

# World Journal of *Clinical Cases*

*World J Clin Cases* 2021 July 26; 9(21): 5754-6177



## Contents

Thrice Monthly Volume 9 Number 21 July 26, 2021

## REVIEW

- 5754 Treatment strategies for hepatocellular carcinoma with extrahepatic metastasis  
*Long HY, Huang TY, Xie XY, Long JT, Liu BX*

## MINIREVIEWS

- 5769 Prevention of hepatitis B reactivation in patients requiring chemotherapy and immunosuppressive therapy  
*Shih CA, Chen WC*
- 5782 Research status on immunotherapy trials of gastric cancer  
*Liang C, Wu HM, Yu WM, Chen W*
- 5794 Therapeutic plasma exchange for hyperlipidemic pancreatitis: Current evidence and unmet needs  
*Zheng CB, Zheng ZH, Zheng YP*
- 5804 Essentials of thoracic outlet syndrome: A narrative review  
*Chang MC, Kim DH*

## ORIGINAL ARTICLE

## Case Control Study

- 5812 Soluble programmed death-1 is predictive of hepatitis B surface antigen loss in chronic hepatitis B patients after antiviral treatment  
*Tan N, Luo H, Kang Q, Pan JL, Cheng R, Xi HL, Chen HY, Han YF, Yang YP, Xu XY*

## Retrospective Cohort Study

- 5822 Tunneled biopsy is an underutilised, simple, safe and efficient method for tissue acquisition from subepithelial tumours  
*Koutsoumpas A, Perera R, Melton A, Kuker J, Ghosh T, Braden B*

## Retrospective Study

- 5830 Macular ganglion cell complex injury in different stages of anterior ischemic optic neuropathy  
*Zhang W, Sun XQ, Peng XY*
- 5840 Value of refined care in patients with acute exacerbation of chronic obstructive pulmonary disease  
*Na N, Guo SL, Zhang YY, Ye M, Zhang N, Wu GX, Ma LW*
- 5850 Facilitators and barriers to colorectal cancer screening in an outpatient setting  
*Samuel G, Kratzer M, Asagbra O, Kinderwater J, Poola S, Udom J, Lambert K, Mian M, Ali E*
- 5860 Development and validation of a prognostic nomogram for colorectal cancer after surgery  
*Li BW, Ma XY, Lai S, Sun X, Sun MJ, Chang B*

**Observational Study**

- 5873** Potential protein-phenotype correlation in three lipopolysaccharide-responsive beige-like anchor protein-deficient patients

*Tang WJ, Hu WH, Huang Y, Wu BB, Peng XM, Zhai XW, Qian XW, Ye ZQ, Xia HJ, Wu J, Shi JR*

- 5889** Quantification analysis of pleural line movement for the diagnosis of pneumothorax

*Xiao R, Shao Q, Zhao N, Liu F, Qian KJ*

**Prospective Study**

- 5900** Preprocedure ultrasound imaging combined with palpation technique in epidural labor analgesia

*Wu JP, Tang YZ, He LL, Zhao WX, An JX, Ni JX*

**Randomized Controlled Trial**

- 5909** Effects of perioperative rosuvastatin on postoperative delirium in elderly patients: A randomized, double-blind, and placebo-controlled trial

*Xu XQ, Luo JZ, Li XY, Tang HQ, Lu WH*

**SYSTEMATIC REVIEWS**

- 5921** Pain assessment and management in the newborn: A systematized review

*Garcia-Rodriguez MT, Bujan-Bravo S, Seijo-Bestilleiro R, Gonzalez-Martin C*

**META-ANALYSIS**

- 5932** Fatigue prevalence in men treated for prostate cancer: A systematic review and meta-analysis

*Luo YH, Yang YW, Wu CF, Wang C, Li WJ, Zhang HC*

**CASE REPORT**

- 5943** Diagnostic discrepancy between colposcopy and vaginoscopy: A case report

*Li Q, Zhang HW, Sui L, Hua KQ*

- 5948** Contrast enhanced ultrasound in diagnosing liver lesion that spontaneously disappeared: A case report

*Wang ZD, Haitham S, Gong JP, Pen ZL*

- 5955** COVID-19 patient with an incubation period of 27 d: A case report

*Du X, Gao Y, Kang K, Chong Y, Zhang ML, Yang W, Wang CS, Meng XL, Fei DS, Dai QQ, Zhao MY*

- 5963** Awake extracorporeal membrane oxygenation support for a critically ill COVID-19 patient: A case report

*Zhang JC, Li T*

- 5972** Meigs syndrome with pleural effusion as initial manifestation: A case report

*Hou YY, Peng L, Zhou M*

- 5980** Giant hemangioma of the caudate lobe of the liver with surgical treatment: A case report

*Wang XX, Dong BL, Wu B, Chen SY, He Y, Yang XJ*

- 5988** Anti-programmed cell death ligand 1-based immunotherapy in recurrent hepatocellular carcinoma with inferior vena cava tumor thrombus and metastasis: Three case reports  
*Liu SR, Yan Q, Lin HM, Shi GZ, Cao Y, Zeng H, Liu C, Zhang R*
- 5999** Minimal deviation adenocarcinoma with elevated CA19-9: A case report  
*Dong Y, Lv Y, Guo J, Sun L*
- 6005** Isolated fungus ball in a single cell of the left ethmoid roof: A case report  
*Zhou LQ, Li M, Li YQ, Wang YJ*
- 6009** Rare case of brucellosis misdiagnosed as prostate carcinoma with lumbar vertebra metastasis: A case report  
*Yan JF, Zhou HY, Luo SF, Wang X, Yu JD*
- 6017** Myeloid sarcoma of the colon as initial presentation in acute promyelocytic leukemia: A case report and review of the literature  
*Wang L, Cai DL, Lin N*
- 6026** Primary follicular lymphoma in the renal pelvis: A rare case report  
*Shen XZ, Lin C, Liu F*
- 6032** Rosai-Dorfman disease in the spleen of a pediatric patient: A case report  
*Ryu H, Hwang JY, Kim YW, Kim TU, Jang JY, Park SE, Yang EJ, Shin DH*
- 6041** Relapsed/refractory classical Hodgkin lymphoma effectively treated with low-dose decitabine plus tislelizumab: A case report  
*Ding XS, Mi L, Song YQ, Liu WP, Yu H, Lin NJ, Zhu J*
- 6049** Disseminated *Fusarium* bloodstream infection in a child with acute myeloid leukemia: A case report  
*Ning JJ, Li XM, Li SQ*
- 6056** Familial hemophagocytic lymphohistiocytosis type 2 in a female Chinese neonate: A case report and review of the literature  
*Bi SH, Jiang LL, Dai LY, Wang LL, Liu GH, Teng RJ*
- 6067** Usefulness of metagenomic next-generation sequencing in adenovirus 7-induced acute respiratory distress syndrome: A case report  
*Zhang XJ, Zheng JY, Li X, Liang YJ, Zhang ZD*
- 6073** Neurogenic orthostatic hypotension with Parkinson's disease as a cause of syncope: A case report  
*Li Y, Wang M, Liu XL, Ren YF, Zhang WB*
- 6081** SATB2-associated syndrome caused by a novel SATB2 mutation in a Chinese boy: A case report and literature review  
*Zhu YY, Sun GL, Yang ZL*
- 6091** Diagnosis and treatment discussion of congenital factor VII deficiency in pregnancy: A case report  
*Yang Y, Zeng YC, Rumende P, Wang CG, Chen Y*

- 6102** Unusual immunohistochemical “null” pattern of four mismatch repair proteins in gastric cancer: A case report  
*Yue M, Liu JY, Liu YP*
- 6110** Generalized periodontitis treated with periodontal, orthodontic, and prosthodontic therapy: A case report  
*Kaku M, Matsuda S, Kubo T, Shimoe S, Tsuga K, Kurihara H, Tanimoto K*
- 6125** Ligamentum flavum hematoma following a traffic accident: A case report  
*Yu D, Lee W, Chang MC*
- 6130** Oral cyclophosphamide-induced posterior reversible encephalopathy syndrome in a patient with ANCA-associated vasculitis: A case report  
*Kim Y, Kwak J, Jung S, Lee S, Jang HN, Cho HS, Chang SH, Kim HJ*
- 6138** Encapsulating peritoneal sclerosis in an AMA-M2 positive patient: A case report  
*Yin MY, Qian LJ, Xi LT, Yu YX, Shi YQ, Liu L, Xu CF*
- 6145** Multidisciplinary diagnostic dilemma in differentiating Madelung’s disease – the value of superb microvascular imaging technique: A case report  
*Seskute G, Dapkute A, Kausaite D, Strainiene S, Talijunas A, Butrimiene I*
- 6155** Complicated course of biliary inflammatory myofibroblastic tumor mimicking hilar cholangiocarcinoma: A case report and literature review  
*Strainiene S, Sedleckaite K, Jarasunas J, Savlan I, Stanaitis J, Stundiene I, Strainys T, Liakina V, Valantinas J*
- 6170** Fruquintinib beneficial in elderly patient with neoplastic pericardial effusion from rectal cancer: A case report  
*Zhang Y, Zou JY, Xu YY, He JN*

**ABOUT COVER**

Editorial Board Member of *World Journal of Clinical Cases*, Jae Gil Lee, MD, PhD, Professor, Surgeon, Department of Surgery, Yonsei University College of Medicine, Seoul 03722, South Korea. jakii@yuhs.ac

**AIMS AND SCOPE**

The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

**INDEXING/ABSTRACTING**

The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJCC as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Ji-Hong Lin; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lai Wang.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

July 26, 2021

**COPYRIGHT**

© 2021 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

# Unusual immunohistochemical “null” pattern of four mismatch repair proteins in gastric cancer: A case report

Meng Yue, Jun-Ying Liu, Yue-Ping Liu

**ORCID number:** Meng Yue 0000-0002-0326-2140; Jun-Ying Liu 0000-0002-9209-6809; Yue-Ping Liu 0000-0002-4582-114X.

**Author contributions:** Yue M collected the patient's clinical data, performed literature review, and drafted the whole manuscript; Liu JY assisted in data collection and literature review; Liu YP helped revise the manuscript; all authors read and approved the final manuscript.

**Informed consent statement:** The patient provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** The authors declare that they have no competing interests to report.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build

Meng Yue, Jun-Ying Liu, Yue-Ping Liu, Department of Pathology, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, Hebei Province, China

**Corresponding author:** Yue-Ping Liu, MD, PhD, Chief Doctor, Professor, Senior Scientist, Department of Pathology, The Fourth Hospital of Hebei Medical University, No. 12 Jiankang Road, Shijiazhuang 050011, Hebei Province, China. [annama@163.com](mailto:annama@163.com)

## Abstract

### BACKGROUND

Immunohistochemical (IHC) staining for mismatch repair (MMR) proteins is useful for gastric cancer treatment and prognosis. Different IHC staining patterns reflect the complex biological phenomena underlying MMR deficiency. We herein report a rare IHC staining pattern of four MMR-related proteins in gastric cancer.

### CASE SUMMARY

A “null” IHC staining pattern of four MMR-related proteins, including MLH1, PMS2, MSH2, and MSH6, in a 67-year-old male patient with gastric cancer pT3N3aM0 revealed promoter hypermethylation of *MLH1*. Next-generation sequencing showed that these four genes exhibited changes. One of these was the somatic mutation of the missing copy number in exon 14 of *MSH2*. Mutation analysis using peripheral blood showed no germline mutations in these four genes. The patient had no history of personal or family tumor history. We classified this case as sporadic. The patient returned to normal after operation, and there were no signs of tumor metastasis and recurrence. After six cycles of adjuvant chemotherapy, the patient was discharged in a stable condition. The patient had a mild reaction to chemotherapy and a good prognosis. At present, 16 mo after the operation, the patient's condition is stable.

### CONCLUSION

Abnormal MMR protein expression, helpful for individualized follow-up care, helped identify a sporadic case lacking familial clinical management implications.

**Key Words:** Gastric cancer; Mismatch repair proteins; Next-generation sequencing; Sporadic; Family management; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Specialty type:** Oncology

**Country/Territory of origin:** China

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**Received:** March 17, 2021

**Peer-review started:** March 17, 2021

**First decision:** April 4, 2021

**Revised:** April 16, 2021

**Accepted:** May 19, 2021

**Article in press:** May 19, 2021

**Published online:** July 26, 2021

**P-Reviewer:** Naem A, Villarejo-Campos P

**S-Editor:** Gong ZM

**L-Editor:** Wang TQ

**P-Editor:** Wang LYT



**Core Tip:** A “null” immunohistochemical staining pattern of mismatch repair (MMR) proteins was revealed, which helped identify this case as sporadic without familial clinical management implications. An in-depth understanding of the abnormal MMR expression is helpful for individualized follow-up treatment and assessment of prognosis.

**Citation:** Yue M, Liu JY, Liu YP. Unusual immunohistochemical “null” pattern of four mismatch repair proteins in gastric cancer: A case report. *World J Clin Cases* 2021; 9(21): 6102-6109

**URL:** <https://www.wjgnet.com/2307-8960/full/v9/i21/6102.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v9.i21.6102>

## INTRODUCTION

Gastric cancer is one of the most common cancers and a major cause of cancer-related deaths worldwide. Its molecular and clinical characteristics are complicated by histological and etiological heterogeneity. Gastric adenocarcinomas are divided into four subtypes according to their molecular features: Tumors exhibiting chromosomal instability, microsatellite instability (MSI)-high (MSI-H), Epstein-Barr virus (EBV) positivity, and genomic stability[1,2]. MSI and molecular typing are essential for the treatment and prognosis of gastric cancer[3,4].

Maintaining the mismatch repair (MMR) pathway is vital for accurate DNA replication and genome stability. Base pair insertion or loss occurs in the microsatellite region due to mismatch repair system defects, and replication errors cause MSI[5,6]. Immunohistochemistry (IHC) testing of four representative MMR-related proteins, MLH1, PMS2, MSH2, and MSH6, can detect a specific gene and help identify patients with Lynch syndrome (LS), an autosomal dominant disease caused by germline mutations in MMR-related genes[7]. IHC is a convenient and affordable method for MSI analysis and has a high sensitivity and specificity. Different IHC staining patterns reflect the complex biological phenomena underlying MMR deficiency. Therefore, it is essential to expand our understanding of abnormal IHC findings and their biological significance. In the present case, IHC testing of four MMR-related proteins revealed abnormal and rare protein expression with an unusual “null” pattern. These MMR-related genes exhibited changes tested by genetic analysis.

## CASE PRESENTATION

### Chief complaints

A 67-year-old male patient presented with upper abdominal discomfort and vomiting.

### History of present illness

The patient experienced upper abdominal discomfort and vomiting for 4 mo. These events occurred without obvious inducement.

### History of past illness

*Helicobacter pylori* infection was not observed. Left inguinal hernioplasty was performed 6 mo ago.

### Personal and family history

No personal or family history of tumors was noted.

### Physical examination

No obvious abnormality.

### Laboratory examinations

Paraffin-embedded blocks of gastric cancer tissues were used for pathologic diagnosis, IHC, and molecular analysis. The tumor showed an infiltrative growth pattern on

gross examination (Figure 1A). Histologically, the tumor was poorly differentiated. It had a solid pattern with necrosis and was heterogeneous with glandular differentiation and prominent tumor-infiltrating lymphocytes (Figure 1B and C). The tumor cells were positive for low-molecular-weight cytokeratin (AE1/AE3, Ventana) (Figure 1D). The combined positive score (CPS) of programmed death-ligand 1 (PD-L1, 22C3, Dako) was high (Figure 1E). *In situ* hybridization of EBV-encoded small RNA was negative (Figure 1F). MMR proteins, including MLH1 (M1, Ventana), PMS2 (A16-4, Ventana), MSH2 (G219-1129, Ventana), and MSH6 (SP93, Ventana), were analyzed using IHC. All four proteins were negative in the tumor cells but positive in the positive control, stromal, and inflammatory cells. IHC results coincided with those of other paraffin blocks (Figure 2). HER2 (4B5, Ventana) was 1+, and Ki-67 (30-9, Ventana) was 60%.

Subsequently, a methylation-specific polymerase chain reaction assay of the *MLH1* promoter region was performed, which revealed promoter hypermethylation of *MLH1*.

Next-generation sequencing (NGS) of genes including *MLH1*, *MSH2*, *MSH6*, and *PMS2* was performed. In addition, 37 genes, including gastrointestinal tumor-related genes such as *AKT1*, *ATM*, *BRCA1*, *BRCA2*, *CDH1*, *EGFR*, *ERBB2*, *HRAS*, *KIT*, *MET*, *PDGFRA*, *PIK3CA*, *PMS1*, *PTCH1*, *SDHB*, *SDHC*, and *SDHD*; genes related to drug metabolism toxicity such as *CYP2D6*, *DPYD*, and *UGT1A1*; and genes related to gastrointestinal therapy, prognosis, and inheritance such as *APC*, *BLM*, *BMPR1A*, *CHEK2*, *EPCAM*, *GALNT12*, *GREM1*, *MUTYH*, *POLD1*, *POLE*, *PTEN*, *SMAD4*, *STK11*, *TP53*, *KRAS*, *NRAS*, and *BRAF*, were identified.

NGS demonstrated that *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes exhibited changes. There was a mutation in the splicing region of exon 12 of *MLH1* (c.1039-13\_1039-8del), a missense mutation in exon 11 of *PMS2* (c.1799T>C, p.Met600Thr), a missing copy number in exon 14 of *MSH2* (Figure 3), and a missense mutation in exon 4 of *MSH6* (c.2693C>A, p.Pro898His). This mutation of *MSH2* may lead to a shift in the subsequent coding frame of *MSH2*, leading to the loss of protein expression. Mutation analysis using peripheral blood showed no germline mutations in these four genes. The presence of *MLH1* promoter methylation and mutation of *MSH2* confirmed MSI-H. The patient had no personal or family tumor history, indicating that this MMR deficiency was highly likely sporadic in nature. Thus, there were no clinical management implications for his family.

The tumor showed several other mutations, including copy number amplification of the *PIK3CA* gene (Figure 3), possibly leading to the upregulation of *PIK3CA* expression. The *PTEN* gene had a frameshift mutation in exon 7 (c.800del, p.Lys267fs) and a nonsense mutation in exon 5 (c.388C>T, p.Arg130). The exon began to shift from the amino acid residue 267 (lysine) in exon 7. Terminators are likely to be introduced into the new reading frame. The amino acid residue 130 encoded by exon 5 was mutated from arginine to the terminator. These two premature terminators may lead to meaningless mRNA degradation, resulting in protein loss. There was a missense mutation of p.g245s in exon 7 of the *TP53* gene and mutations in the splicing region of exon 6 of the *ATM* gene (c.497-5\_497-4del) and exon 12 of the *MET* gene (c. 2584-13\_2584-9del).

### Imaging examinations

Computed tomography showed space-occupying lesions in the gastric cardia and fundus and multiple slightly enlarged peripheral lymph nodes around the stomach.

### Endoscopy

Gastroscopy revealed a large mass in the gastric body. The endoscope could not pass through the gastric body.

### Biopsy

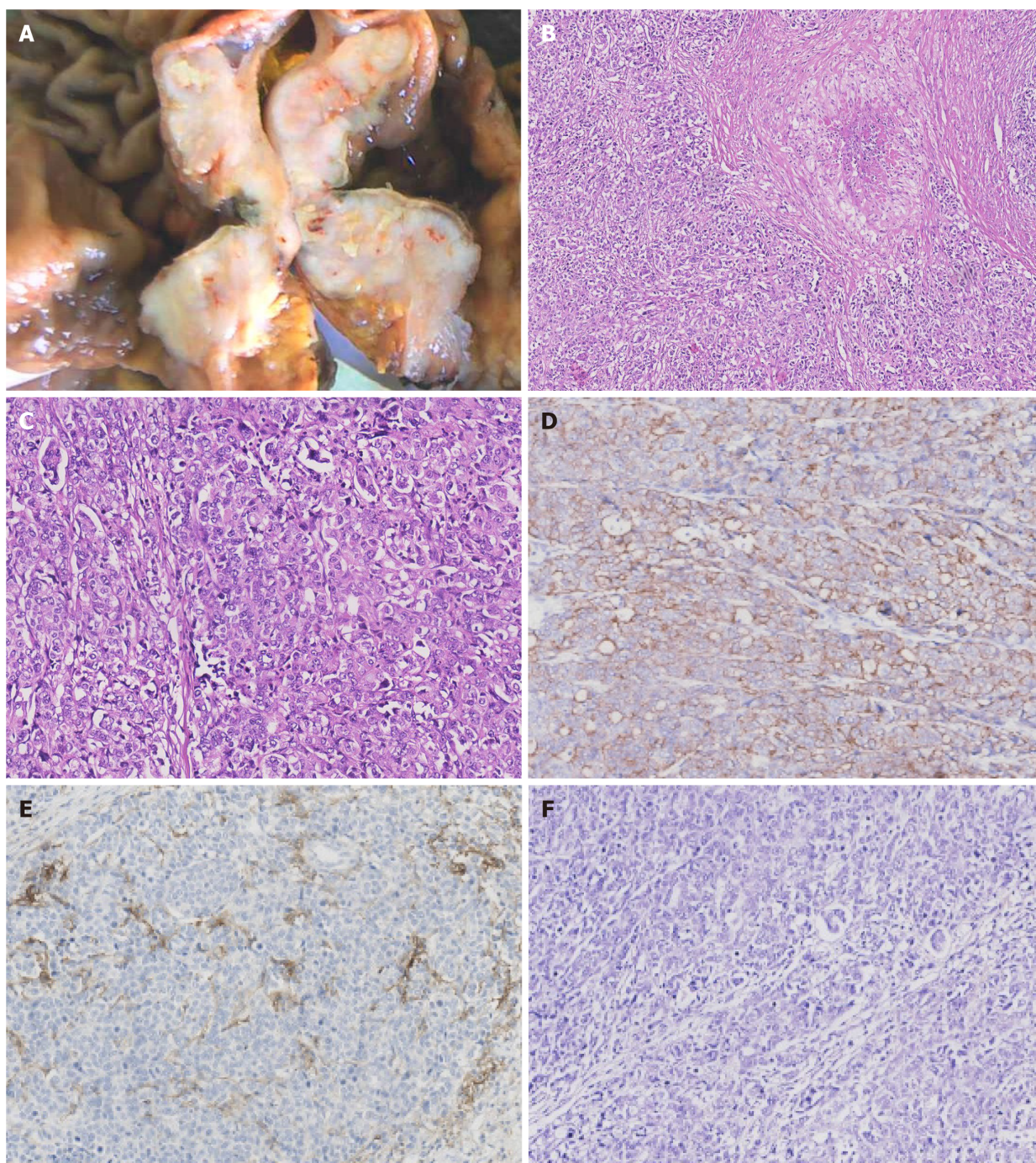
Biopsy showed severe dysplasia and canceration of the glandular epithelium.

---

## FINAL DIAGNOSIS

---

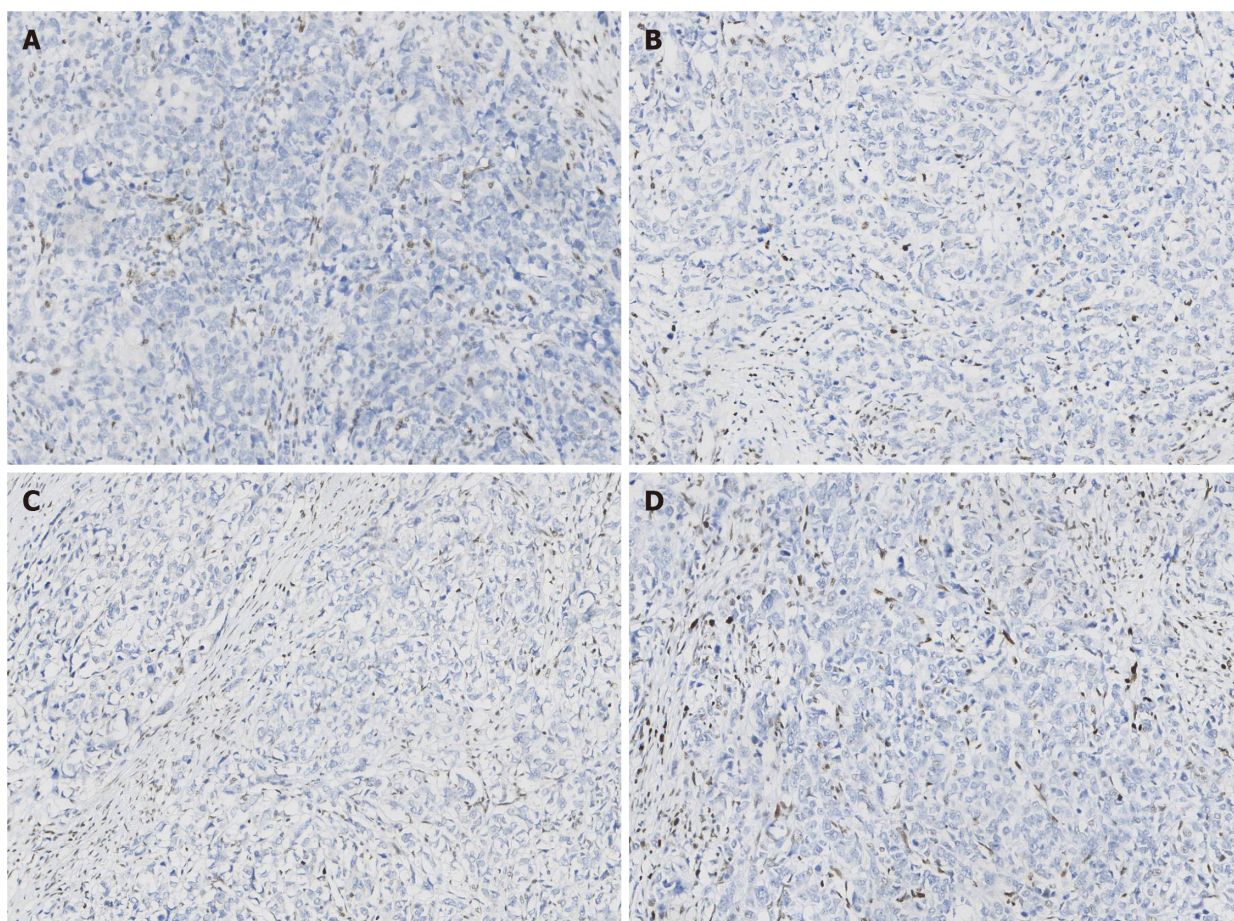
The results showed a 5-cm pT3N3aM0 adenocarcinoma. Furthermore, 7 of the 21 lymph nodes showed metastasis and a “null” IHC staining pattern of four MMR-related proteins, including *MLH1*, *PMS2*, *MSH2*, and *MSH6*. Thus, this case belongs to the MSI-H subtype of gastric adenocarcinoma.



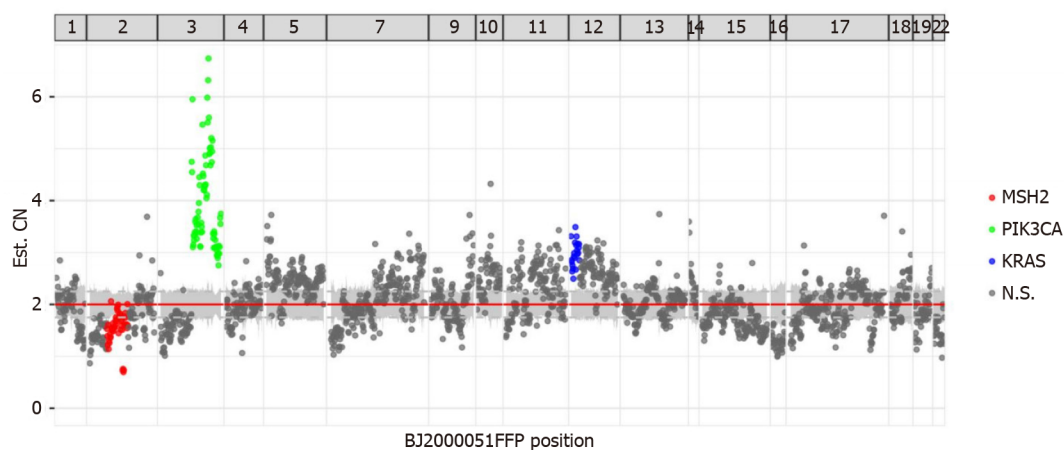
**Figure 1 Pathological characteristics.** A: Gross appearance of the tumor; B: Microscopic appearance of the tumor with necrosis; C: Microscopic appearance of the tumor with solid pattern and lymphatic stroma; D: The tumor cells were positive for cytokeratin AE1/AE3 by immunohistochemical staining; E: High expression of PDL1 (22C3) CPS>1; F: Epstein-Barr virus encoded small RNA was negative (figures at 100-200 × magnification).

## TREATMENT

Total gastrectomy was performed, and 21 lymph nodes were dissected. The patient returned to normal after operation. Nine months after the operation, the patient was admitted to the hospital for continued treatment. Ultrasound results showed several solid nodules in the patient's inguinal region, and biopsy results revealed normal lymph tissue. There were no signs of tumor metastasis or recurrence. After six cycles of adjuvant chemotherapy, the patient's response to chemotherapy was mild. The patient was satisfied with the treatment results.



**Figure 2 Expression of mismatch repair-related proteins by immunohistochemical staining.** The tumor cells were completely negative for all four proteins. A: MLH1; B: PMS2; C: MSH2; D: MSH6 (all images at 200 × magnification).



**Figure 3 Results of next-generation sequencing.** The mutation of *MSH2* and amplification of *PIK3CA* were observed.

## OUTCOME AND FOLLOW-UP

The patient was asked to undergo follow-up every 3 mo. The patient was discharged in a stable condition for 16 mo after the operation. At present, the prognosis is good, but the long-term prognosis is yet to be determined.

**Table 1 Summary of clinicopathological features of null mismatch repair immunohistochemical staining pattern reported in the literature**

Case No.	Age (yr)	Sex	Location	<i>MLH1</i> promoter methylation status	<i>MSH2</i> status	<i>BRAF</i> status	Specimen tested	Ref.
1	72	Female	Colorectal cancer	Hypermethylation	Germline G587R mutation	Negative	Resection	Hagen <i>et al</i> [8], 2011
2	80	Female	Colorectal cancer	Hypermethylation	Three somatic mutations ( <i>MSH2</i> c.1861 C>T (p.R621*) in exon 12, c.298G>A (p.V100I) and c.633dupG (p.K212Efs*20))	Mutation	Resection	Wang <i>et al</i> [9], 2017
3	76	Male	Ascending colon	Hypermethylation	Unknown	Mutation	Biopsy	Westwood <i>et al</i> [10], 2019

## DISCUSSION

Hagen *et al*[8] first reported this “null” IHC staining pattern of all four MMR proteins in colorectal cancer due to germline *MSH2* mutation and somatic *MLH1* hypermethylation in a 71-year-old female patient with LS. Using microscopy, the morphology observed in that case was similar to that observed in our case, but the gene expression was inconsistent. That patient had a history of colon cancer and ureteral cancer. She also had a strong family history of tumors. All these findings confirmed the diagnosis of LS. However, our case was sporadic.

Wang *et al*[9] found that the four MMR protein deficiencies in an 80-year-old female patient with colorectal cancer were highly likely sporadic, and no high-risk surveillance protocols were recommended to the patient or her family members. The morphology and gene expression observed in their case were similar to those observed in our case. They found promoter hypermethylation of *MLH1* and double somatic truncating mutations in *MSH2*. They also found a BRAFV600E mutation. In our case, we found promoter hypermethylation of *MLH1* and a missing copy number in exon 14 of *MSH2*. Westwood *et al*[10] found that the percentage of additional partial or complete loss of *MSH2* and *MSH6* in *MLH1*-deficient CRC patients was 0.48% (4/829). Additionally, IHC staining showed complete null expression of MMR proteins in only one colon cancer case, but it showed strong staining for all four proteins in rectal cancer. Unfortunately, biopsy was the only available procedure for testing in colon cancer. Further genetic analysis showed *MLH1* promoter hypermethylation and BRAFV600E mutation. A summary of the “null” IHC staining pattern of all four MMR proteins reported in the literature is provided in Table 1.

MSI tumors with *MLH1* methylation were associated with BRAFV600E mutation only in the colon but not in the stomach[11]. The BRAFV600E mutation was not detected in our case, which illustrates this point. Additionally, no abnormalities were found at the detection sites of *KRAS*, *NRAS*, and *HRAS*, which is also different from that in colon cancer.

All the above mentioned studies reported colorectal cancer cases but not gastric cancer cases. Cho *et al*[12] reported five cases in which all four MMR proteins were negative and none of 580 cases showed a single MMR protein loss by IHC; further genetic testing was not performed except for PCR analysis of MMR genes. In contrast, we retrospectively collected the data of 2808 cases of postoperative gastric cancer from the Fourth Hospital of Hebei Medical University from May 2017 to August 2020 and found that only this case was completely negative. Thus, the incidence rate was 0.0356%. Fifteen cases showed only negative results for *PMS2*, and three cases were negative for *MSH6*. The reasons for these differences remain unclear. The standard used by Cho *et al*[12] for judgement of negative results was complete loss or < 20% focal weak equivocal nuclear staining. We consider that our judgment standard was stricter; thus, the total number of negative cases was lower. Additionally, we tested more cases and identified cases with a single negative MMR protein. In another 464 cases of gastric cancer, the co-negative percentage of *MLH1* and *MSH2* was 4.4%[13]. These researchers used tissue microarrays for testing. However, there was potential heterogeneity in the use of tissue microarrays. In-depth genetic testing was not performed. Therefore, our case is the first to reveal this rare IHC staining pattern of four MMR proteins in gastric cancer and show differences in gene expression in colorectal cancer. We believe that this is not a common phenomenon in gastric cancer since it has not been previously reported in detail in the stomach.

Patients with MSI-H gastric cancer are usually older, with the majority being women. The cancer is mostly located in the distal part of the stomach; most of the cases are intestinal-type as per Lauren's classification and show less lymph node metastasis. They have a lower recurrence rate and better prognosis compared to those of other subgroups[1]. However, our patient was an aged man with cancer located near the cardia. Although the tumors were heterogeneous, the intestinal-type part only occupied a small portion of the tumor. Kawazoe *et al*[14] showed that PD-L1 expression (22C3) in immune cells (ICs) was associated with EBV positivity and lymph node metastasis. Our case showed the expression of PD-L1 only on ICs and high CPS with EBV negativity and lymph node metastasis. MSI status is considered a practical alternative to the immunotherapy response. Immunotherapy is recommended for patients with MSI-H[15]. However, our patient did not receive any immunotherapy, but the patient's condition remained stable after 9 mo, and there was no sign of recurrence or metastasis. Additionally, this patient had a large tumor size, many lymph node metastases, and specificity of gene expression. These findings are unusual compared with those in other cases; thus, the patient was asked to undergo follow-up regularly for safety precautions.

## CONCLUSION

Here, we report a sporadic case with unusual MMR IHC and gene patterns in gastric adenocarcinoma. The patient had a mild reaction to chemotherapy and a good prognosis, and no clinical management implications for the family were identified. An in-depth understanding of the abnormal expression of MMR is helpful for individualized follow-up treatment and assessment of prognosis.

## ACKNOWLEDGEMENTS

The authors thank all the clinicians and nurses involved in the treatment of this case.

## REFERENCES

- 1 **Cancer Genome Atlas Research Network.** Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; **513**: 202-209 [PMID: 25079317 DOI: 10.1038/nature13480]
- 2 **Kato H, Ishikawa S.** Genomic pathobiology of gastric carcinoma. *Pathol Int* 2017; **67**: 63-71 [PMID: 28004449 DOI: 10.1111/pin.12493]
- 3 **Zappasodi R, Merghoub T, Wolchok JD.** Emerging Concepts for Immune Checkpoint Blockade-Based Combination Therapies. *Cancer Cell* 2018; **33**: 581-598 [PMID: 29634946 DOI: 10.1016/j.ccell.2018.03.005]
- 4 **Zhao X, Dai D, Li X, Shen B, Chen X, Shu Y, Wang D.** A polymorphism within the mismatch repair gene predicts prognosis and adjuvant chemotherapy benefit in gastric cancer. *Gastric Cancer* 2019; **22**: 1121-1129 [PMID: 30989434 DOI: 10.1007/s10120-019-00962-8]
- 5 **Liu D, Keijzers G, Rasmussen LJ.** DNA mismatch repair and its many roles in eukaryotic cells. *Mutat Res* 2017; **773**: 174-187 [PMID: 28927527 DOI: 10.1016/j.mrrev.2017.07.001]
- 6 **Lee V, Murphy A, Le DT, Diaz LA Jr.** Mismatch Repair Deficiency and Response to Immune Checkpoint Blockade. *Oncologist* 2016; **21**: 1200-1211 [PMID: 27412392 DOI: 10.1634/theoncologist.2016-0046]
- 7 **Kawakami H, Zaan A, Sinicrope FA.** Microsatellite instability testing and its role in the management of colorectal cancer. *Curr Treat Options Oncol* 2015; **16**: 30 [PMID: 26031544 DOI: 10.1007/s11864-015-0348-2]
- 8 **Hagen CE, Lefferts J, Hornick JL, Srivastava A.** "Null pattern" of immunoreactivity in a Lynch syndrome-associated colon cancer due to germline MSH2 mutation and somatic MLH1 hypermethylation. *Am J Surg Pathol* 2011; **35**: 1902-1905 [PMID: 22067334 DOI: 10.1097/PAS.0b013e318237c6ab]
- 9 **Wang T, Stadler ZK, Zhang L, Weiser MR, Basturk O, Hechtman JF, Vakiani E, Saltz LB, Klimstra DS, Shia J.** Immunohistochemical null-phenotype for mismatch repair proteins in colonic carcinoma associated with concurrent MLH1 hypermethylation and MSH2 somatic mutations. *Fam Cancer* 2018; **17**: 225-228 [PMID: 28819720 DOI: 10.1007/s10689-017-0031-9]
- 10 **Westwood A, Glover A, Hutchins G, Young C, Brockmoeller S, Robinson R, Worrlow L, Wallace D, Rankeillor K, Adlard J, Quirke P, West N.** Additional loss of MSH2 and MSH6 expression in sporadic deficient mismatch repair colorectal cancer due to MLH1 promoter hypermethylation. *J Clin Pathol* 2019; **72**: 443-447 [PMID: 30723092 DOI: 10.1136/jclinpath-2018-205687]
- 11 **Liu Y, Sethi NS, Hinoue T, Schneider BG, Cherniack AD, Sanchez-Vega F, Seoane JA, Farshidfar F,**

- Bowlby R, Islam M, Kim J, Chatila W, Akbani R, Kanchi RS, Rabkin CS, Willis JE, Wang KK, McCall SJ, Mishra L, Ojesina AI, Bullman S, Pedamallu CS, Lazar AJ, Sakai R; Cancer Genome Atlas Research Network, Thorsson V, Bass AJ, Laird PW. Comparative Molecular Analysis of Gastrointestinal Adenocarcinomas. *Cancer Cell* 2018; **33**: 721-735. e8 [PMID: [29622466](#) DOI: [10.1016/j.ccell.2018.03.010](#)]
- 12 **Cho J**, Kang SY, Kim KM. MMR protein immunohistochemistry and microsatellite instability in gastric cancers. *Pathology* 2019; **51**: 110-113 [PMID: [30497803](#) DOI: [10.1016/j.pathol.2018.09.057](#)]
  - 13 **Bae YS**, Kim H, Noh SH. Usefulness of Immunohistochemistry for Microsatellite Instability Screening in Gastric Cancer. *Gut Liver* 2015; **9**: 629-635 [PMID: [26343070](#) DOI: [10.5009/gnl15133](#)]
  - 14 **Kawazoe A**, Shitara K, Kuboki Y, Bando H, Kojima T, Yoshino T, Ohtsu A, Ochiai A, Togashi Y, Nishikawa H, Doi T, Kuwata T. Clinicopathological features of 22C3 PD-L1 expression with mismatch repair, Epstein-Barr virus status, and cancer genome alterations in metastatic gastric cancer. *Gastric Cancer* 2019; **22**: 69-76 [PMID: [29859006](#) DOI: [10.1007/s10120-018-0843-9](#)]
  - 15 **Chivu-Economescu M**, Matei L, Necula LG, Dragu DL, Bleotu C, Diaconu CC. New therapeutic options opened by the molecular classification of gastric cancer. *World J Gastroenterol* 2018; **24**: 1942-1961 [PMID: [29760539](#) DOI: [10.3748/wjg.v24.i18.1942](#)]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

