Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4180-24
Intern Med 64: 1189-1193, 2025
http://internmed.jp

【 CASE REPORT 】

Glioblastoma Arising in Lynch-like Syndrome after Repeated Development of Colorectal Cancers

Ayako Togawa[1], Masayuki Ueno[1,2], Mari Yamaoka[1,3], Kensuke Takada[4], Shinichi Nishina[5,6], Yuki Ikeda[1], Yosuke Uenishi[1], Ayako Hata[1], Toshifumi Mano[1], Toshikazu Moriwaki[1], Hirokazu Mouri[1] and Motowo Mizuno[1]

Abstract:
We herein report a patient with Lynch-like syndrome in whom a brain tumor (glioblastoma) developed after repeated resection of colorectal cancer. The patient had a significant family history of cancer. Immunohistochemical expression of mismatch repair proteins was decreased in both brain and colon tumors, but no pathogenic variant of the related genes was detected. Although brain tumors occasionally develop in Lynch syndrome, they have not been reported in cases of Lynch-like syndrome. This first report of Lynch-like syndrome with the development of glioblastoma suggests the need for further investigation on the surveillance of brain tumors in patients with this syndrome.

Key words: mismatch repair deficiency, brain tumor, Turcot syndrome, hereditary nonpolyposis colorectal cancer

(Intern Med 64: 1189-1193, 2025)
(DOI: 10.2169/internalmedicine.4180-24)

Introduction

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer, is an autosomal dominant hereditary disorder primarily caused by germline variants of mismatch repair (MMR) genes (1). Deficiency in the MMR function increases the risk of a range of malignant tumors, such as colorectal, endometrial, gastric, ovarian, small bowel, renal, and brain cancers (1). The definitive diagnosis of Lynch syndrome requires detection of pathogenic mutations in MMR genes, *EPCAM*, or abnormal methylation in the promoter region of *MLH1*. In some cases, clinical and immunohistochemical evidence of Lynch syndrome is present; however, the genetic abnormalities described above are absent, which is defined as Lynch-like syndrome (2).

Possible reasons for the absence of pathogenic abnormalities in these genes in Lynch-like syndrome include unknown pathogenic mutations in MMR genes, germline mutations in other genes affecting the MMR system, and hypermethylation of tumor suppressor genes (2). However, the clinical characteristics of Lynch-like syndrome have not been fully elucidated, and the development of brain tumors in this syndrome has not been reported (3).

We herein report a case of glioblastoma in a patient with Lynch-like syndrome. This case report was prepared according to the CARE guidelines (4).

Case Report

A 45-year-old man was referred to our hospital after surgery for early-onset advanced rectal cancer at 32 years old. He had a strong family history of cancers, including stomach, colon, and prostate cancers in his father and ovarian and uterine cancers in his sister (Fig. 1). Lynch syndrome was suspected because of the early onset of rectal cancer

[1]Department of Gastroenterology and Hepatology, Kurashiki Central Hospital, Japan, [2]Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, Japan, [3]Department of Gastroenterology and Hepatology, Seiyu Clinic, Japan, [4]Department of Neurosurgery, Kurashiki Central Hospital, Japan, [5]Department of Medical Oncology, Kurashiki Central Hospital, Japan and [6]Department of General Surgery, Kurashiki Central Hospital, Japan
Received: May 23, 2024; Accepted: August 16, 2024; Advance Publication by J-STAGE: September 27, 2024
Correspondence to Dr. Masayuki Ueno, masayukiu@kuhp.kyoto-u.ac.jp

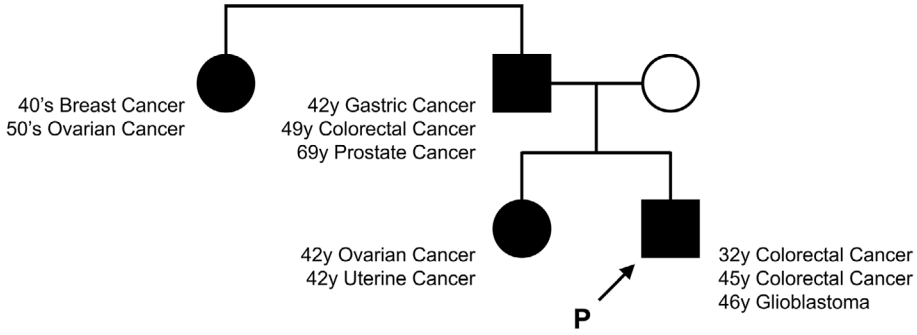

Figure 1. **A family pedigree illustrating the patient's and his relatives' history of cancers. Squares represent men, and circles represent women. Black-filled symbols indicate individuals with a history of cancer. P: proband**

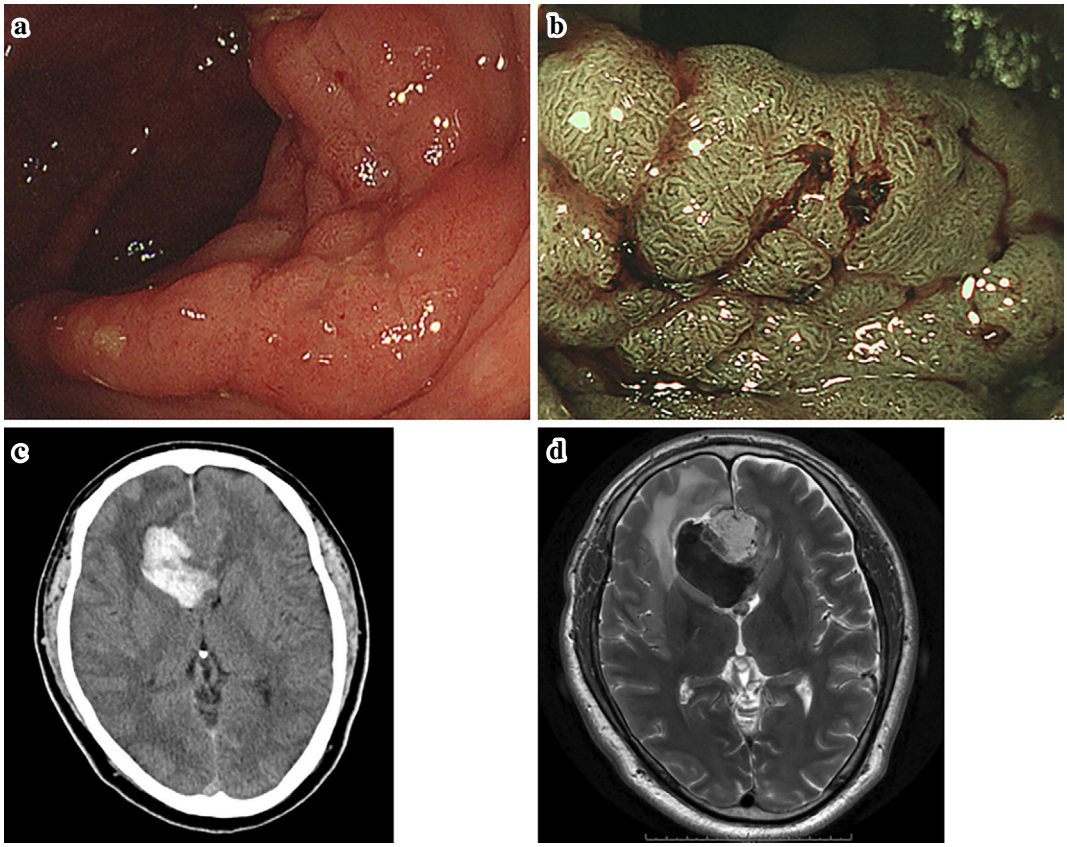

Figure 2. **Endoscopic findings of the transverse colon cancer (a, b) and computed tomography and contrast-enhanced magnetic resonance imaging of the brain tumor (c, d). (a) A laterally spreading tumor (granular type) is present in the transverse colon. (b) Magnified narrow-band imaging of the tumor surface reveals irregular surface and vessel patterns in most examined areas. (c) Computed tomography. A bleeding brain tumor is present in the midline of the subfalcine region. (d) T2-weighted image of contrast-enhanced magnetic resonance imaging. The tumor has a high signal intensity on T2-weighted images with extensive edematous changes in the surrounding area.**

and the patient's family history.

As a representative of his family, his sister underwent genetic testing (ACTRisk™, ACT Genomics, Taipei, Taiwan) of 67 genes associated with hereditary tumor syndromes, including *APC*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*, and no germline pathogenic variants were detected. During surveillance colonoscopy in our hospital, early-stage adenocarcinoma in the transverse colon (Fig. 2a, b) and multiple adenomatous lesions throughout the entire colon were detected. The adenocarcinoma was resected with endoscopic submucosal dissection, and a pathological examination revealed well-differentiated tubular adenocarcinoma [pT1a (SM1), Ly (-), V (-), pHM0, pVM0]. Cold snare polypectomy was performed for 17 adenomas.

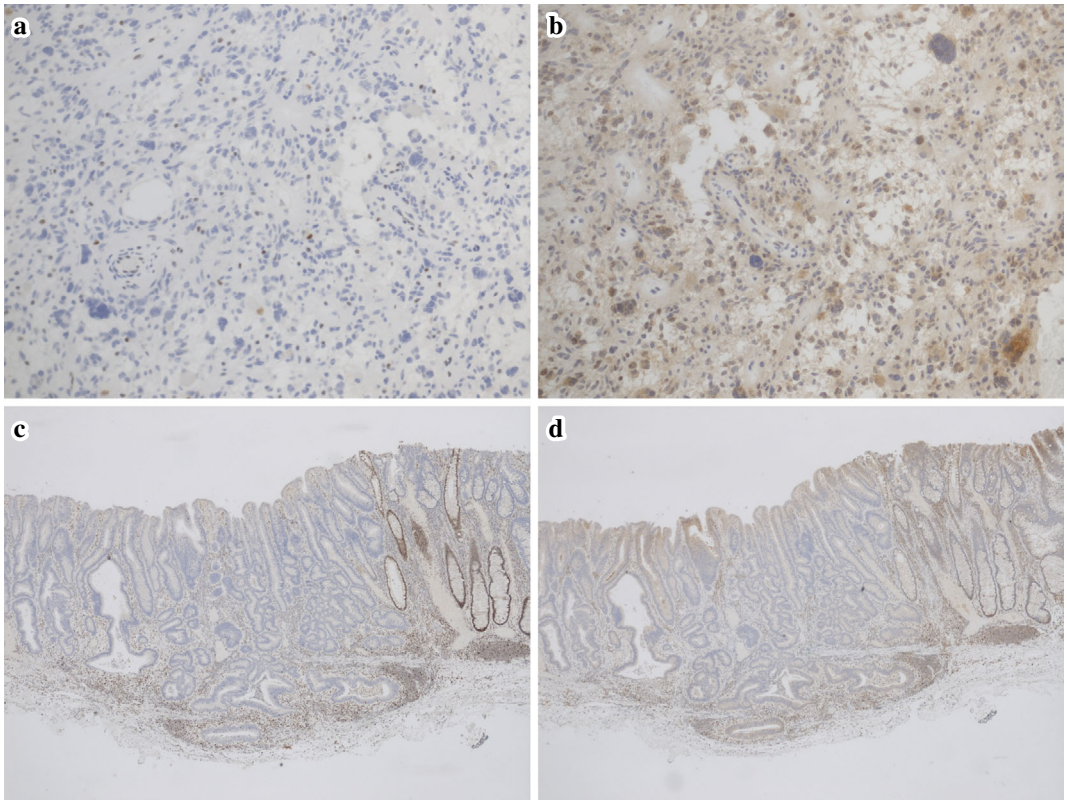

Figure 3. Immunohistochemical staining for MSH2 and MSH6 in the brain tumor and the transverse colon cancer. Immunohistochemical staining of MSH2 (a, c) and MSH6 (b, d) is negligible or low in both glioblastoma (a, b, ×20) and colonic adenocarcinoma (c, d, ×10).

At 46 years old, he presented with sudden headache and vomiting. Head computed tomography and contrast-enhanced magnetic resonance imaging revealed a brain tumor with recent hemorrhaging (Fig. 2c, d). After 23 days of conservative treatment with strict blood pressure control, the brain tumor was resected. A pathological examination of the resected tumor revealed a grade 4 glioblastoma. Immunostaining of the tissues for MMR proteins revealed decreased expression of MSH2 and MSH6 (Fig. 3a, b). Lynch-like syndrome was suspected, and additional immunostaining of the tissue of the resected transverse colon cancer was performed; as in the brain tumor, the expression of MSH2 and MSH6 was low (Fig. 3c, d). Based on these immunohistochemical findings and the results of previous genetic testing, Lynch-like syndrome was diagnosed according to the guidelines of the Japanese Society for Cancer of the Colon and Rectum (1).

The patient's postoperative course was uneventful. Intensive modulated radiation therapy (60 Gy/30 fractions) with temozolomide (140 mg, once daily, for 42 days followed by 28 days of interruption, repeated as 1 cycle) was started 23 days after brain surgery. He completed six planned cycles of temozolomide treatment without severe adverse events, except for grade 3 lymphocyte reduction during the first cycle.

Eight months after the completion of temozolomide therapy, recurrent tumors were found in the right frontal lobe, left cerebellum, and dura mater. Comprehensive genomic profiling (OncoGuide™ NCC OncoPanel System, Sysmex, Kobe, Japan) of the resected glioblastoma tissue was performed. No germline pathogenic variants in 124 targeted genes, including *APC*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, were identified, but microsatellite instability-high and a high tumor mutation burden (38 mut/Mb) were revealed. Although treatment with temozolomide has been reported to increase the number of somatic mutations through alteration of the MMR system (5), this influence was irrelevant in this case because the analyzed brain tissue was resected before temozolomide treatment. Pembrolizumab was started (200 mg, every 3 weeks) and was underway as of the preparation of this report.

Discussion

This case report describes a patient with Lynch-like syndrome in whom glioblastoma developed after repeated treatment of colorectal cancer. Brain tumors occasionally develop in hereditary colorectal cancer syndromes referred to as Turcot syndrome (6). Turcot syndrome is divided into two subtypes (7): Type I is associated with Lynch syndrome and is characterized by concomitant glial tumors and relatively few colonic polyps, and Type II is associated with familial adenomatous polyposis (FAP) and is characterized by thousands of colonic polyps and an increased risk of medulloblastoma. However, brain tumors have not been reported in Lynch-like syndrome.

Our case met the criteria for the diagnosis of Lynch-like

syndrome, as described in the guidelines of the Japanese Society for Cancer of the Colon and Rectum (1). The immunohistochemical absence of MSH2 and MSH6 proteins in both colorectal cancer and glioblastoma strongly suggests germline abnormalities of *MSH2*, and the microsatellite instability and high tumor mutation burden further align with the characteristics of Lynch syndrome (6). However, no pathogenic variants of known genes causing Lynch syndrome were identified in our patient or his sister; thus, a diagnosis of Lynch-like syndrome was made. Because neither ACTRisk™ nor the OncoGuide™ NCC OncoPanel System cover all types of genetic alterations in the *MSH2* gene, we speculate that the presence of unrevealed genetic abnormalities is one possible interpretation for the negative genetic testing in this patient.

Regarding characteristics of intestinal and concomitant extraintestinal malignant tumors in Lynch-like syndrome and Lynch syndrome, conflicting results have been reported: Mas-Moya et al. (8) reported that colorectal cancer in Lynch-like syndrome was likely present in the right colon and that the prevalence of concurrent or metachronous multiple cancers was low compared to the prevalence in Lynch syndrome. In contrast, Xu et al. (9) found that colorectal cancer associated with Lynch-like syndrome was more likely to arise in the rectum than in the colon and that there was no significant difference in the risk of metachronous colorectal cancer and extracolonic cancers between Lynch-like syndrome and Lynch syndrome. Although whether or not patients with Lynch-like syndrome have the same risk of developing brain tumors as those with Lynch syndrome is unclear, our case indicates that glioblastoma does occur in Lynch-like syndrome. The absence of previous reports on the concomitant brain tumors in Lynch-like syndrome could be due to the small number of reported cases of this syndrome or its rarity.

The risk of colorectal and other cancers in hereditary tumor syndromes depends on the pathogenic genes responsible. For example, patients with Li-Fraumeni syndrome have a higher risk of brain tumors than those with Lynch syndrome or FAP (10). In Lynch syndrome, patients with mutations in the *MSH2* gene carry a higher risk of extracolonic cancers and a lower risk of colorectal cancer than those with mutations in other MMR genes (11). Thus, identifying the gene responsible is important for the management of hereditary tumor syndromes. Although no *MSH2* gene abnormality was detected in our case, negative immunohistochemical findings for MSH2 protein suggested a *MSH2* gene abnormality, implying a high risk of extraintestinal tumors. Even in cases of Lynch-like syndrome, in which no genetic abnormality is identified, managing the disease according to the characteristics caused by the genetic abnormality, as inferred from the results of immunohistochemical examinations and other tests, may be important.

In patients with Lynch syndrome (12) and Lynch-like syndrome (13), a regular endoscopic examination of the colon and monitoring of related tumors, such as uterine, ovarian, gastric, duodenal, and urinary tract cancers, is recommended. A consensus has not been reached on surveillance for brain tumors in Lynch-like syndrome or Lynch syndrome, although brain tumors are the second leading cause of death in Lynch syndrome patients (14). Our present findings in this case suggest that surveillance of brain tumors may be beneficial in patients with Lynch-like syndrome.

In conclusion, we described the first case of glioblastoma in a patient with Lynch-like syndrome. Whether or not brain tumor surveillance is required in this syndrome warrants further investigation.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors thank Dr. William R. Brown from the University of Colorado School of Medicine (Denver, USA) for his assistance with the English language editing and manuscript preparation. We also thank Drs. Midori Sato and Minami Kakiuchi for their helpful discussions and comments on pathological interpretations.

References

1. Tomita N, Ishida H, Tanakaya K, et al.; Japanese Society for Cancer of the Colon, Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2020 for the Clinical Practice of Hereditary Colorectal Cancer. Int J Clin Oncol **26**: 1353-1419, 2021.
2. Martínez-Roca A, Giner-Calabuig M, Murcia O, et al. Lynch-like syndrome: potential mechanisms and management. Cancers (Basel) **14**: 1115, 2022.
3. Nugroho PP, Ghozali SAS, Buchanan DD, Pisano MI, Reece JC. Risk of cancer in individuals with Lynch-like syndrome and their families: a systematic review. J Cancer Res Clin Oncol **149**: 25-46, 2023.
4. Gabnier JJ, Gunver K, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. Glob Adv Health Med **2**: 38-43, 2013.
5. Crisafulli G, Sartore-Bianchi A, Lazzari L, et al. Temozolomide treatment alters mismatch repair and boosts mutational burden in tumor and blood of colorectal cancer patients. Cancer Discov **12**: 1656-1675, 2022.
6. Ueno A, Yokota M, Ueno M, Kawamoto K. Colorectal cancer in adolescent and young adults: epidemiology in Japan and narrative review. J Gastrointest Oncol **14**: 1856-1868, 2023.
7. Paraf F, Jothy S, Van Meir EG. Brain tumor-polyposis syndrome: two genetic diseases? J Clin Oncol 1997 **15**: 2744-2758, 1997.
8. Mas-Moya J, Dudley B, Brand RE, et al. Clinicopathological comparison of colorectal and endometrial carcinomas in patients with Lynch-like syndrome versus patients with Lynch syndrome. Human Pathol **46**: 1616-1625, 2015.
9. Xu Y, Huang Z, Li C, et al. Comparison of molecular, clinicopathological, and pedigree differences between Lynch-like and Lynch syndromes. Front Genet **11**: 991, 2020.
10. Johansson G, Andersson U, Melin B. Recent developments in brain tumor predisposing syndromes. Acta Oncol **55**: 401-411, 2016.
11. Sehgal R, Sheahan K, O'Connell PR, Hanly AM, Martin ST, Winter DC. Lynch syndrome: an updated review. Genes (Basel) **5**: 497-507, 2014.
12. Vasen HF, Blanco I, Aktan-Collan K, et al.; the Mallorca group.

Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut **62**: 812-823, 2013.

13. Ladabaum U. What is Lynch-like syndrome and how should we manage it? Clin Gastroenterol Hepatol **18**: 294-296, 2020.

14. de Jong AE, Hendriks YM, Kleibeuker JH, et al. Decrease in mortality in Lynch syndrome families because of surveillance. Gastroenterology **130**: 665-671, 2006.