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# Unravelling the genetic puzzle in rectal carcinoma with colonic polyposis

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## Abstract

**Introduction:** Colorectal cancer (CRC) is a leading cause of cancer-related morbidity and mortality worldwide. Hereditary forms, such as familial adenomatous polyposis (FAP) and Lynch syndrome, significantly impact disease onset, progression, and management. This study provides a structured overview of diagnostic approaches in CRC, specifically focusing on Lynch syndrome and FAP, including its attenuated variant.

**Methods:** A 51-year-old male presented with altered bowel habits and rectal pain, with a family history of endometrial and oropharyngeal cancers. Colonoscopy revealed a rectosigmoid ulcer and multiple sessile polyps throughout the colon. Biopsy confirmed well-differentiated adenocarcinoma with high-grade dysplasia in rectal polyps. He underwent neoadjuvant chemoradiation followed by total proctocolectomy. Immunohistochemistry showed isolated loss of MSH6 protein. Genetic testing revealed a pathogenic APC gene mutation.

**Results:** This case highlights the complex interaction between APC mutations and mismatch repair (MMR) protein deficiencies. Isolated MSH6 loss may raise suspicion for Lynch syndrome; however, since MSH6 functions with MSH2—an essential component of MMR—the intact expression of MSH2 reduces the likelihood of Lynch syndrome. The presence of ~30 polyps and APC mutation supports a diagnosis of attenuated FAP rather than Lynch syndrome.

**Conclusion:** This case underscores the importance of integrating molecular diagnostics in CRC evaluation. Genetic testing is essential for differentiating between FAP, Lynch syndrome, and other hereditary syndromes, enabling precise clinical management and family risk assessment.

***Keywords:*** colorectal cancer; APC mutation; attenuated FAP; Lynch syndrome; MMR genes; MSI

## Introduction

According to the GLOBOCAN 2022 data, there were approximately 20 million new cancer cases and 9.7 million cancer-related deaths [1]. Lung cancer is the leading cancer diagnosis, accounting for nearly 2.5 million new cases (12.4% of all cancers) and is also the leading cause of cancer death (18.7%), followed by colorectal cancer (9.3%). Studies, particularly those involving large families and twins, have shown that approximately 20 - 35% of colorectal cancers (CRCs) have a familial and hereditary component [2]. Familial non syndromic colorectal carcinoma is one of the most prevalent yet less noticeable forms of colorectal cancer. As specific genetic markers for these common familial colorectal cancers are not yet identified, screening and surveillance are based on family history [3]. First degree relatives of a bowel cancer patient over age 50 have a 2 - 3 times higher risk than the general population [4]. If the patient was diagnosed before 45 or if two first

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degree relatives had CRC, the risk rises to 3 - 6 time [5]. But, if diagnosed after 60, only routine screening may be needed [6-8].

In early onset carcinomas (under 50 years old), a hereditary cause can be identified in approximately 13% of instances, with prevalence varying between 9 - 26 % across different studies. Genome wide association studies are frequently used in these cases [9]. Recently, the threshold for routine genetic testing has lowered due to reduced costs, the availability of more accessible automated panels, and greater public awareness, which may result in an increase in the identification of hereditary causes in the coming years [10].

The current study aims to provide a structured overview of the diagnosis in CRC, namely Lynch syndrome and familial adenomatous polyposis (FAP)/attenuated FAP.

## Material and methods

This is a retrospective study of a 51 year-old male presented with complaints of altered bowel habits associated with rectal pain, on and off fever for the past four months. The patient did not have any comorbidities. The study was done in the year 2024 at Meenakshi Medical College Hospital and Research Institute, Kanchipuram. His mother suffers from endometrial carcinoma and his maternal uncle had succumbed to oropharyngeal carcinoma. On digital rectal examination and proctoscopy, the patient had a growth at 7 cm from anal verge. Multiple sessile polyps were palpable in the rectum. The lowest polyp was 3 cm from anal verge, at a 7 o' clock position, measuring 1 x 0.5 cm. Anal tone was normal. Prostate was clinically normal and there were no pelvic deposits. Colonoscopy showed an ulceroproliferative growth at 10 cm from anal verge extending proximally to rectosigmoid with multiple rectal polyps. Multiple sessile polyps were noted in sigmoid, descending, transverse, hepatic flexure, ascending colon, caecum and ileocecal valve. PET CT showed hypermetabolic, malignant wall thickening in the upper rectum with diffuse mesorectal fat stranding. Colonoscopic biopsy from rectal growth was reported as well differentiated adenocarcinoma and the polyp was a tubular adenoma with high grade dysplasia. Patient was started on chemoradiation therapy for a period of one month.

All procedures performed in the current study were approved by national research ethics committee in accordance with the 1964 Helsinki declaration and its later amendments.

Baseline hematological investigations, blood urea nitrogen, serum creatinine and serum electrolytes were within normal limits. High risk informed consent was obtained from the patient. The patient underwent total proctocolectomy with total mesorectal excision and permanent end ileostomy. There was a bulky rectum, and the rest of the colon grossly appeared normal. There was no gross extraserosal disease or pelvic lymphadenopathy. Liver was normal. Peritoneal and omental surface appeared normal and there was no free fluid. Postoperative period was uneventful. The specimen was sent for histopathological examination.

Tissue processing was done, and sections were stained with hematoxylin and eosin. Immunohistochemistry of the four important mismatch repair proteins was carried out by standard protocol for formalin fixed paraffin embedded tissue sections. Antigen retrieval was done using TRIS EDTA (Tromethamine-ethylenediaminetetraacetic acid) buffer by microwave method followed by primary antibody incubation, detection by HRP (horse radish peroxidase) conjugated secondary antibodies, DAB (diaminobenzidine) chromogen and counter staining with hematoxylin with appropriate controls. Intact nuclear staining with brown colour indicates presence of MMR (mismatch repair) protein and loss of nuclear staining indicates deficiency of MMR proteins. Sequencing of the APC (Adenomatous polyposis coli) protein coding regions was performed using Illumina next generation sequencing (NGS) systems at a mean coverage of 80 - 100X in the target region. GATK (Genome Analysis Tool Kit) best practice framework was followed for variant identification. Geneyx (version 5.12) was used for variant annotation, analysis and reporting.

## Results

*Histopathological study*

We received a total proctocolectomy specimen measuring 140 cm in length with a segment of ileum 7 cm in length and appendix measuring 4 cm in length. External surface was congested, and the tumor perforation site was not identified. On the cut surface, 30 polyps, both sessile and pedunculated, of varying sizes were noted throughout the proctocolectomy specimen (Figure 1) largest polyp measuring 2 x 1 x 0.6 cm and smallest measuring 0.5 x 0.5 x 0.2 cm. Cut surface of all the polyps were grey white. A grey white stellate shaped scar (Figure 2) was seen in the rectum measuring 2 x 1 cm. Appendix appeared normal. Two lymph nodes were identified and dissected.

Sections studied from the stellate scar showed ulcerated rectal mucosa with residual malignant adenocarcinoma (Figure 3a). The tumor cells were seen floating in the pools of extracellular mucin and infiltrating into muscularis propria. Lymphovascular invasion was

identified and perineural invasion was not identified. Diagnosis of well differentiated adenocarcinoma with pathological staging ypT2 N0 Mx was given.

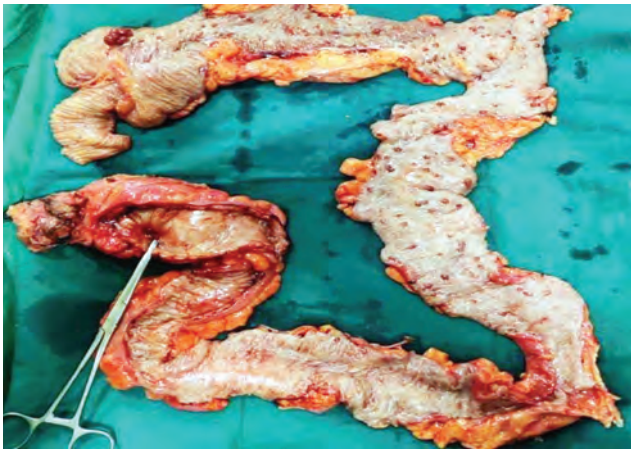

**Figure 1:** Gross specimen of total proctocolectomy with total mesorectal excision.

**Figure 2:** Gross specimen showing multiple polyps in the colon with a scar in the rectum.

Sections from the rectal polyp showed features of adenomatous polyp with high grade dysplasia. Sections from all the polyps in caecum and colon showed features of adenomatous polyp with low grade dysplasia (Figure 3b).

*Immunohistochemistry (IHC) report*

Since the patient had a family history of malignancies and multiple polyps were noted in the patient's colon, IHC and genetic testing was also done to rule out familial forms. The IHC testing for MMR proteins showed loss of nuclear expression in MSH6 alone (Figure 4a), whereas MLH1, MSH2 and PMS2 had shown intact nuclear expression (Figure 4b).

*Hereditary cancer gene panel*

The results showed that the index patient was heterozygous for a likely pathogenic variant in the APC gene (Table 1).

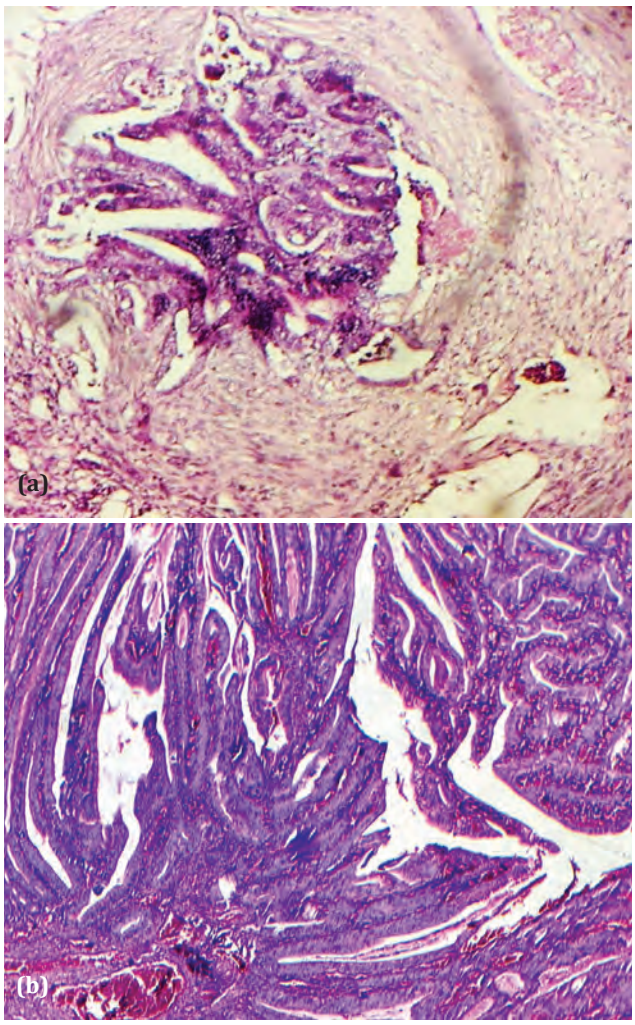


**Figure 3:** (a) Hematoxylin and eosin stained microscopic image under 40X showing well differentiated adenocarcinoma rectum and (b) Hematoxylin and eosin stained microscopic image under 4X showing adenomatous polyp with high grade dysplasia.

## Discussion

Colorectal cancer is a heterogeneous disease that arises from stepwise accumulation of genetic and epigenetic abnormalities. Adenomatous polyps are precursors to most colorectal adenocarcinomas. At least three distinct genetic pathways, the chromosomal instability pathway, microsatellite instability (MSI) pathway and epigenetic instability pathway have been described. The APC/β-catenin pathway through increased Wnt signalling is activated in the classical adenoma-carcinoma sequence with mutation in APC gene, TP53, KRAS, PI3KCA. The MSI pathway is associated with DNA mismatch repair and accumulation of mutations in microsatellite repeat regions of the genome. Epigenetic events, the most common of which is methylation-induced gene silencing, may enhance progression along both pathways [11]. A subset of colorectal cancers, called CpG island methylator phenotype (CIMP) is caused by promoter hypermethylation [12]. APC gene, a tumor suppressor

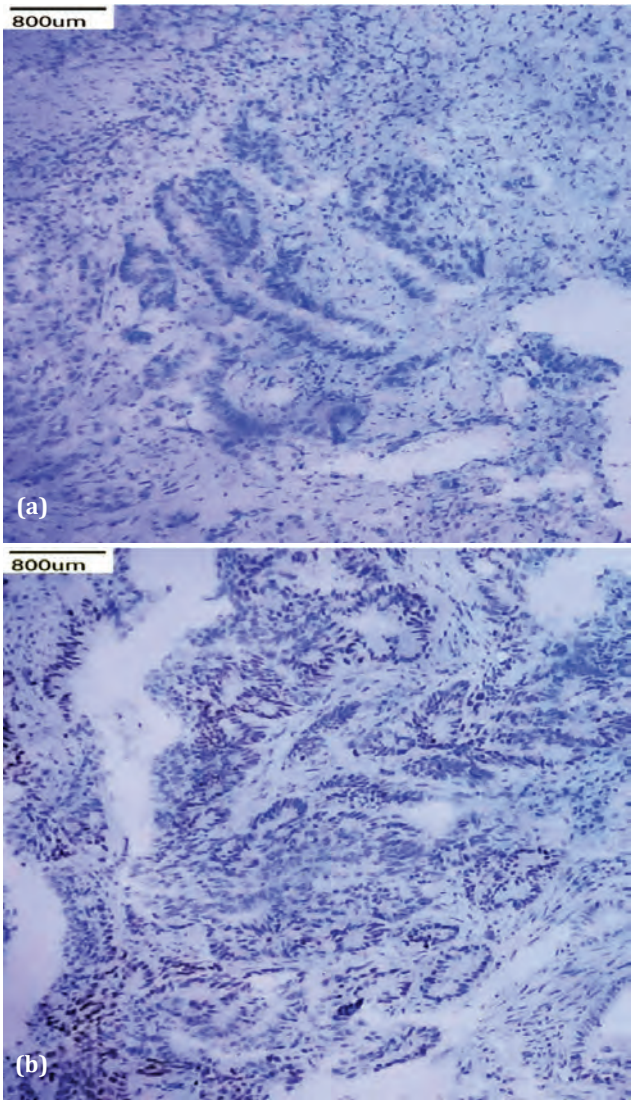


**Figure 4:** (a) IHC testing for MMR proteins showing loss of nuclear expression in MSH6. and (b) IHC testing for MMR proteins showing intact nuclear expression in MLH1.

gene controls cell proliferation, differentiation. cell adhesion, migration and genomic stability by binding to and promoting degradation of beta catenin, a component of the Wnt signalling pathway [13]. Loss of APC function, due to mutations produce truncated APC protein leading to the accumulation of β catenin in the nucleus, which causes activation of transcription factors MYC and cyclin D1 that promote proliferation.

Upto 80% of sporadic cancers typically include mutation of APC early in the neoplastic process. FAP, an autosomal dominant disorder is caused by mutations in the APC gene and is characterized by development of hundreds to thousands of colorectal adenomatous polyps in early life, with a 100% risk of turning malignant if untreated [14]. A milder form, attenuated FAP, is associated with fewer polyps (10 -100), later onset of colorectal cancer with predominant location in the proximal colon and a lower overall cancer risk compared to classic FAP [15]. In the MSI pathway, there is either mutation or epigenetic silencing of MMR genes that are involved in repair of base-base mismatch during DNA replication in proliferating cells. Of the several MMR proteins, MLH1, MSH2, MSH6, PMS2 or EPCAM (encodes a protein that regulates MSH2) are important. MSI accounts for nearly 15% of sporadic colorectal tumors and for nearly all colorectal tumors that develop in patients with Lynch syndrome or hereditary non-polyposis colorectal cancer (HNPCC) [16].

Lynch syndrome accounts for 2 to 4% of all colorectal cancers, making it the most common syndromic form of colorectal cancer. A majority of HNPCC cases are caused by mutations in MSH2 or MLH1. Patients with HNPCC inherit one defective DNA repair gene and one normal

**Table 1:** Hereditary cancer gene panel report of the patient.

| *Gene and Transcript* | *Variant* | *Location* | *Zygosity* | *In silico Parameters*** | *Disorder (OMIM)* | *Inheritance* | *Variant Classification* |
|---|---|---|---|---|---|---|---|
| APC NM_000038.6 | C.568G>T p.Glu 190* | Exon 6 | Heterozygous | CADD: 40 | Familial Adenomatous Polyposis I; Desmoid disease, Hereditary DESMD:135290 Gastric Adenocarcinoma and proximal polyposis of the stomach; GAPS:619182 | Autosomal Dominant | Likely pathogenic |
| ENG NM_001114753.3 | c.1774G>A p.Val592Met | Exon 14 | Heterozygous | CADD:27.6 SIFT: Deleterious MT: Damaging | Telangiectasia, Hereditary, Hemorrhagic, TYPE I; HHTI:187300 | Autosomal Dominant | Uncertain Significance |

copy. When the normal copy is lost due to mutation or epigenetic changes, mutations rapidly build up in microsatellite DNA sites [17, 18]. Lynch syndrome is characterized by an increased risk for colorectal cancer and cancers of the endometrium, ovary, stomach, small bowel, urinary tract, biliary tract, brain, skin, pancreas, and prostate [19].

In the present case, since the patient had a family history of endometrial and oropharyngeal malignancy among first degree relatives, possibility of Lynch syndrome was thought of. Hence, IHC of the four most important MMR proteins namely MLH1, MSH2, MSH6, PMS2 was carried out. There was only isolated loss of nuclear expression in MSH6 protein whereas other proteins showed intact nuclear expression. MSH6 forms heterodimers with MSH2 and the loss of MSH6 expression can be compensated by other MMR proteins potentially mitigating the impact on MSI status [20]. MSI status can also vary depending on tumor type, location and underlying genetic alteration. Isolated loss of MSH 6 might not always lead to high microsatellite instability (MSI-H). MSH6 deficient tumors may exhibit varying levels of MSI including low level instability (MSI-L) or even microsatellite stability (MSS). Hence in cases where MSH6 is lost but MSH2 remains intact, the clinical significance must be interpreted with caution, particularly in the absence of other strong features of Lynch syndrome. Since the patient also had 30 colorectal polyps, mutational analysis for APC gene was carried out. Results showed a heterozygous mutation in the exon 6 of APC gene, where guanine is replaced by thymine at 568$^{th}$ nucleotide position of the coding DNA sequence. This nucleotide substitution results in the premature stop codon with a change in the amino acid sequence especially glutamic acid at 190$^{th}$ position producing a truncated APC protein (Table 1).

These findings suggests that the patient is a carrier of APC gene mutation. The presence of 30 polyps in the colon, rectal cancer and APC gene mutation implies a high risk of attenuated FAP. Mutations associated with the attenuated FAP are seen mostly in the 5' region of the gene, exon 3 and 4 [21]. They present with two to more than 500 adenomas. Whereas, mutations occurring in the 3'end of exon 15 have less than 50 adenomas [22]. Patients with exon 9 mutations may have 1 to 150 adenomas without upper GI manifestations. Increased phenotypic variability in polyp number was observed in AFAP families carrying germline APC mutations in the 5'end. Extracolonic features may be more common in patients with mutations in the 3' end. The occurrence of MSH6 mutation might be a secondary event in attenuated FAP or tumor heterogeneity specific to rectal carcinoma or epigenetic silencing of MSH6 gene or the loss could be attributed to adjuvant onco-radiation [23, 24].

The combination of APC gene mutation and loss of MSH6 protein in this patient highlights the complexity of hereditary cancer syndromes and the need for comprehensive genetic evaluation. Recent case reports highlight a potential association between MSH6 germline variants and attenuated FAP. Ha *et al.*[25] presented two cases of attenuated FAP where patients harbored germline MSH6 mutation, detected through next-generation sequencing. Both patients showed multiple colorectal adenomas, and one had synchronous colorectal cancer, yet no recurrence was observed following total colectomy over a three-year follow-up. These findings suggest that MSH6 mutations, classically associated with Lynch syndrome, may also underlie attenuated adenomatous polyposis phenotypes, underscoring the importance of including MSH6 in genetic evaluation of patients presenting with attenuated polyposis. In addition to MSH6-associated cases of attenuated adenomatous polyposis, previous reports have demonstrated considerable phenotypic heterogeneity among patients with germline mutations in classical polyposis-related genes. Bhatnagar *et al.*[26] also described a case of attenuated FAP in a patient presenting with multiple gastric polyps and ampullary adenocarcinoma, but without a significant family history or rectal involvement. The features were reported as consistent with attenuated FAP despite the presence of a novel APC mutation. Together with the findings of Ha *et al*.[25] and Bhatnagar *et al*.[26] it is emphasized the importance of comprehensive genetic evaluation in patients with atypical polyposis phenotypes, and support expanding molecular testing beyond classic gene panels when encountering uncertain or attenuated clinical presentations. These findings strongly corroborate with the results of our study. The limitations of the current study are that the samples could not be obtained from the family members for genetic study and Next Generation Sequencing is not carried out to assess the status of microsatellite instability. Instead, IHC analysis of the four most important MMR genes is done in this study.

## Conclusion

Currently, the diagnosis of colorectal cancer requires both morphologic and molecular characterization. Genetic analysis is pivotal in patients with adenomatous polyposis to differentiate between FAP and Lynch syndrome. It is essential for risk assessment, genetic screening and presymptomatic diagnosis of the disease among family members. Integrating molecular diagnostics into colorectal cancer management is the key to preventive medicine in families burdened with inherited mutations and facilitates effective targeted interventions that improves patient prognosis.

## Conflicts of interest

Authors declare no conflicts of interest.

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