力差分别为26、14.10、21.50和5.10 mm Hg　2b　首次术后测压,所有支架两端均无明显压力差　2c　二次术前测压,上矢状窦前部至右侧横窦、上矢状窦前后部、右侧横窦狭窄两端压力差分别为44、33.30和11.10 mm Hg　2d　二次术后测压,支架两端无明显压力差

Figure 2　Lateral views of DSA before and after two stenting by venous sinus manometry during the first admission. The pressure differences before the first surgery between the anterior part of the superior sagittal sinus and the proximal end of the right transverse sinus, the two ends of the posterior superior sagittal sinus stenosis, the two ends of the right transverse sinus stenosis, and the two ends of the right internal juglar vein stenosis were 26, 14.10, 21.50 and 5.10 mm Hg (Panel 2a). There was no significant pressure difference between all stents after the first surgery (Panel 2b). The pressure differences before the second surgery between the anterior part of the superior sagittal sinus and the right transverse sinus, the anterior and posterior part of the superior sagittal sinus and the two ends of the right transverse sinus stenosis were 44, 33.30 and 11.10 mm Hg (Panel 2c). There was no significant pressure difference between all stents after the second surgery (Panel 2d).

织,组织学观察(HE染色),左侧顶叶水肿的白质内可见肿瘤细胞增生浸润,细胞密度偏低,部分胞核呈明显异型性,未见微血管增生及明确坏死(图6a);免疫组化染色(DAB法),肿瘤细胞胞核表达少突胶质细胞转录因子2(Olig-2)、X连锁α地中海贫血伴精神发育迟滞综合征蛋白(ATRX)、DNA拓扑异构酶Ⅱ(DNA TopoⅡ)、组蛋白H3第27位赖氨酸三甲基化(H3K27Me3),Ki-67抗原标记指数为5%~10%(图6b);胞质表达胶原纤维酸性蛋白(GFAP)、波形蛋白(Vim)、微管相关蛋白-2(MAP-2)、B细胞淋巴瘤/白血病-2(Bcl-2)、O^6-甲基鸟嘌呤-DNA甲基转移酶(MGMT);胞质和胞核共表达表皮生长因子受体(EGFR)、S-100蛋白(S-100)。最终诊断为胶质母细胞瘤(WHOⅣ级)。后因左眼失明、右眼仅存光感,且反复癫痫发作至当地医院就医(12月28日),并行左侧额叶胶质母细胞瘤切除术+脑室腹腔分流术+Omaya囊装置植入术(12月30日)。术后病理学检查提示为高级别胶质母细胞瘤(WHOⅣ级),*IDH*野生型。术后放化疗效果欠佳,于2020年8月死亡。

讨　论

胶质母细胞瘤是成人最常见且最具侵袭性和增殖性的原发性中枢神经系统肿瘤[3-4],具有显著的细胞多形性、内皮增生和推压边缘之特点[5],尤以*IDH*野生型最为常见[6],根据2021年WHO中枢神

表1 二次入院后脑脊液检查结果

Table 1. Results of CSF after the second admission

脑脊液检查	压力（mm H_2O）	白细胞计数（$\times 10^6$/L）	蛋白定量（mg/L）	葡萄糖（mmol/L）
检测时间				
2019-05-16	280	8	540	2.09
2019-05-20	330	2	460	2.20
2019-05-23	330	4	630	2.02
2019-06-03	>330	10	520	2.50
2019-08-29	>330	7	1020	1.50
2019-08-30	>330	5	820	1.94
2019-09-04	>330	9	930	1.79
正常参考值	80~180	0	150~450	2.50~4.40

图3 二次入院时头部影像学所见 3a，3b 横断面抑脂FLAIR成像和T_2WI显示，左侧侧脑室枕角旁呈高信号（箭头所示） 3c 矢状位增强MRBTI显示，脑静脉窦、脑深静脉、皮质静脉管壁均无明显增厚强化，仅上矢状窦局部硬脑膜强化（箭头所示） 3d 侧位增强MRV显示，上矢状窦显影断续（箭头所示）

Figure 3 Head imaging findings on the seccond admission Axial fat suppression FLAIR (Panel 3a) and T_2WI (Panel 3b) showed the hyperintensity in the inferior horn of left lateral ventricle (arrows indicate). Sagittal enhanced MRBTI showed no obvious enhancement in venous sinus, deep cerebral vein and cortical vein, only enhancement in local dura of superior sagittal sinus (arrow indicates, Panel 3c). Enhanced lateral view of MRV showed intermittent development in superior sagittal sinus (arrow indicates, Panel 3d).

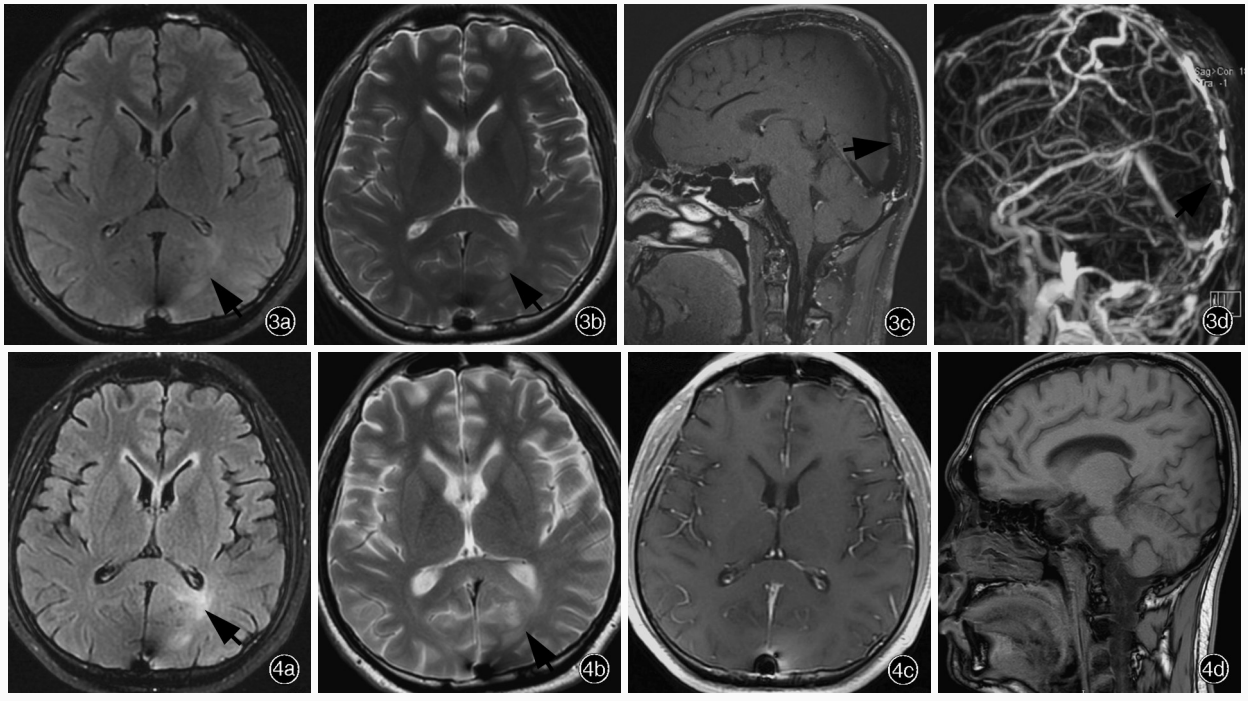


图4 三次入院时头部MRI所见 4a 横断面抑脂FLAIR成像左侧侧脑室枕角旁呈高信号（箭头所示），且较前明显 4b 横断面T_2WI左侧侧脑室枕角旁呈高信号（箭头所示） 4c 横断面增强T_1WI上述病灶区无明显强化 4d 矢状位增强T_1WI上述病灶区无明显强化

Figure 4 Head MRI findings on the readmission Axial fat suppression FLAIR showed hyperintensity in the inferior horn of left lateral ventricle (arrow indicates, Panel 4a), obvious than before. Axial T_2WI showed hyperintensity in the inferior horn of left lateral ventricle (arrow indicates, Panel 4b). Axial (Panel 4c) and sagittal (Panel 4d) enhanced T_1WI showed no obvious enhancement in focus.

经系统肿瘤分类（第五版）中基于形态学、免疫学、分子生物学和遗传学的肿瘤分类，胶质母细胞瘤为WHOⅣ级[7]。胶质母细胞瘤早期影像学表现不典型，进展至晚期，MRI可呈现T_1WI低信号、T_2WI高信号或混杂信号，增强后肿瘤灶呈明显强化。其标准治疗方案为肿瘤切除术、放疗和化疗，但所有治疗方案均属于姑息性干预措施[8]，多数患者于初诊6~12个月内死亡，即使重复施行切除术、放疗或挽救性化疗，其总的平均生存期也仅为14.6个月[9-10]。胶质母细胞瘤患者预后不良的原因有多种，主要与手术干预的局限性、多种药物的耐药性，以及放疗范围不确定性等因素有关[11-12]。

本文患者早期影像学检查占位表现不明显，主要以颅内高压表现占主导，外院最初考虑为特发性高颅压，经大剂量激素冲击及脱水等药物治疗视力障碍仍进行性加重，后拟诊为恶性颅内高压，施行

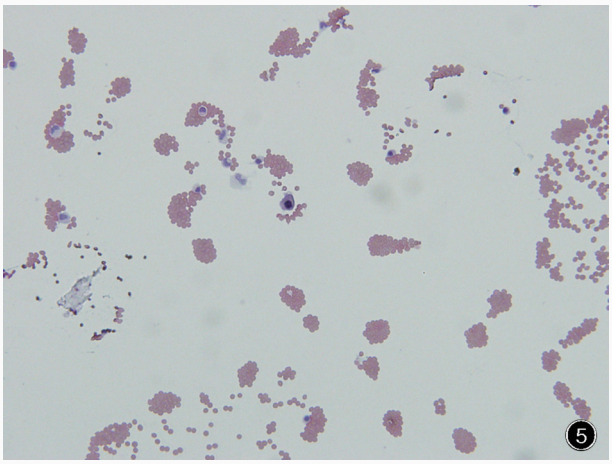
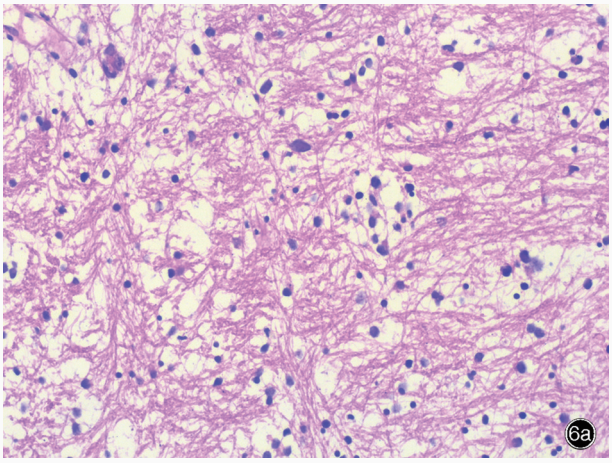
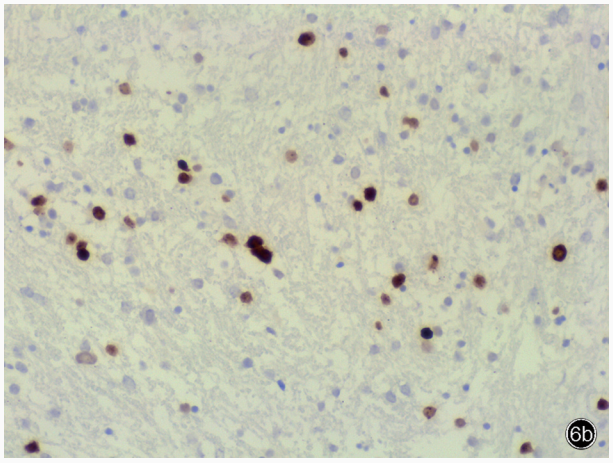


图5　三次入院后脑脊液细胞学检测，光学显微镜下可见核大、呈深染的异形细胞　HE染色　低倍放大　**图6**　左侧顶叶组织活检术光学显微镜所见　中倍放大　6a　水肿的白质内可见肿瘤细胞浸润、增生，细胞密度偏低，部分胞核呈明显异型性，未见微血管增生及坏死　HE染色　6b　肿瘤细胞胞核表达Ki-67抗原　免疫组化染色（DAB法）

Figure 5　Cytology of CSF on the third admissions, light microscopy showed heteromorphic cells with large, hyperchromatic nuclei.　HE staining　Low power magnified　**Figure 6**　Light microscopy findings of biopsies from the left parietal lobe　Median power magnified　All edematous white matter with proliferative infiltration of tumor cells, low cell density, some nuclei with obvious heterogeneity, without microvascular proliferation and clear necrosis (Panel 6a).　HE staining　Tumor cells nucleus expressed Ki-67 (Panel 6b).　Immunohistochemical staining (DAB)





脑静脉窦支架植入术。对于某些恶性特发性高颅压患者，脑静脉窦支架植入术可作为视神经鞘开窗术或脑脊液分流术的替代方案，及时手术干预可以最大程度地增加视力恢复机会[13]；依据本文患者脑静脉窦狭窄两端压力差先后植入13枚支架，但术后并未达到预期的疗效，颅内高压未得到缓解，头痛症状仍间歇性发作。引发我们对特发性高颅压支架植入术的思考，在McDougall等[14]开展的一项Meta分析中，共纳入32项计186例行支架植入术的特发性高颅压患者，4例（2.15%）术后症状进一步加重，18例（9.68%）症状无改善，117例（62.90%）症状部分好转，47例（25.27%）症状完全缓解，预后良好组植入支架前狭窄两端平均压力差高于预后不良组[（22.8 ± 11.5）mm Hg对（17.4 ± 8.0）mm Hg，P = 0.033]，两组患者术后平均压力差异不具统计学意义[（2.8 ± 4.0）mm Hg对（2.7 ± 2.0）mm Hg，P = 0.934]，提示唯有选择合适的开放压力值方能使高于该压力值的特发性高颅压患者术后获益。有研究显示，脑脊液引流通畅后脑静脉窦狭窄和狭窄两端压力差甚至可以完全消失[15]。Biousse等[16]针对特发性高颅压的病因学研究发现，颅内压升高可导致脑静脉窦狭窄，从而加重静脉回流障碍，影响脑脊液重吸收，进一步加剧颅内高压，形成恶性循环，在这种情况下，当狭窄两端压力差过高时，仍可通过支架植入术防止静脉壁塌陷。值得注意的是，脑静脉窦狭窄分为内生型和外压型两种[17]，内生型是管腔内病变造成静脉回流障碍致脑静脉窦狭窄；外压型则是由肿瘤压迫等因素造成颅内高压，导致脑静脉窦受压、窦壁塌陷，最终形成外压型狭窄。内生型狭窄导致的颅内高压，当狭窄两端呈现明显的压力差（≥8 mm Hg）时，可通过脑静脉窦支架植入术加以纠正；而由外压型狭窄导致的颅内高压，则应优先处理原发病变，效果欠佳者可考虑脑室-腹腔分流术或腰大池-腹腔分流术，提示由外压型狭窄导致的颅内高压患者不宜行支架植入术[17]。本文患者为胶质母细胞瘤导致的恶性颅内高压，脑静脉窦狭

窄类型为外压型，因此并不适合行支架植入术。

本文患者入院后多次行腰椎穿刺脑脊液检查，蛋白定量较高、葡萄糖较低，提示细胞代谢旺盛，排除感染因素后经脑脊液和组织病理学证实为胶质母细胞瘤，但其入院后多次MRI增强扫描肿瘤灶未见明显强化表现，推测可能与疾病早期血-脑屏障未受累，强化剂难以到达肿瘤灶有关，此外肿瘤组织血管密度低、血运不丰富[18]也是增强扫描病灶无明显强化的重要原因之一，从而加大临床诊断难度。胶质母细胞瘤患者颅内压升高的可能病理生理学机制：(1)血-脑屏障破坏。肿瘤瘤体压迫周围微血管，使局部脑血流量(CBF)减少、流速降低[19-21]，随着肿瘤细胞不断增殖形成血-肿瘤屏障脉管系统，这种极具异质性的脉管系统具有不均匀渗透性，小分子物质主动流出[22]；与此同时，肿瘤细胞代谢及营养需求增加使微血管模式发生改变并形成新生血管[23-25]，与正常血-脑屏障相比更易发生渗漏[24]，使肿瘤周围组织水肿，继而诱发颅内高压[26]。(2)功能淋巴系统回流障碍。既往研究认为脑组织缺乏淋巴系统，脑脊液通过蛛网膜颗粒吸收后进入脑静脉窦[27-28]；但近年研究发现，上矢状窦和横窦等硬脑膜窦中存在广泛的功能性淋巴管，脑膜间隙和脑实质可以通过功能性淋巴管排出脑脊液以及免疫细胞等[29-30]。目前有关功能淋巴系统的概念已有新的扩展，涉及血管旁途径，即邻近的蛛网膜下腔和脑间质液(ISF)的脑脊液，可通过功能淋巴系统进入脑膜淋巴管，进而转移到颈部淋巴结[31]。颈部淋巴结是胶质母细胞瘤颅外转移的常见部位[32-33]，亦支持脑组织中存在功能性淋巴系统的理论。Schwalbe[34]以普鲁士蓝为示踪剂，证实犬及家兔的蛛网膜下腔与颈部淋巴系统之间存在联系，Koh等[35]对多位学者不同时期的研究进行总结，亦证实Schwalbe[34]的结论。Ma等[36]通过MRI监测携带P40D680 NIR示踪剂的胶质瘤模型小鼠，观察到载瘤小鼠脊髓蛛网膜下腔至淋巴系统通路中有脑脊液流出。淋巴管流出功能在中枢神经系统中具有重要作用，尽管肿瘤相关血管网存在渗漏和水肿形成，脑脊液仍可通过淋巴管流出[34-36]。(3)物理性占位。随着肿瘤瘤体的增大，胶质母细胞瘤及其导致的相关水肿使脑组织占据更多的颅内空间，挤压蛛网膜下腔从而阻碍脑脊液循环[37]。我们推测本文患者所表现出的颅内高压可能即与脑血管壁渗漏、肿瘤周围组织水肿、脑脊液淋巴流出受阻有关[36]。

综上所述，恶性颅内高压伴脑静脉窦狭窄存在压力差的患者并非支架植入术的最佳适应证，尤其是外压型狭窄患者，同时需排除颅内肿瘤占位所诱发的颅内高压。胶质母细胞瘤患者的早期影像学表现不典型，其临床症状可能仅表现为恶性颅内高压，易被忽视，临床医师需提高诊断与鉴别诊断能力，早期进行积极治疗。

利益冲突 无

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