·论　著·

脑室播散型复发性胶质母细胞瘤放疗联合靶向治疗及免疫治疗后存活2.5年1例报道并文献复习

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【摘要】**目的** 探讨脑室播散型复发性胶质母细胞瘤(GBM)的治疗方法及疗效。**方法** 回顾性分析1例脑室播散型复发性GBM的临床资料,并结合相关文献进行总结分析。**结果** 1例57岁男性,因右侧颞枕叶占位,行开颅手术全切除病变,术后病理显示IDH野生型GBM(WHO分级4级),MGMT启动子非甲基化;术后给予标准Stupp方案治疗。术后1年复查MRI发现左侧脑室壁近室间孔处及透明隔结节样强化,考虑疾病进展,进行化疗5 d,因并发严重免疫抑制合并重症肺炎而停止化疗;4个月后复查MRI发现左侧尾状核头、胼胝体膝、透明隔结节样强化灶显著增大,对新发病灶行三维调强放疗;1个月复查MRI显示病变继续进展,双侧脑室及第四脑室软膜强化,考虑脑室播散。采用帕博利珠PD-1单抗和贝伐珠单抗治疗2个疗程,病灶完全消失。2年后,病人自行停用单抗治疗。停用半年复查MRI发现左侧脑室内广泛病灶,继续采用单抗治疗,但病变仍快速进展;1个月后复查MRI显示左侧侧脑室及第四脑室被强化的病灶完全填充,2个月后,病人死亡。**结论** 本文病例总生存期超过4年,自脑室播散后总生存期维持约2.5年。这提示放疗+靶向+免疫的联合治疗方案可能成为复发性GBM病人的可选治疗方案之一。

【关键词】胶质母细胞瘤;脑室播散;靶向治疗;免疫治疗;放射治疗

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Radiotherapy combined with targeted therapy and immunotherapy for ventricular disseminated recurrent glioblastoma surviving for 2.5 years: a case report and literature review

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【**Abstract**】 **Objective** To explore the treatment methods and efficacy of ventricular disseminated recurrent glioblastoma multiforme (GBM). **Methods** A retrospective analysis was conducted on the clinical data of a patient with ventricular disseminated recurrent GBM, and the relevant literature was summarized and analyzed. **Results** The patient was a 57-year-old male who underwent craniotomy for total resection of a right temporal-parietal lobe mass. The postoperative pathology showed IDH wild-type GBM (WHO grade 4) with unmethylated MGMT promoter. The patient received standard Stupp protocol treatment after surgery. One year after surgery, MRI showed nodular enhancement near the interventricular foramen and septum pellucidum on the left ventricular wall, suggesting disease progression. Five days of chemotherapy was administered, but it was stopped due to severe immunosuppression and severe pneumonia. Four months later, MRI showed significant enlargement of nodular enhancement in the left caudate nucleus, genu of the corpus callosum, and septum pellucidum. Three-dimensional intensity-modulated radiotherapy was performed on the new lesions. One month later, MRI showed continued disease progression with soft meningeal enhancement in both lateral ventricles and the fourth ventricle, indicating ventricular dissemination. Subsequently, two courses of combined treatment with pembrolizumab (PD-1 inhibitor) and bevacizumab were administered, and the lesions completely disappeared. Two years later, the patient stopped the monoclonal antibody treatment on his own. Six months after drug withdrawal, MRI showed extensive lesions in the left ventricle. Monoclonal antibody treatment was resumed, but the lesions still progressed rapidly. One month later, MRI showed that the left lateral ventricle and the fourth ventricle were completely filled with enhanced lesions. The patient died two months later. **Conclusion** The total survival period of this case exceeded 4 years, and the survival period after ventricular dissemination was approximately 2.5 years. This suggests that radiotherapy combined with targeted therapy and immunotherapy may be a potential treatment option for patients with recurrent GBM.

【**Key words**】Glioblastoma; Ventricular dissemination; Targeted therapy; Immunotherapy; Radiotherapy

胶质母细胞瘤(glioblastoma,GBM)是成人最常见的原发性恶性脑肿瘤,即使采用最大范围安全切除联合替莫唑胺(temozolomide,TMZ)同步放化疗及TMZ辅助化疗的Stupp方案治疗,中位生存期也仅有14.6~16个月[1,2],5年生存率仅约6.8%[3]。所有GBM术后均会复发,复发后中位总生存期仅约9个月[4]。术后局部复发是最常见的复发形式,但部分病人会

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出现沿脑室播散造成中枢神经系统远隔转移。目前，复发性GBM没有标准的治疗方案，再次手术、放疗、靶向治疗、免疫治疗、肿瘤电场治疗等为可选择的治疗方案。近年来，多模态联合治疗方案成为复发性GBM的治疗新方向[5]。本文报道1例脑室播散型复发性GBM，应用放疗联合靶向治疗及免疫治疗后存活2.5年。

1 病例资料

57岁男性，因头痛3个月、加重1 d于2018年9月24日急诊入院。体格检查：记忆力下降，未发现其他神经系统阳性体征；KPS评分100分。急诊CT发现右侧颞枕部占位伴周围低密度，考虑颅内肿瘤伴水肿可能。MRI显示右侧颞枕叶T_1低信号、T_2高信号、DWI高信号占位，呈现不均匀明显强化，考虑高级别胶质瘤可能（图1A~F）。2018年11月8日，行开颅手术切除右侧颞枕叶占位病变。术后72 h复查CT显示肿瘤全切除（图1G）。术后病理示IDH野生型GBM（WHO分级4级；图1H），MGMT启动子非甲基化。术后1个月起予标准Stupp方案治疗，即同步放化疗（TMZ，75 mg/m2，同步放疗2 Gy×30次）及TMZ辅助化疗（150~200 mg/m2）。每2~4个月规律随访，直至2019年9月16日，头MRI示左侧脑室壁近室间孔处及透明隔结节样强化，考虑疾病进展（progressive disease，PD）可能。1个月后复查，PD明确，遂于2019年10月18日进行化疗5 d（依托泊苷100 mg+卡铂100 mg，鞘内注射甲氨蝶呤10 mg×3）。由于化疗后出现严重免疫抑制继发重症肺炎，遂停用该化疗方案。2020年3年6日复查头MRI示左侧尾状核头、胼胝体膝、透明隔结节样强化灶较前显著增大，2020年3月28日针对新发病灶行三维调强放疗。2020年4月28日头MRI示病变继续进展，双侧脑室及第四脑室软膜强化，考虑脑室播散。在肿瘤持续PD的情况下，完善分子评估显示肿瘤突变负荷（tumor mutation burden，TMB）高达515.9/Mb，伴POLE基因14号外显子突变c.1381T>C(p.

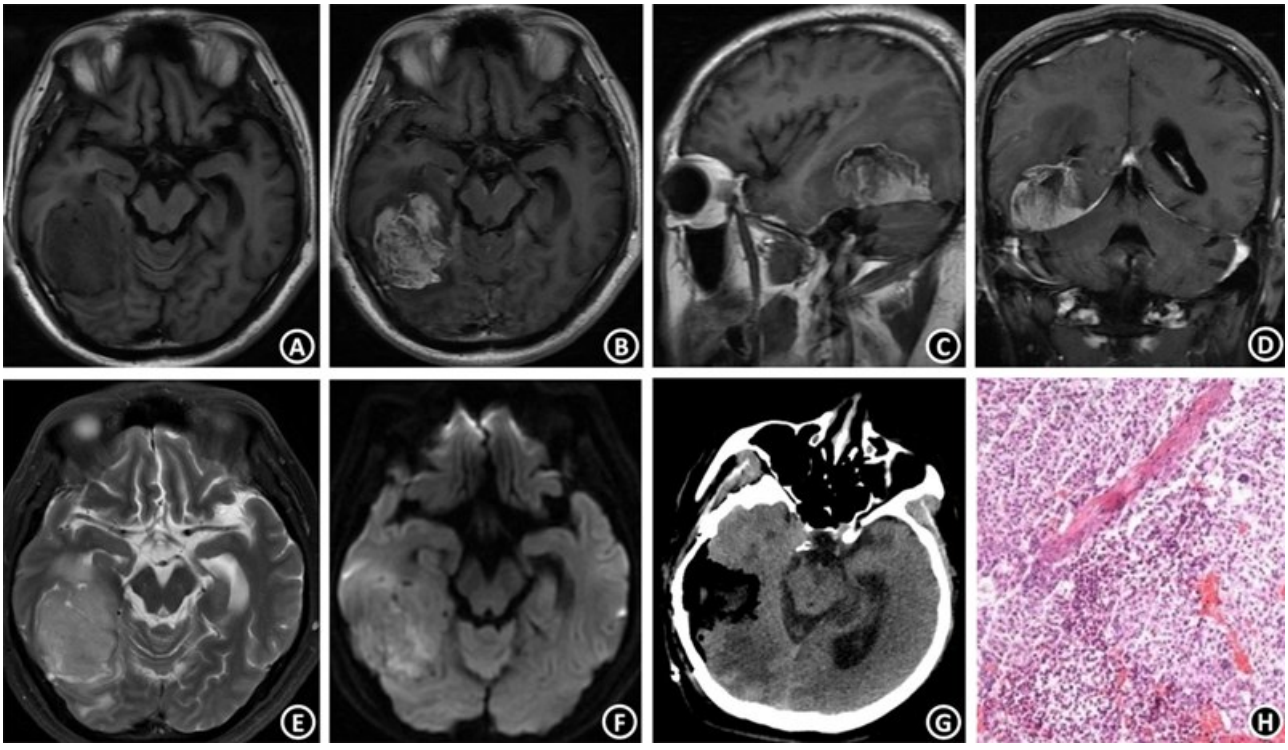

图1 右侧颞枕叶胶质母细胞瘤手术前后影像及术后病理表现

A-F. 术前MRI显示右侧颞枕叶占位病变，表现为T_1低信号、不均匀强化伴瘤内坏死、T_2高信号伴瘤周水肿、DWI高信号；G. 术后72 h复查头CT示肿瘤切除满意，瘤腔内未见出血；H. 术后病理（HE，×200）示胶质母细胞瘤（WHO 4级）

Figure 1 Preoperative and postoperative images and postoperative pathological manifestations of a patient with right temporoparietal glioblastoma

A-F: Preoperative MRI shows a space-occupying lesion in the right temporoparietal lobe, presenting as low signal on T_1, heterogeneous enhancement with intratumoral necrosis, high signal on T_2 with peritumoral edema, and high signal on DWI. G: Head CT 72 hours after surgery shows satisfactory tumor resection, and no hemorrhage is seen in the tumor cavity. H: Postoperative pathology (HE, ×200) shows glioblastoma (WHO grade 4).

Ser461Pro)。多学科会诊考虑手术可能无法带来生存获益,但该类肿瘤对免疫治疗倾向于显著获益,且联用贝伐珠单抗可协同抑制免疫治疗导致的脑水肿副反应,遂予以帕博利珠PD-1单抗(100 mg,每月一次)及贝伐珠单抗(200 mg,每两周一次),1个月为一个疗程)。一个疗程治疗后,颅内强化病灶缩小90%,达到部分缓解(partial response,PR);第二个疗程治疗后,病灶完全消失,评估达到完全缓解(complete response,CR)。自2020年5月11日开始,病人持续接受以上联合方案,直至2021年7月26日自行停用贝伐珠单抗、2022年2月11日自行停用潘博丽珠单抗。整个联合治疗过程中,病人的耐受良好,且未发生药物相关的并发症。病人肿瘤CR状态持续至2022年3月23日,头MRI示右侧脑室后角新发强化病灶。该病灶在随后的随访中持续增大,2022年9月1日发现左侧脑室内广泛病灶,ASL序列及PWI序列均显示高灌注。2022年9月起再次启用以上联合方案,但病变仍继续快速进展。2022年10月复查头MRI示左侧脑室及四脑室被强化的病灶完全填充(图2)。病人在后续2个月内,意识状态快速下降,病人家属选择接受安宁缓和医疗,最终于2022年12月3日死亡。

2 讨 论

复发性GBM的预后极差,至今仍无标准治疗方案[7]。本文病例MGMT启动子非甲基化的脑室播散的IDH野生型复发性GBM,由于肿瘤伴随有POLE驱动基因突变且TMB极高,联合应用放疗+抗血管内皮生长因子(vascular endothelial growth factor,VEGF)靶向治疗+抗PD-1免疫治疗后仅2个周期即出现完全缓解;脑室播散后生存期维持约2年半,总生存期达49个月。该病人的特殊点在于免疫检查点抑制剂和靶向治疗单药在治疗复发性GBM效果不佳的情况下,提供了联合治疗成功的例子。

神经肿瘤治疗反应评价(response assessment in neuro-oncology,RANO)标准是胶质瘤治疗后随访监测的公认标准[8],在此基础上,如病人接受免疫治疗则采用改良的神经肿瘤免疫治疗反应评价(immunotherapy response assessment for neuro-oncology,iRANO)标准进行评价[9]。本文病人首次出现放射治疗区域外的增强病灶时,随访采用RANO标准,而应用联合治疗方案后的随访采用iRANO标准。NCCN指南对复发性GBM提出多个推荐治疗方案,但无1级推荐方案。针对VEGF的贝伐珠单抗靶

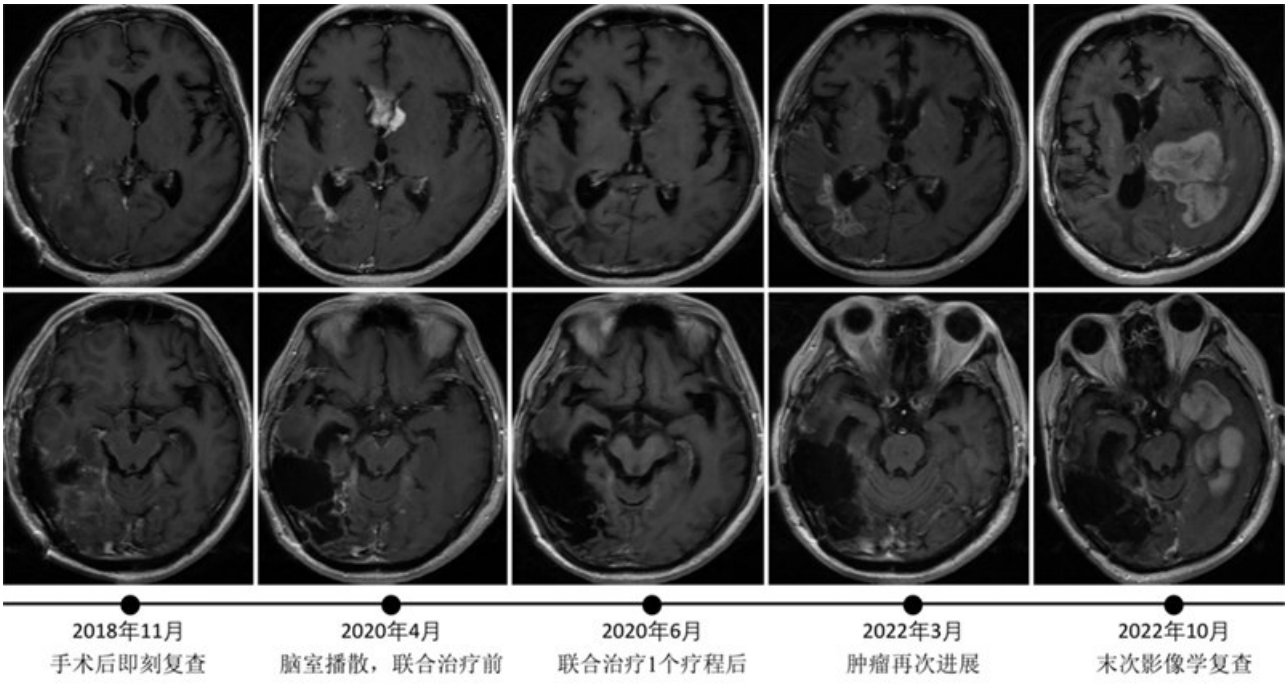

图2 右侧颞枕叶胶质母细胞瘤手术前后影像

以时间为轴线,展示了MRI在随访过程中的重要节点变化过程

Figure 2 Preoperative and postoperative images of a patient with right temporoparietal glioblastoma

The timeline shows the significant changes in MRI during the follow-up.

向治疗虽能够提高病人的无进展生存期，但无法改善病人的整体预后[4]。Checkmate 143临床试验比较了抗PD-1免疫治疗与抗VEGF靶向治疗，但仍未得出免疫治疗可提高复发GBM病人总生存的证据[10]。2021年4月，Sahebjam等[5]开展的Ⅰ期临床试验结果显示，放疗联合贝伐珠单抗靶向治疗及潘博丽珠免疫治疗可显著提高复发高级别胶质瘤病人生存期。虽然目前仍无大型Ⅲ期临床试验对联合治疗在提高复发GBM生存方面的确证结果，但上述联合治疗方案已在国际和国内逐步得到认可和应用。

本文病人从2020年3月底开始接受联合治疗方案，但以上联合方案在当时对高级别胶质瘤有生存获益的报道还未公开发布[6]。当时选择应用联合治疗的原因有两个：①对于TMB高的GBM以及伴有POLE基因突变的高级别胶质瘤，文献报道肿瘤对免疫治疗极为敏感，可提高病人生存期[11-13]；②免疫治疗单药可能加重局部脑水肿，贝伐珠单抗联合免疫治疗可辅助减轻水肿，提高病人的治疗耐受性，改善病人依从性。

术中开放脑室的GBM病人术后易出现肿瘤细胞随脑脊液流动而导致的播散进展。该类病人病情发展快，预后差，中位生存时间仅2~5个月[14]。本文病人在应用放疗联合靶向治疗及免疫治疗后，脑室播散病变迅速达到部分缓解、完全缓解，提示放疗+靶向+免疫的联合治疗方案可作为脑室播散性复发GBM病人的可选治疗方案。

MGMT启动子非甲基化的GBM病人对TMZ等烷化剂化疗反应不佳，新诊断GBM病人预后仅约12.7个月，显著差于MGMT启动子甲基化病人的中位生存期（21.7个月）[15]。本文病人接受联合放疗+靶向+免疫治疗后，总生存期达到49个月，也提示以上联合治疗方案可能作为MGMT启动子非甲基化的GBM复发时的可选治疗方案。

术后全病程管理对于改善GBM病人的预后至关重要。由于肿瘤在术后进展迅速，中位无进展生存期仅6个月且中位总生存期仅14.6~16个月，因此每2~4个月一次的随访可帮助及早发现病情改变，并及时做出治疗方案的更改。结合门诊随访、电话随访、网络随访，我院脑胶质瘤病人可达到2~4个月/次的规范化随访频率。

总之，本文病例为MGMT启动子非甲基化、高TMB、伴有POLE驱动基因突变的IDH野生型GBM病人，在接受TMZ同步放化疗及辅助化疗后疾病仍快速进展，并出现脑室播散；联合应用放疗+贝伐珠单抗靶向治疗+潘博丽珠单抗免疫治疗后，病人病情完全缓解，总生存期超过4年。这提示放疗+靶向+免疫的联合治疗方案可能成为复发性GBM病人的可选治疗方案之一，也有待随机对照临床试验的进一步验证。

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