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Tumor Discovery

CASE REPORT

Biallelic *MUTYH* gene mutation resulting in fluoropyrimidine-resistant advanced rectal cancer: A case report

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Abstract

Colorectal cancer (CRC) is a leading cause of cancer-related mortality worldwide and the third most common cancer in Thailand. Approximately 2% – 5% of CRC cases are associated with inherited cancer syndromes, whereas the majority is sporadic. Herein, we have reported the case of a 32-year-old male with poorly differentiated middle rectal adenocarcinoma (T4bN1M1, Stage IV) that was refractory to fluoropyrimidine-based chemotherapy. Genetic profiling revealed a homozygous c.934-2A>G mutation in the *MUTYH* gene, which disrupted the DNA repair. Despite palliative radiation (30 Gy in 10 fractions) and systemic therapies (capecitabine plus oxaliplatin + panitumumab and fluorouracil, leucovorin, and irinotecan + bevacizumab), the disease progressed rapidly. Third-line therapy with Irinotecan plus oxaliplatin demonstrated initial success (partial response). Eventually, disease progression ensued. This report highlights the challenges of managing CRC caused by biallelic *MUTYH* mutations and emphasizes the importance of comprehensive genomic profiling for guiding therapeutic decisions. A review of similar cases in the literature is also presented.

Keywords: Colorectal neoplasms; Colonic neoplasms; Rectal neoplasms; Colorectal neoplasms; Hereditary non-polyposis; Antineoplastic agents; *MUTYH*

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1. Background

Colorectal cancer (CRC) is a primary global health concern, accounting for > 9% of cancer-related deaths annually.[1] In Thailand, CRC is the third most common malignancy. Although most CRC cases are sporadic, 2% – 5% are hereditary and linked to genetic syndromes, such as Lynch syndrome (LS) and familial adenomatous polyposis (FAP).[2]

LS, which is caused by mutations in mismatch repair (MMR) genes such as *MLH1*, *MSH2*, *MSH6*, and *PMS2*, is associated with microsatellite instability (MSI) and early-onset CRC.[2-5] FAP, an autosomal dominant syndrome is caused by mutations in *APC*. FAP is associated with the development of numerous polyps and a high risk of CRC.[2,6] In contrast, MUTYH-associated polyposis (MAP) is an autosomal recessive syndrome

caused by biallelic mutations in the *MUTYH* gene, which encodes a DNA glycosylase that is essential for oxidative damage repair.[7,8]

MUTYH mutations are associated with an increased risk of CRC.[9] However, their clinical significance remains uncertain.[10,11] Variants such as c.934-2A>G, which have been identified predominantly in Asian populations, may disrupt splicing and impair the DNA repair function of the *MUTYH* gene.[12,13]

Herein, we report the case of a young Thai male with advanced rectal cancer who harbored a homozygous c.934-2A>G mutation, while emphasizing the mutation's clinical relevance and implications for treatment.

2. Case presentation

A 32-year-old Thai male presented with recurrent urinary tract infections and sepsis caused by *Escherichia coli*. Computed tomography (CT) imaging revealed a 10-cm ulcerated rectal mass invading the urinary bladder. Colonoscopy confirmed the presence of poorly differentiated adenocarcinoma, which exhibited positive immunohistochemical staining for CK20 and CDX2 and negative staining for CK7. Molecular testing revealed wild-type *BRAF*, *KRAS*, and *NRAS* genes and a proficient MMR status, excluding LS. The patient was diagnosed with rectal cancer and the TNM stage of the tumor was T4bN1M1 (Stage IV).

Given the advanced stage of the tumor, the multidisciplinary tumor board advised palliative colostomy and administration of radiation therapy (30 Gy in 10 fractions) to alleviate the symptoms. First-line treatment with capecitabine plus oxaliplatin (CAPOX)[14,15] and panitumumab[16,17] was initiated. Despite the administration of four chemotherapy cycles (each lasting 3 weeks; Figure 1), the carcinoembryonic antigen (CEA) levels increased tenfold, from 2.93 to 102.54 ng/dL. Furthermore, CT imaging revealed multiple liver metastases (Figure 2).

Second-line therapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI) was administered in addition to bevacizumab.[18-20] Disease progression, in the form of new lung metastases, was observed after 2 months. The CEA level increased to 860.32 ng/dL. Comprehensive genomic profiling revealed a homozygous c.934-2A>G *MUTYH* mutation.[21] This variant, which is linked to altered splicing, is associated with disrupted DNA repair. There were no mutations of the *MLH1*, *MSH2*, *MSH3*, *MSH6*, *PMS2*, *APC*, *PTEN*, *ATM*, *AXIN2*, *STK11*, *SMAD4*, *TP53*, *CDH1*, *CHEK2*, and *EPCAM* genes.

Third-line treatment with irinotecan and oxaliplatin (IROX)[22] led to a partial response, with CEA levels decreasing to 27.71 ng/mL after the fourth cycle and improved performance status. However, oxaliplatin hypersensitivity limited the treatment to eight cycles. After 16 months of stable disease, progression was observed in the form of new metastatic lesions. The patient declined further systemic therapy and transitioned to end-of-life care. He passed away peacefully just 1 month period after the disease progression. He cannot fit for the 4th-line treatment of regorafenib.

3. Discussion

MUTYH was first described in 2002 and is on the chromosome 1p34.3-1p32.1. The gene encodes a DNA glycosylase that is crucial for repairing oxidative damage.[23,24] Biallelic mutations in *MUTYH* lead to MAP, which is characterized by multiple adenomas and an elevated risk of CRC. In Asian populations, variants such

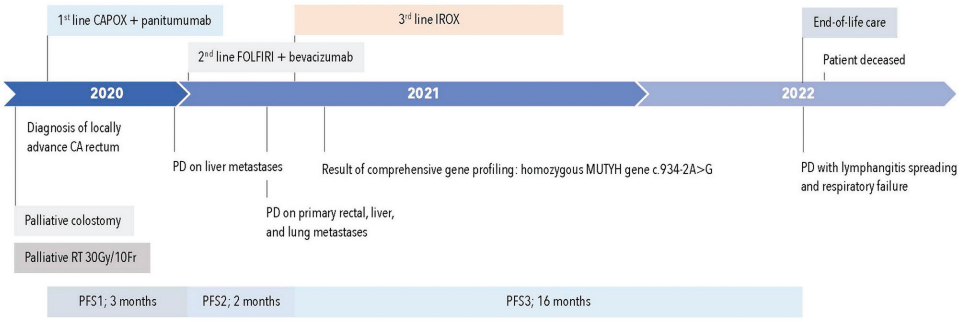


Figure 1. The patient's treatment timeline. In late 2020, the patient was diagnosed with advanced rectal cancer, and he underwent a palliative colostomy to prevent obstruction and radiation. The first-line treatment included CAPOX and panitumumab. The second-line therapy included FOLFIRI and bevacizumab. Both lines of treatment were ineffective within the first 2 months. The third line of treatment, which included IROX, was highly effective. In addition, a homozygous *MUTYH* gene mutation was detected. The patient responded well to this treatment for 16 months. Subsequently, the disease progressed. End-of-life care was initiated as the patient refused further treatment. The patient eventually passed away 1 month after the cessation of chemotherapy.
Abbreviations: CA: Cancer; CAPOX: Capecitabine plus oxaliplatin; Fr: Fractions; FOLFIRI: Fluorouracil, leucovorin, and irinotecan; Gy; Gray; IROX: Irinotecan plus oxaliplatin; PD: Progression of disease; PFS: Progression-free survival; RT: Radiation therapy.

Table 1. Summary of the previously reported cases of CRC with MUTYH mutations

Study	Mutation	Clinical presentation	Treatment regimens	Outcome
Current Case (2024)	Homozygous c.934-2A>G	Middle rectal adenocarcinoma (Stage IV) with bladder invasion	CAPOX+panitumumab; FOLFIRI+bevacizumab; IROX	Stable disease for 16 months with IROX before disease progression
Miyaki *et al.*[28]	c.934-2A>G	Multiple adenomas CRC diagnosed at 40 years of age	Surgery+5-FU-based chemotherapy	Disease-free survival for 18 months
Nielsen *et al.*[13]	Y179C, G396D	Advanced CRC with polyposis	FOLFIRI+bevacizumab	Stable disease for 12 months
Taki *et al.*[25]	c.934-2A>G	Rectal adenocarcinoma with local invasion	Surgery+XELOX+bevacizumab	Progression-free survival of 10 months
Tao *et al.*[27]	c.312C>A (Y104X)	Advanced rectal cancer and recurrent polyps	5-FU+leucovorin	Rapid progression despite standard chemotherapy
Cleary *et al.*[23]	Y179C, G396D	Early-onset CRC and polyposis	Surgery, observation	Long-term survival after surgical resection
Sampson *et al.*[29]	G382D	Advanced CRC with few polyps	FOLFIRI	Partial response followed by disease progression

Abbreviations: CAPOX, XELOX: Capecitabine plus oxaliplatin; CRC: Colorectal cancer; IROX: Irinotecan plus oxaliplatin; FOLFIRI: Fluoropyrimidine, leucovorin, irinotecan; 5-FU: fluoropyrimidine.

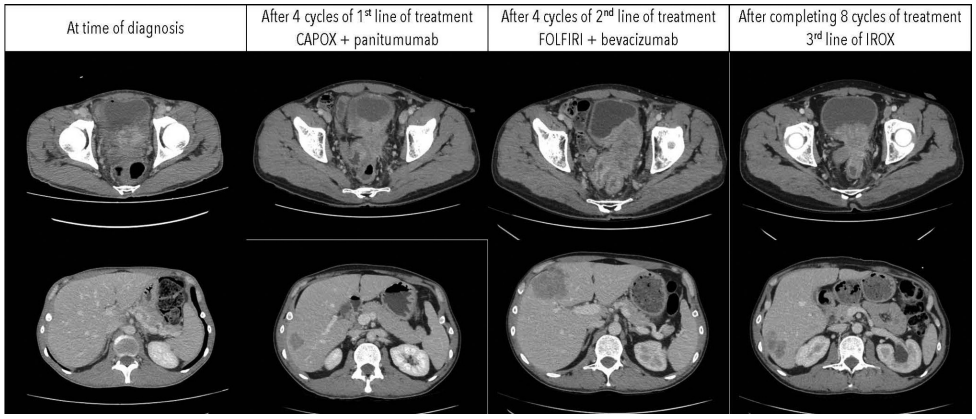


Figure 2. The patient's CT scans at different stages of treatment. The first CT was obtained at the time of diagnosis. The subsequent CTs were obtained after the first line of treatment (CAPOX with panitumumab), the second line of treatment (FOLFIRI with bevacizumab), and the third line of treatment (IROX) were completed.
Abbreviations: CT: Computed tomography; CAPOX: Capecitabine plus oxaliplatin. FOLFIRI: Fluorouracil, Leucovorin, and Irinotecan; IROX: Irinotecan and Oxaliplatin.

as c.934-2A>G21 are linked to CRC, disrupting splicing and impairing DNA repair mechanisms.[25-27]

The refractory response to fluoropyrimidine-based therapies in pur patient highlights the challenges of managing CRC associated with *MUTYH* mutations. Fluoropyrimidine resistance may result from impaired DNA repair, as observed in other MUTYH-associated CRCs (Table 1). The effectiveness of IROX in our patient demonstrates the potential of non-fluoropyrimidine regimens in similar cases.

Although targeted therapies for MUTYH-associated CRC are limited, comprehensive genomic profiling can guide personalized treatment. In our patient, genomic insights informed the use of IROX, which provided temporary disease control. Further studies are required to elucidate the clinical significance of *MUTYH* mutations and optimize therapeutic strategies.

4. Conclusion

This case report highlights the aggressive nature of CRC with a homozygous c.934-2A>G *MUTYH* mutation and the challenges associated with treatment resistance. Comprehensive genomic profiling was pivotal in guiding therapy, emphasizing its importance in young patients with CRC.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Tawasapon Thambamroong
Formal analysis: Tawasapon Thambamroong
Investigation: All authors
Methodology: All authors
Writing – original draft: Tawasapon Thambamroong
Writing – review & editing: Tawasapon Thambamroong

Ethics approval and consent to participate

Not applicable.

Consent for publication

The patient's next of kin provided consent for the publication of this case report.

Availability of data

Not applicable.

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