DOI: 10.7860/JCDR/2025/78040.20843

Case Report

Genetics Section

Colorectal Carcinoma in a Young Male Diagnosed as Lynch Syndrome with a Rare PMS2 Pathogenic Germline Variant: A Case Report

VIJAYASHREE S GOKHALE[1], VINEETHA NAGA LAKSHMI GIDUTURI[2], MAHABIR PRASAD MISHRA[3], MAYUR AMBEKAR[4], DNYANADA SHRIRANG GOKHALE-AGASHE[5]

ABSTRACT

Colorectal cancers in young people can be due to inherited mutations in 5-10% of cases, among which Lynch syndrome is the most common. Lynch syndrome is defined as a genetic susceptibility to various types of cancer, with non polyposis colorectal cancer being one of the more common types. A man in his 20s presented with abdominal pain and haematochezia. Upon investigation, the transverse colon showed well-differentiated adenocarcinoma, accompanied by multiple tubulovillous adenomatous polyps of the sigmoid colon with high-grade dysplasia. He underwent surgery followed by chemotherapy, resulting in clinical improvement, resolution of symptoms and a decrease in tumour size and metastasis. Results of genomic testing identified a pathogenic variant located in intron 12 of the PMS2 gene (postmeiotic segregation increased 2), confirming Lynch syndrome. This syndrome, characterised by the PMS2 variant, is extremely rare compared to mutations in other DNA mismatch repair genes such as MLH1, MSH2, MSH6, and EPCAM. Lynch syndrome is thought to account for 2-3% of colorectal cancer cases worldwide and 10-15% of cases in India. The diagnosis of Lynch syndrome is complex and often necessitates a multifaceted approach that includes a thorough evaluation of the patient's clinical history, clinical evaluation, laboratory testing, and histopathological reporting of biopsy specimens, followed by genetic counselling and genetic testing. His final diagnosis was colorectal cancer with adenomatous polyposis and Lynch syndrome associated with the PMS2 variant.

Keywords: Amsterdam criteria, Bethesda guidelines, Genetic counselling, Genetic testing, Non polyposis colorectal

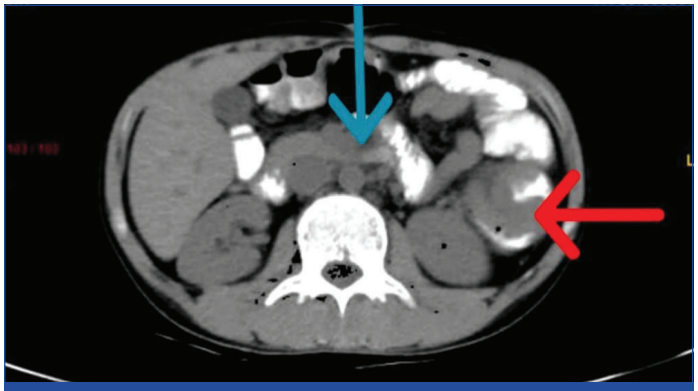
CASE REPORT

A 20-year-old male presented to the outpatient department with a history of abdominal pain and passing blood per rectum for the last four days. The abdominal pain had a gradual onset was dull and achy and was associated with intermittent cramping. The blood passed per rectum was bright red and intermittent with stools. There was no history of fever, cold, cough, melena, haematemesis, weight loss, jaundice, vomiting, nausea or constipation. There was no family history of colorectal cancer.

On examination, the pulse was 106 beats per minute, blood pressure was 110/70 mmHg, oxygen saturation level was 98% on room air and the respiratory rate was 14 breaths per minute. Pallor was present, with no icterus or signs of hepatocellular failure. There were no nevi or pigmentation on the lips, buccal mucosa, cheeks, face or on the body. No clubbing, lymphadenopathy or oedema of the feet were observed. On systemic examination, the abdomen showed no tenderness or organomegaly and other systems were normal.

Laboratory tests revealed a haemoglobin level of 7.6 grams per deciliter (g/dL) (normal-13.5-17.5 g/dL), indicating microcytic hypochromic anaemia; a total bilirubin level of 1.7 milligrams per deciliter (mg/dL) (direct 0.8/indirect 0.9 mg/dL) (normal- total -0.1-1.2 mg/dL, direct 0-0.3 mg/dL, indirect-0.1-0.9 mg/dL); serum urea of 23 mg/dL (normal-6-24 mg/dL); and serum creatinine of 0.69 mg/dL (normal-0.6-1.2 mg/dL). Prothrombin time – International Normalised Ratio (PT-INR) and serum amylase and lipase were within normal limits.

Contrast Enhanced Computed Tomography (CECT-AP) [Table/Fig-1] revealed asymmetrical wall thickening of the proximal jejunal bowel loops, several enlarged lymph nodes in the mesentery and a concealed perforation that was suggestive of neoplastic origin, with a possibility of adenocarcinoma or lymphoma, along with hepatosplenomegaly.

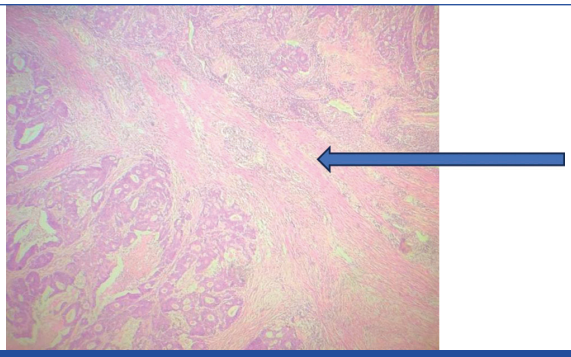


[Table/Fig-1]: Showing CECT AP axial view blue arrow mark showing multiple sessile as well as pedunculated polypoid lesions in the rectum, sigmoid and descending colon, likely neoplastic with enlarged lymph nodes and red arrow showing metastatic hypodense liver lesions.

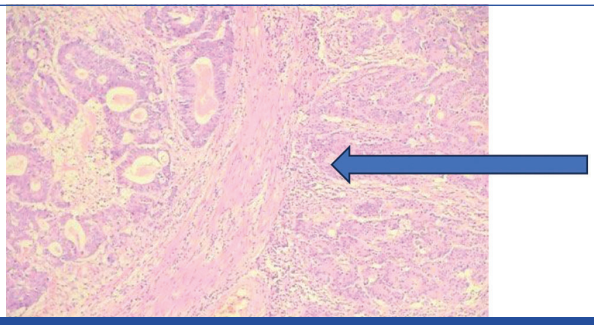
Colonoscopy revealed multiple large bowel pedunculated and sessile polyps occluding the lumen.

Histopathological biopsy of the colonic polyp [Table/Fig-2,3] showed that the transverse colon had well-differentiated adenocarcinoma with regional lymph node metastasis in two lymph nodes. All margins were negative for invasive carcinomas and multiple tubular and tubulovillous adenomatous polyps of the sigmoid colon exhibited high-grade dysplasia. A terminal ileum polyp with hyperplastic Peyer's patches showed lamina propria with lymphoplasmacytic infiltrates and eosinophils. The stroma displayed a haphazard arrangement of muscular tissue and blood vessels, suggestive of benign hamartomatous polyps.

Immunohistochemistry (IHC) staining of the tumour was not performed as genetic testing was opted for by the surgeon and



[Table/Fig-2]: Arrow showing adenocarcinoma invading into muscularis propria (H&E staining, 100x magnification).



[Table/Fig-3]: Arrow showing well-differentiated adenocarcinoma (Haemotoxin and eosin staining, with 40x magnification). All margins are negative for invasive carcinoma with multiple tubular and tubulovillous adenoma.

oncophysician instead. Positron Emission Tomography-computed tomography revealed multiple Fluorodeoxyglucose (PET-FDG) avid pedunculated polypoidal lesions in the rectum, rectosigmoid, sigmoid and descending colon, along with neoplastic involvement and metastatic lesions in the liver, with uptake in a few iliac and mesenteric lymph nodes. Differential diagnosis included malignancy and intestinal tuberculosis.

Treatment: Segmental jejunal resection, enucleation of the liver lesion and total proctocolectomy with end ileostomy and side-to-side duodenojejunal anastomoses were performed. Additionally, the patient underwent six cycles of adjuvant chemotherapy, consisting of injection Oxaliplatin 180 mg intravenously and tablet Capecitabine 500 mg orally. This regimen was used because Oxaliplatin damages DNA, while Capecitabine inhibits DNA synthesis, providing a synergistic effect that improves overall survival and response rates and acts as a first-line treatment for metastatic colorectal carcinoma.

The patient was evaluated for family history for at least three generations, comprising first-degree, second-degree and third-degree relatives; however, this was negative for any colorectal carcinomas. Subsequently, he was assessed for the following criteria:

Amsterdam criteria [1]: The following two criteria were fulfilled out of six:

1. At least one tumour should be diagnosed before the age of 50 years;
2. Tumours should be verified by histopathological examination.

Revised Bethesda guidelines [1]:

1. Colorectal Carcinoma (CRC) diagnosed in a patient aged <50 years.
2. CRC with MSI-1 phenotype diagnosed in a patient aged <60 years.

Therefore, following genetic counselling, the patient was recommended to undergo genetic testing. The Illumina NovaSeq 6000 NGS platform's comprehensive hereditary 330 cancer panel was used to check for genomic variations in the patient [Table/Fig-4]. Genomic testing results revealed a pathogenic variation in intron 12 of the PMS2 gene (NM_000535.7). Due to the early-onset of the disease and numerous colorectal polyps at such a young age, genetic testing was conducted despite a negative family history, indicating that he may have been the index case.

Pathogenic variant detected related to the clinical Phenotype

Key Findings:

Gene & Transcript	Location	Variant	Zygosity/ Inheritance	OMIM Phenotype	Clinical Significance
PMS2 (-) NM_000535.7	Intron 12	c.2174+1G>A (Splice donor variant)	Homozygous /Autosomal Dominant /Autosomal Recessive	1. Lynch syndrome 2. Mismatch repair cancer syndrome 4	Pathogenic (PM2, PVS1, PP5)

**Genetic test results are reported based on the recommendations of American College of Medical Genetics*

[Table/Fig-4]: Genetic testing shows homozygous variant in intron 12 of gene PMS2.

Final diagnosis of the patient: CRC with adenomatous polyposis, a case of Lynch syndrome with a PMS2 variant. The patient is currently asymptomatic and is on regular follow-up. Advice regarding genetic testing and financial assistance programs was given to the first-degree relatives.

DISCUSSION

Lynch syndrome is a syndrome of cancer predisposition [2]. It results from a germline mutation in one of four Mismatch Repair (MMR) genes: MLH1, MSH2, MSH6, and PMS2. Large deletions in a non mismatch repair gene called Epithelial Cellular Adhesion Molecule (EPCAM), which silences MSH2 expression, have also been found to cause Lynch syndrome [1-4].

Lynch syndrome increases the risk of Hereditary Non Polyposis Colorectal Cancer (HNPCC). Not all family members of individuals with HNPCC have Lynch syndrome, and not all family members of individuals with Lynch syndrome have HNPCC. Furthermore, Lynch syndrome may rarely be associated with multiple polyps showing high-grade dysplasia, as seen in index case. Previously, Microsatellite Instability (MSI) testing of the tumour specimen was the first step in evaluating for Lynch syndrome.

Currently, genetic testing and the integration of Next Generation Sequencing (NGS) of tumour tissue serve as initial diagnostic steps. Lynch syndrome is an autosomal dominant condition in which first-degree relatives have a 50% chance of being affected [2]. In index patient, genetic panel testing was conducted after a colonoscopic biopsy showed colorectal cancer, as the patient was young and fulfilled the Amsterdam II criteria. There was no obtainable family history. In a reported case of a 19-year-old female with Lynch syndrome, there was a history of oesophageal cancer in a cousin; however, this individual also consumed alcohol [5]. According to MedDRA, Lynch syndrome is categorised under congenital, familial and genetic disorders (SMQ), and gastrointestinal premalignant disorders (SMQ) [6].

The PMS2 (c.2174+1G>A) variant is extremely rare in the global population and was not reported in phase 3 of the 1000 Genomes Project. The pathogenicity of the PMS2 variant was determined by the ACMG (American College of Medical Genetics and Genomics) guidelines, along with NGS, bioinformatics analysis, haplotype calling and copy number variant analysis.

The majority of PMS2 carriers are undiagnosed because they do not have cancer or because affected carriers do not undergo genetic testing and examination, as they lack recognised risk factors that could indicate Lynch syndrome in their personal or family history [7]. Patients are evaluated for family history across at least three generations, comprising first-degree, second-degree and third-degree relatives, under the following criteria [8,9]:

- Amsterdam Criteria [1].
- Revised Bethesda Guidelines [1,10].

Index patient fulfilled two of the Amsterdam criteria and two of the revised Bethesda criteria.

The treatment for colorectal cancer is primarily surgical. The biopsy is subjected to IHC, which looks for the proteins expressed by the

major MMR genes [8]. MMR genes are necessary for correcting incorrect pairing of nucleotide bases during DNA replication. If mismatches are not resolved, the risk of cancer increases.

The National Comprehensive Cancer Network (NCCN) guidelines recommend the use of Pembrolizumab or Nivolumab in the management of metastatic CRCs with deficient mismatch repair [1,8,11]. Genetic counselors play a crucial role in coordinating testing, providing counselling and instituting proper screening procedures for affected family members. In index case, genetic counselling was performed by an oncophysician and the treating physicians, confirming a diagnosis of Lynch syndrome and CRC. The staging of the tumour is T3N1M1.

The guidelines outlined by the US Multi-Society Task Force for patients with Lynch syndrome and colorectal cancer recommend that the primary treatment is colectomy with ileo-rectal anastomosis, along with regular follow-up colonoscopies.

CONCLUSION(S)

Index case patient was young, had colorectal cancer and presented with adenomatous polyposis. Additionally, the patient met two of the Amsterdam II criteria and two of the Bethesda Guidelines criteria, and genetic testing revealed a PMS2 variant. Therefore, the diagnosis was colorectal cancer associated with Lynch syndrome. Any young patient diagnosed with colorectal cancer should undergo genetic testing for Lynch syndrome and if found positive, first-degree relatives should also be tested and offered surveillance.

REFERENCES

[1] Renuka IV, Aparna C. Lynch syndrome-A case report with review of literature. Int J Cont Med Res. 2016;3(3):804-06.
[2] Bhattacharya P, Leslie SW, McHugh TW. Lynch syndrome (hereditary nonpolyposis colorectal cancer). StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. PMID: 28613748. Last update June 8 2024..
[3] Yurgelun MB, Allen B, Kaldate RR, Bowles KR, Judkins T, Kaushik P, et al. Identification of a variety of mutations in cancer predisposition genes in patients with suspected lynch syndrome. Gastroenterology. 2015;149(3):604-13.
[4] Lynch HT, De la Chapelle A. Hereditary colorectal cancer. N Eng J Med. 2003;348(10):919-32.
[5] Iqbal A, Rabat SK, Kaur R, Waqas M, Badar S, Haider F, et al. A case of lynch syndrome-associated colorectal adenocarcinoma in a 19-year-old female patient. Cureus. 2023;15(11):e48740.
[6] Lynch syndrome- Classes. NCBO BioPortal. Available from: https://bioportal.bioontology.org›ontologies›MEDDRA Medical Dictionary for Regulatory Activities Terminology (MedDRA). Last uploaded: January 16, 2025.
[7] Goodenberger ML, Thomas BC, Johnson DR, Boland CR, Plon SE, Clendenning M, et al. PMS2 monoallelic mutation carriers: The known unknown. Genet Med. 2016;18(1):13-19. [Advance online publication: 09 April 2015].
[8] Nowak JA, Yurgelun MB, Bruce JL, Rojas-Rudilla V, Hall DL, Shivdasani P, et al. Detection of mismatch repair deficiency and microsatellite instability in colorectal adenocarcinoma by targeted next-generation sequencing. J Mol Diagn. 2017;19:84-91. Doi: 10.1016/j.jmoldx.2016.07.010.
[9] Samadder NJ, Smith KR, Wong J, Thomas A, Hanson H, Boucher K, et al. Cancer risk in families fulfilling the Amsterdam criteria for Lynch syndrome. JAMA Oncology. 2017;3(12):1697-701.
[10] Umar A, Boland CR, Terdiman JP, Syngal S, Chapelle AD, Rüschoff J, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Nat Cancer Institute. 2004;96(4):261-68.
[11] Giardiello FM, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, et al. Guidelines on genetic evaluation and management of Lynch syndrome: A consensus statement by the US Multi-Society Task Force on colorectal cancer. Gastroenterology. 2014;147:502-26. Doi: 10.1053/j.gastro.2014.04.001.

PARTICULARS OF CONTRIBUTORS:
1. Professor, Department of Internal Medicine, Dr. D. Y. Patil Vidyapeeth, Pune, Maharashtra, India.
2. Resident, Department of Internal Medicine, Dr. D. Y. Patil Vidyapeeth, Pune, Maharashtra, India.
3. Resident, Department of Internal Medicine, Dr. D. Y. Patil Vidyapeeth, Pune, Maharashtra, India.
4. Assistant Professor, Department of Internal Medicine, Dr. D. Y. Patil Vidyapeeth, Pune, Maharashtra, India.
5. Clinical Curation Scientist, University of Western Australia, South Metropolitan Health Service, Perth, Western Australia.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Vineetha Naga Lakshmi Giduturi,
B-49, Old Girls Hostel, Dr. D. Y. Patil Medical College and Hospital, Pimpri,
Pune-411018, Maharashtra, India.
E-mail: vineetha16giduturi@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jan 14, 2025
- Manual Googling: Feb 20, 2025
- iThenticate Software: Mar 04, 2025 (10%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jan 13, 2025**
Date of Peer Review: **Feb 07, 2025**
Date of Acceptance: **Mar 06, 2025**
Date of Publishing: **Apr 01, 2025**