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Case Report

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Recurrent Glioblastoma with Turcot Syndrome

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ABSTRACT

Turcot syndrome (TS) is an extremely rare genetic disorder characterized by the concurrent occurrence of primary brain tumors and colorectal cancer. The prognosis for patients with TS is typically poor. A 57-year-old man with TS who developed recurrent glioblastoma and had a family history of colon cancer is reported. In 2022, the patient underwent robot-assisted stereotactic surgery for the resection of a central nervous system (CNS) tumor. Molecular genetic analysis identified microsatellite instability in the DNA mismatch repair (MMR) gene, confirming the diagnosis of TS. Additional mutations in the ATM and TP53 genes were also detected, which are rarely associated with TS. Despite treatment with the Stupp regimen, the patient experienced acute neurological deterioration, ultimately resulting in death 15 months after the onset of symptoms. Molecular diagnostics play a crucial role in guiding appropriate care and management for patients with TS. Early diagnosis, genetic testing, and preventive measures are essential for the effective management of this condition.

KEYWORDS: Turcot syndrome, Diffuse astrocytoma, Recurrent tumors of the central nervous system

INTRODUCTION

TS is a rare condition characterized by the co-occurrence of multiple gastrointestinal colon polyps and CNS neuroepithelial tumors (4). Brain tumors associated with TS vary in type, often presenting as single glioblastomas, medulloblastomas, or astrocytomas (6). The presence of multiple CNS tumors in TS is exceptionally rare, and the syndrome typically manifests in early adolescence. TS can be genetically classified into two subtypes: familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC) (12). Furthermore, TS is divided into type I, characterized by glial tumors with fewer polyps and cancers, and type II, characterized by extensive polyps and a higher risk of medulloblastoma (4).

Since the initial identification of TS, the literature has been limited to isolated case reports and small case series. TS type I commonly involves glioblastomas associated with mutations in DNA MMR genes, particularly in the hMLH1 gene. Herein, we present a case of TS with a unique progression from wild-type diffuse astrocytoma to glioblastoma, resulting in rapid neurological decline and ultimately leading to the patient's death.

CASE REPORT

In July 2021, a 57-year-old male presented with episodes of involuntary head movement, left-sided facial numbness, and a skewed mouth. Each episode lasted approximately one

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minute and resolved spontaneously. The patient's medical history included open surgery for colon cancer in 2003, with no recurrence noted during regular colonoscopies. He had a 40-year history of smoking and a family history of colorectal cancer affecting his grandfather, father, and sister.

Physical examination revealed a 12-cm surgical scar extending from below the umbilicus to the symphysis pubis and a café-au-lait spot on the skin (Figure 1). A brain MRI (Figure 1) performed upon admission showed long T1 and T2 patchy signals in the right frontal lobe-corona radiata, without enhancement on contrast imaging. MRS indicated a Cho/Cr peak ratio of 0.81–1.94 (Figure 1), suggesting a non-neoplastic lesion. However, 11C-methionine PET/CT (Figure 1) revealed a slightly hypodense lesion in the right frontal lobe, exhibiting increased methionine uptake, which was indicative of a neoplastic process. Due to the lesion's location in a functional area of the right frontal lobe and its diffuse nature, a stereotactic biopsy was performed after obtaining consent from the patient's family.

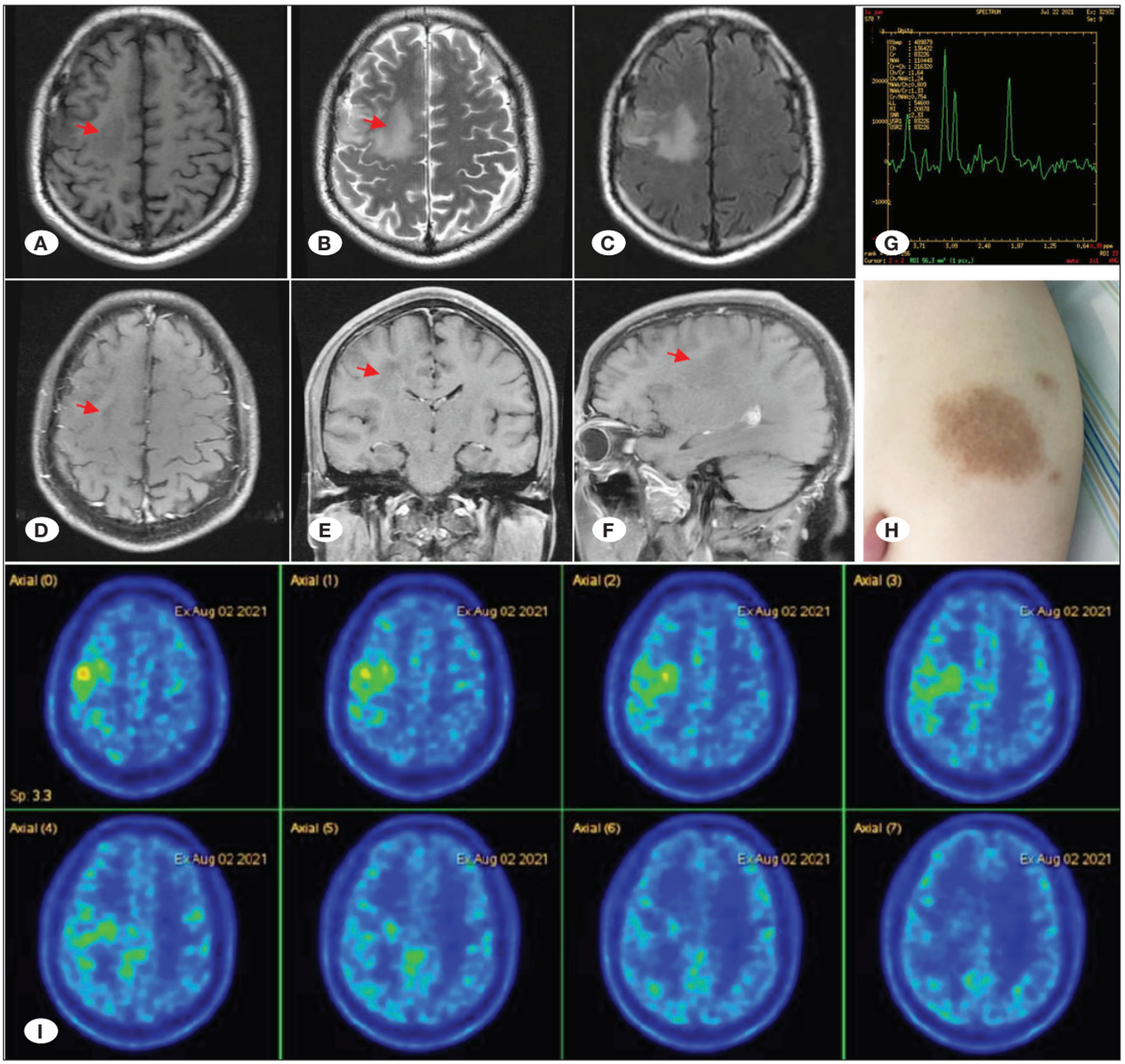

Figure 1: A) T1WI; **B)** T2WI; **C)** Flair; **D, E, F)** T1CE in transection, coronal, and sagittal positions. Brain MRI revealed long T1 and T2 patchy signals in the right frontal lobe-corona radiata. **G)** MRS indicated a Cho/Cr peak ratio of 0.81–1.94. **H)** Photograph of the patient skin caf´e-au-lait spot. **I)** 11C-methionine PET/CT showed enhance signal in right frontal lobe-corona region.

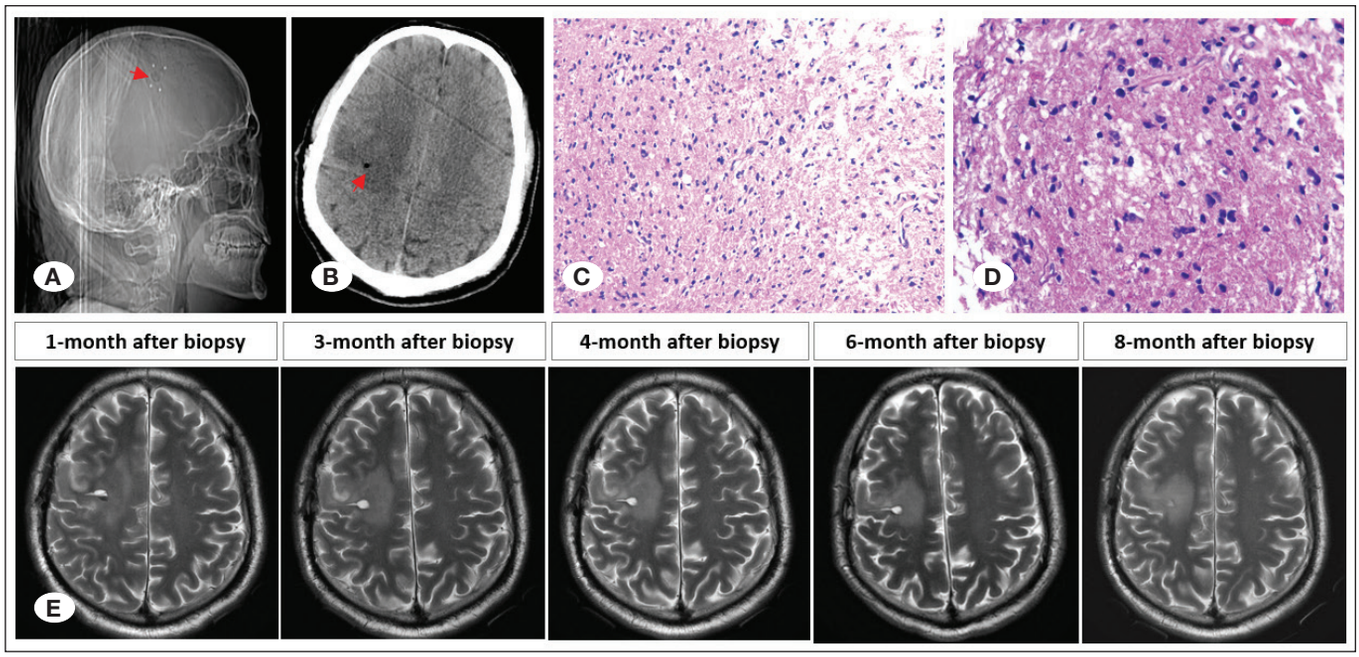

Figure 2: A, B) Postoperative X-ray images of the patient showed the surgical site. **C, D)** Histopathology showed diffuse astrocytoma (WHO grade II) in the primary biopsy. **E)** Brain MRI of patients 1 to 8 months after surgery.

The patient underwent a robot-assisted stereotactic lesion biopsy, and histopathology confirmed the presence of a WHO grade II diffuse astrocytoma (Figure 2). The immunohistochemistry results are summarized in Table I. Based on the 5th Edition WHO Classification of CNS Tumors, the morphology was consistent with a grade II IDH wild-type diffuse astrocytoma, which warranted consideration as a higher WHO grade. Subsequent gene sequencing (Table I) revealed high microsatellite instability (MSI-H) with a tumor mutation burden of 16.71. Furthermore, a frameshift mutation in the ATM gene (c.640del, p.Ser214Profs*16) with 24.8% abundance, along with an MSH2 mutation, confirmed the diagnosis of IDH wild-type astrocytoma and TS type I. The patient received treatment with the standard Stupp regimen, which included one month of concurrent chemoradiotherapy. The radiotherapy regimen consisted of GTV1: 2GY/30F/60GY and CTV1: 1.8GY/30F/54GY, while temozolomide was administered at a dose of 200 mg/m² on days 1–5, every 28 days for six cycles. Follow-up brain MRI demonstrated lesion shrinkage (Figure 2).

In June 2022, 10.5 months after the surgery and two months following the completion of chemotherapy, the patient presented with blurred vision. Upon examination, the patient exhibited clear consciousness, impaired cognition, slow movements, slurred speech, binocular papilledema, grade 2 muscle strength in the left limb, and grade 4 muscle strength in the right limb. MRI revealed the presence of multiple space-occupying lesions in the posterior third ventricle, right basal ganglia, and subependymal area, accompanied by obstructive hydrocephalus (Figure 3). To alleviate the hydrocephalus, the patient underwent a third ventriculostomy procedure under general anesthesia. Simultaneously, an endoscopic tumor biopsy was performed near the interventricular foramen, which revealed

Table I: The Summary of Immunohistochemical Results and Gene Detection Data

Protein	Result	Gene	Result
IDH1	(-)	IDH1	(-)
EMA	(-)	IDH2	(-)
ATRX	(-)	1p/19q	Non-codeletion
H3K27ME3	(+)	MGMT methylation	(-)
H3K27M	(-)	ATRX	(-)
BCL2	(+)	TERT	(-)
BCL6	(-)	BRAF	(-)
MUM1	(-)	EGFR	(-)
C-MYC	(-)	PTEN	(-)
Ki-67	(+, >5%)	PIK3CA	(-)
Olig-2	(+)	CDKN2A	(-)
S-100	(-)	CDKN2B	(-)
P53	(-)	ATM	Ser214Profs*16 24.8%
SYN	(-)	TP53	D41Ifs*2 36.5% R267W 33.3%
CD3	(-)	NF1	(-)
CD5	(-)	NF2	(-)
CD10	(-)	MEN1	(-)
CD19	(-)	TSC1	(-)
CD34	(+)	TSC2	(-)
D20	(-)	APC	(-)
		MMR	MSH2 deficiency

the presence of IDH wild-type glioblastoma (WHO grade IV) in the right basal ganglia (Figure 4). The molecular pathology results included IDH1(-), ATRX(+), H3K27M(-), H3K27Me3(+), and CDKN2A/B(-). Following the surgery, a marked improvement in postoperative hydrocephalus was observed. Three weeks after the surgical intervention, the patient reported improved vision and relief from headaches. Muscle strength was assessed as grade 4 in both the left and right limbs. The pa-

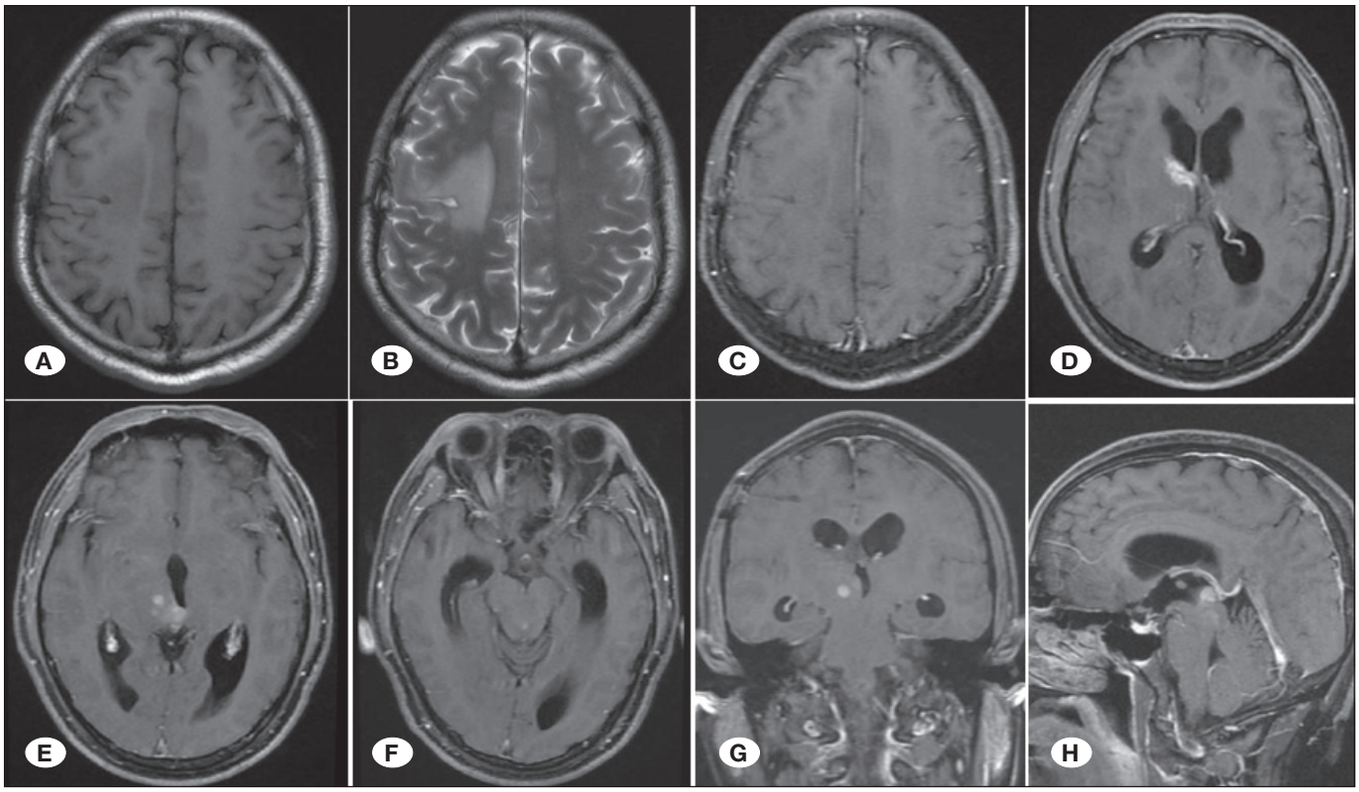

Figure 3: A) T1WI; **B)** T2WI; **C-H)** T1+C. There was no significant change in the original right-side lesions. MRI indicated multiple space-occupying lesions in the posterior third ventricle, right basal ganglia, and subependymal area, with obstructive hydrocephalus.

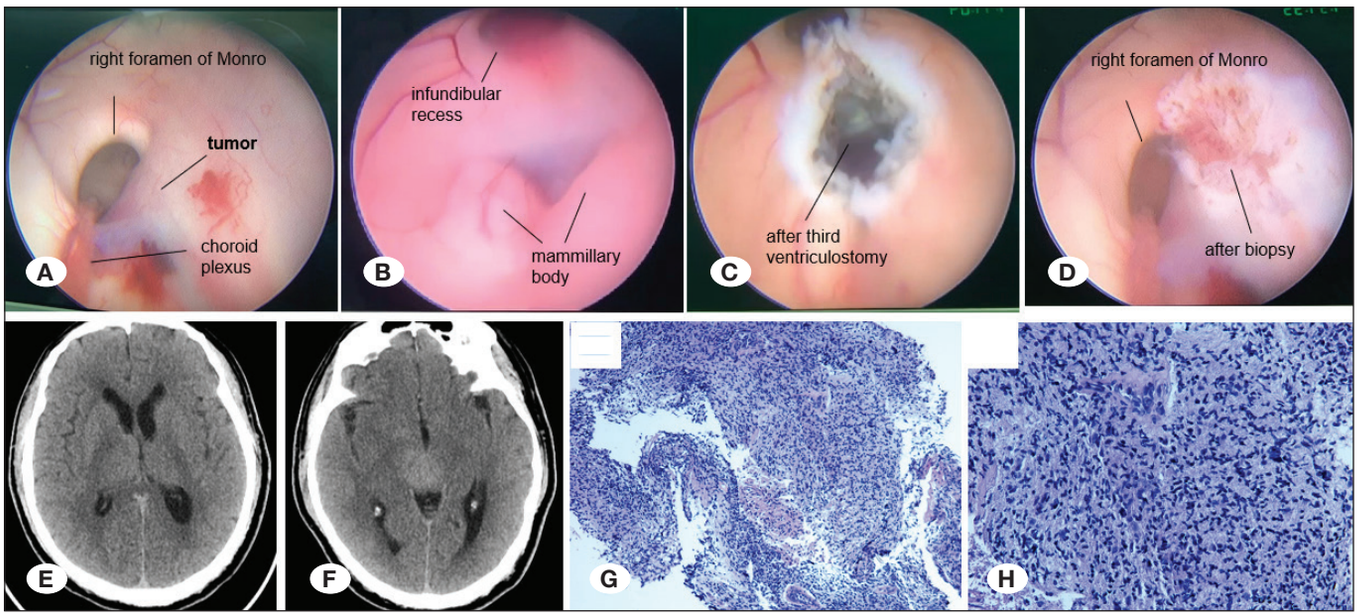

Figure 4: A-D) Endoscopic third ventriculostomy and biopsy of the foramen of Monro tumor performed successively under ventriculoscopy. **(E, F)** The postoperative hydrocephalus was significantly relieved. Histopathology revealed **(G, H)** IDH wild-type glioblastoma (WHO grade IV) in the right basal ganglia.

tient received treatment with temozolomide and bevacizumab and was subsequently discharged on August 1, 2022. However, the patient was readmitted on August 12, 2022, due to further alterations in consciousness. Repeat imaging revealed a significant enlargement of the right thalamus lesion, which compressed the brainstem (Figure 5). The patient experienced an acute deterioration and ultimately succumbed to his illness 15 months after the onset of neurological symptoms.

DISCUSSION

The present case report discusses TS, a rare and heterogeneous syndrome characterized by the association between primary brain tumors and colorectal polyposis, with only approximately 150 cases documented in the literature (2,9).

McKusick first described TS and suggested an autosomal recessive inheritance pattern. However, the onset of colonic polyposis during adolescence, which carries a high risk of malignancy and eventual CNS involvement, is a common feature of TS (11). In one notable family case, three siblings had colorectal adenocarcinoma, with two developing colonic adenomatosis and a 13-year-old relative presenting with TS. These observations suggest that TS may involve an autosomal gene with pleiotropic and variable expression (3). In the present case, a history of colorectal polyposis across three generations suggests a possible dominant inheritance pattern.

TS is considered a phenotypic variant of HNPCC and FAP. HNPCC is attributed to germline mutations in DNA MMR genes, including MLH1, PMS1, PMS2, MSH2, or MSH6 (5), with an MSH2 mutation confirmed in the patient presented here. Turcot syndrome is thought to develop from the loss of two alleles of the tumor suppressor gene and is classified into two main subtypes: Turcot syndrome 1 and Turcot syndrome 2, determined by the mutated genes. Turcot syndrome 1 is caused by the loss of two wild-type alleles of one or more genes involved in DNA MMR, while Turcot syndrome 2 is caused by the loss of two wild-type alleles of the APC gene (8). Characteristic skin manifestations, such as café-au-lait spots, melanocytic nevi, or aggressive fibromatosis, are exhibited by approximately 50% of TS patients. Café-au-lait spots are more frequently observed in TS type I patients, which was also noted in the case presented herein.

In the present case, the patient had a history of colorectal cancer and glioma, with café-au-lait spots observed on physical examination. Molecular analysis of the tumor specimen confirmed a deficiency in the MMR gene MSH2, leading to a diagnosis of TS type I. A stereotactic biopsy of the lesion revealed a WHO grade II diffuse astrocytoma with wild-type isocitrate dehydrogenase (IDH) status. Although molecular alterations such as EGFR amplification, gain of chromosome 7 with loss of chromosome 10 (+7/-10), or TERT promoter mutations could indicate a diagnosis of IDH-wildtype glioblastoma, none of these alterations were identified in this particular case. Given the prognostic implications associated with the IDH wild-type status, treatment was administered following a protocol typically used for higher WHO grade tumors, de-

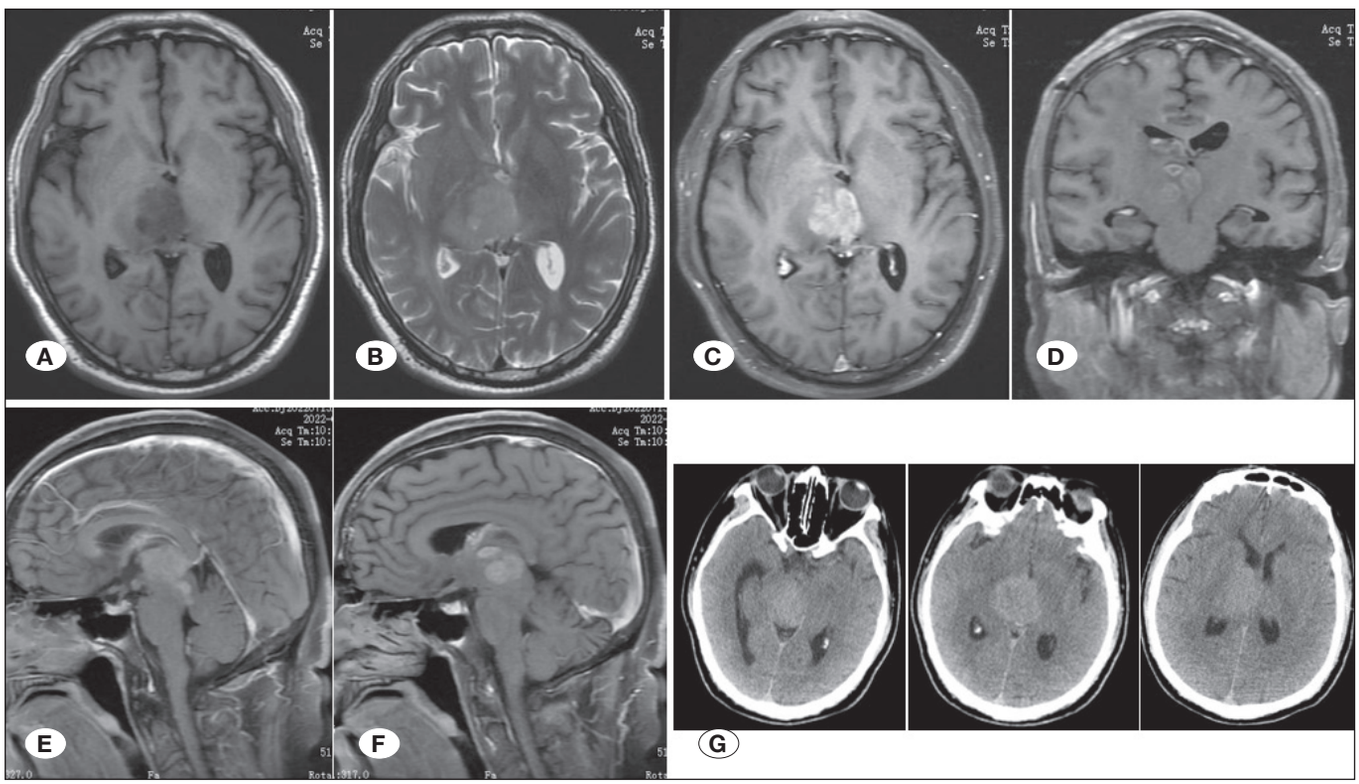

Figure 5: A) T1WI; **B)** T2WI; **C-F)** T1+C; **G)** CT. Head CT was re-examined on August 12 **(G)**, and compared with brain MRI **(A-F)** on July 23, the lesions of the right thalamus were significantly enlarged and compressed the brain stem.

spite insufficient evidence to support a grade IV classification. Subsequent genetic sequencing confirmed the deficiency in MSH2, with no mutation detected in the adenomatous polyposis coli (APC) gene, and treatment was continued using the Stupp regimen.

Distinguishing TS from similar syndromes, such as neurofibromatosis type I (NF-1) or constitutional mismatch repair deficiency syndrome (CMMRDS), is crucial due to overlapping features, including café-au-lait spots and increased malignancy risks. NF-1 increases susceptibility to CNS tumors and gliomas, while CMMRDS predisposes patients to various malignancies (10). Genetic analysis plays a vital role in achieving an accurate diagnosis, underscoring the critical importance of molecular pathology in glioma diagnosis. Lynch syndrome, another genetic disease caused by mutations in MMR genes such as MLH1, MSH2, MSH6, and PMS2, results in defective DNA mismatch repair function, increasing the risk of colorectal, endometrial, ovarian, and other cancers. However, compared to Turcot syndrome type I, the risk of developing central nervous system tumors is relatively low in Lynch syndrome (1). Differential diagnosis between TS type I and Lynch syndrome should be based on clinical presentation, family history, and genetic testing results.

TS is associated with a poor prognosis, especially in patients presenting with both CNS tumors and colorectal cancer. Among the various tumor types, glioblastoma multiforme generally confers the worst outcomes, with an average survival of approximately 27 months (4). The management of TS primarily focuses on early diagnosis, genetic testing, and preventive care. Upon tumor development, treatment is supplemented by surgical resection, chemotherapy, and, in some cases, radiotherapy. In the present case, the patient underwent two biopsies and received concurrent chemoradiotherapy, adjuvant chemotherapy, dose-dense temozolomide, and bevacizumab. Although the initial treatment showed effectiveness, the patient ultimately succumbed to tumor recurrence and ventricular dissemination, resulting in a survival period of 14 months. In contrast, a case of CMMRD concurrent with glioblastoma has been reported, in which the patient exhibited good tolerance and efficacy following combined treatment with nivolumab and CCNU, leading to continuous tumor remission (7). This suggests the potential efficacy of immune checkpoint inhibitors in the treatment of hypermutated tumors.

CONCLUSION

In conclusion, TS results from germline defects in either the APC gene or DNA mismatch-repair genes. Molecular diagnostics play a crucial role in guiding appropriate care and management for patients with TS. Effective management of TS involves early diagnosis, genetic testing, and preventive measures.

Declarations

Funding: There is no funding for this case report.

Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

Ethics Approval: This case report was written in accordance with COPE guidelines and complies with the CARE statement. The manuscript adheres to the principles outlined in the 1964 WMA Declaration of Helsinki. All procedures performed and treatments received were part of routine care. The patient and his family kindly provided consent for the reporting of his case, which included imaging and histology. Anonymity is guaranteed in keeping with Information Governance stipulations of the National Health Service.

Patient Consent: The patient has kindly provided informed consent for publication of his case and for use of his imaging, and patient anonymity is hereby respected. This is confirmed in an entry in the patient's medical notes. Receipt of patient consent is guaranteed by Weiguo Hu.

AUTHORSHIP CONTRIBUTION

Study conception and design: QC, WH
Data collection: GD, ZF
Analysis and interpretation of results: ZF, WH
Draft manuscript preparation: ZF, GD, JZ
Critical revision of the article: GD, QC, QS
All authors (ZF, GD, JZ, QS, BL, ZX, HH, NZ, HO, QC, WH) reviewed the results and approved the final version of the manuscript.

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