Synchronous multiple primary gastrointestinal cancers with CDH1 mutations: A case report

Mu-Ni Hu, Wei Lv, Rui-Yue Hu, Yi-Fan Si, Xiao-Wen Lu, Yan-Juan Deng, Huan Deng

Abstract

BACKGROUND

Synchronous multiple primary cancers (SMPC) mean two or more malignant tumors occurring simultaneously and with different origins no matter what types they are or where they are located. The carcinogenesis of SMPC often involves variations of some specific genes. However, the correlation between CDH1 mutations and synchronous multiple primary gastrointestinal cancers is largely unknown.

CASE SUMMARY

A 62-year-old woman had sustained abdominal pain for one week and visited our hospital. Gastrointestinal endoscopy revealed multiple small polypoid lesions in both the stomach and colorectum. Computed tomography and laboratory results were within normal limits. Pathological evaluation confirmed signet ring cell carcinoma without obvious metastatic evidence. Malignant cells
showed negativity for E-cadherin and positivity for β-catenin in the cytoplasm and nucleus. DNA sequencing performed on paraffin-embedded tissue revealed two exactly coincident alterations in \( CDH1 \), \( C.57T>G \) and \( C.1418A>T \).

**CONCLUSION**

This case suggests that the combination of \( CDH1 \) mutations and WNT/β-catenin signaling activation contributes to the carcinogenesis of gastrointestinal SMPC.

**Key words:** Multiple primary cancers; \( CDH1 \); Signet ring cell carcinoma; Stomach; Colon; Case report

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** A 62-year-old woman was admitted with abdominal pain for one week. Gastrointestinal endoscopy revealed multiple small polypoid lesions in both the stomach and colorectum. A diagnosis of primary signet ring cell carcinoma was established based on the combination of pathological and imageologic evaluations. E-cadherin expression was downregulated in the malignant cells, where β-catenin was aberrantly translocated to the cytoplasm and nucleus. DNA sequencing indicated \( C.57T>G \) and \( C.1418A>T \) in \( CDH1 \), suggesting the important role of \( CDH1 \) mutations in the pathogenesis of synchronous multiple primary gastrointestinal cancers.

**INTRODUCTION**

Synchronous multiple primary cancers (SMPC) are defined as two or more primary malignancies with different origins detected in a person within 6 months\(^{[1-3]}\). Although accumulating evidence suggests that genetic alterations are responsible for the tumorigenesis of SMPC, the underlying molecular mechanisms are unclear\(^{[4]}\). E-cadherin, a member of the cadherin family, is a calcium-dependent glycoprotein composed of five extracellular cadherin repeats and can serve as one of the most important elements in cell-cell adhesion in epithelial cells. E-cadherin can regulate cell adhesion and polarity by binding p120 and β-catenin\(^{[5]}\). Thus, loss of E-cadherin gene (\( CDH1 \)) has been linked with hereditary diffuse gastric cancer as well as other cancers with a high propensity for vascular invasion and metastasis\(^{[6,7]}\). Genetic variations of \( CDH1 \) promote the detachment of malignant cells from primary site\(^{[8]}\). Except for its essential role in carcinogenesis, the crosstalk between E-cadherin and other signaling pathways, including p27, Hippo, WNT/β-catenin, and rho family GTPase, also contributes to the progression of malignant tumors\(^{[9-11]}\).

Although \( CDH1 \) has been proposed as a tumor suppressor gene, the relationship between \( CDH1 \) mutations and the risk of SMPC, especially in the gastrointestinal system, is largely unknown. Here, we report the first case of synchronous multiple primary gastrointestinal cancers, developing in the stomach and colorectum, with \( CDH1 \) mutations.

**CASE PRESENTATION**

**Chief complaints**

A 62-year-old women presented to the department of gastroenterology with abdominal pain and vomiting for 1 week.

**History of present illness**

The patient’s symptoms started a week ago.

**History of past illness**
The patient had a free previous medical history.

**Endoscopic examinations**
The patient underwent gastroscopy, by which multiple circumferential and polypoid masses, approximately 5 mm in the greatest diameter, in the mucosal surface of the gastric corpus and duodenum bulb were observed. The lesions were characterized by surface congestion and erosion, however, the surrounding mucosa appeared smooth and normal (Figure 1A and 1B). These lesions were clearly distinct from classic gastric adenocarcinoma by its island-like growth pattern. Meanwhile, colonoscopy also found multiple masses, three in the hepatic flexure of the colon, one in the transverse colon, two in the descending colon, and one in the rectum, all of which showed a similar morphology to their counterparts in the stomach (Figure 1C and 1D).

**Pathological examinations**
The diagnosis of signet ring cell carcinoma was established based on the pathological evaluation of biopsy specimens (Figure 2A). Periodic acid Schiff (PAS) positivity revealed the presence of mucin in the cytoplasm (Figure 2B). Antibody for E-cadherin decorated normal epithelial cells, rather than surrounding signet ring cells (Figure 2C). Abnormal cytoplasmic and nuclear positivity of β-catenin in cancer cells further encouraged the possibility that CDH1 alterations served as an important intrinsic driver (Figure 2D). Of note is the fact that the poor differentiated cells were restricted to the mucosa.

**Imaging examinations**
The abdominal computed tomography (CT) scan showed local inconspicuous wall thickening in the stomach, duodenum, colon and rectum, prompting that all may be primary lesions (Figure 3A-D).

**CDH1 sequencing**
Sequencing was employed to confirm the alterations of CDH1 using DNA extracted from paraffin-embedded tissues. PCR amplification was performed using primers for 16 exons of CDH1 as described by a previous study[12]. DNA sequence was analyzed using the DNA sequencer (ABI Prism, Applied Biosystems) according to the manufacturer’s instructions. This experiment was repeated three times to insure the accuracy of results. Specimens exhibited uniform CDH1 alterations C.57T>G and C.1418A>T (Figure 4).

**MULTIDISCIPLINARY EXPERT CONSULTATION**

**Huan Deng, PhD, MD, Department of Pathology/Molecular Medicine and Genetics Center, the Fourth Affiliated Hospital of Nanchang University; Renmin Institute of Forensic Medicine in Jiangxi**

The pathological evaluation of biopsy specimens clearly showed their malignant characteristics. All lesions were diagnosed as poorly signet ring cell carcinomas, which were restricted to the mucosa. Combined with CT findings, these lesions should be derived from different cellular origins. Meanwhile, the immunophenotype of the lesions showed downregulation of E-cadherin and abnormal cytoplasmic and nuclear positivity for β-catenin in cancer cells, supporting the possibility that CDH1 alteration served as an important intrinsic driver during carcinogenesis of gastrointestinal SMPC.

**Nong-Rong Wang, Department of Gastroenterology, the Fourth Affiliated Hospital of Nanchang University**

Multiple circumferential and polypoid masses in the gastrointestinal mucosa were observed by endoscopy. All the lesions have uniform morphological features and were clearly distinct from classic adenocarcinoma because of their island-like growth pattern. The clinical and pathological features support the diagnosis of SMPC. We should distinguish such cases from metastatic cancers based on comprehensive analysis of the results of endoscopy, pathology, positron emission tomography (PET)-CT, and laboratory tests. For patients with SMPC, we need to consider the possibility of heredity, thus relevant genetic testing should be recommended for the patient as well as his/her immediate familial members.

**You-Jun Liu, Department of Radiology, the Fourth Affiliated Hospital of Nanchang University**

CT results mainly indicated that the lesions were inconsiderable, consistent with the characteristics of early primary gastrointestinal cancers. However, it is hard to give
Figure 1 Endoscopy results. Multiple small polypoid lesions without stalk were observed in A: The stomach; B: The duodenum; C: The colon; D: The rectum.

Further precise evidences within the limits of inspection items. More substantial data should be obtained to avoid the pitfall of benign diseases or metastatic lesions.

**FINAL DIAGNOSIS**

The final diagnosis of the presented case is synchronous multiple primary gastrointestinal cancers with CDH1 mutations.

**TREATMENT**

The patient was discharged without any treatments.

**OUTCOME AND FOLLOW-UP**

The patient past away in one year.

**DISCUSSION**

The diagnosis of SMPC must meet the following four criteria: (1) Each tumor is malignant; (2) Tumors occur in different organs within 6 months; (3) Each tumor has its own metastatic pathway; and (4) The diagnosis of metastatic or recurrent tumors can be excluded[13,14]. We describe here a patient with synchronous multiple primary gastrointestinal cancers. The small polypoid lesions with distinctive boundary scattered throughout the stomach and colorectum. A combined analysis of restricted distribution of typical signet ring cells in the mucosa and CT findings further supported the diagnosis of primary cancers, rather than invasive or metastatic diseases.

Gene alterations contribute to the initiation of tumor genesis[4,16]. Substantial evidence reveals that CDH1 mutations and subsequent E-cadherin dysregulation play a key role in the development of hereditary diffuse gastric cancer (HDGC) as well as
lobular breast cancer\cite{17,18}. Patients with HDGC also face a higher risk of primary malignancies in the colonrectum, thyroid, ovary, lung, prostate, salivary gland, and pancreas compared with the normal population\cite{19,20}. A recent study reported a case in which \textit{CDH1} mutations are involved in synchronous appendiceal and intramucosal gastric signet ring cell carcinomas\cite{20}. However, the relationship between \textit{CDH1} mutations and synchronous multiple primary gastrointestinal cancers has not been introduced before.

In this study, malignant tissues exhibited two \textit{CDH1} alterations: C.57T>G and C.1418A>T. Immunohistochemistry results further demonstrated the aberrant expression of \textit{CDH1} encoding protein E-cadherin. The downregulation of E-cadherin initiates the carcinogenesis cascade and enhances the motility of tumor cells through crosstalk with other vital signaling pathways such as WNT/β-catenin\cite{21,22}. E-cadherin forms a dimeric complex with β-catenin on the cell membrane. The loss of binding region leads to the aberrant translocation of β-catenin from membrane to the cytoplasm and nucleus, where β-catenin binds TCF/LEF family and serves as a transcription factor to promote tumorigenesis\cite{23}.

In this study, we attempted to gain further insights into the patient’s family history. Her sisters also died from malignant gastric tumor without definite histopathological type. We lack more substantial evidence to support our hypothesis that it is a hereditary disease because her family members refused to do gene sequencing. Clinical experts are expected to distinguish multiple primary gastrointestinal cancers from metastatic counterparts, which enquires us to perform full diagnostic evaluations, involving endoscopy, PET/CT, and pathological biopsy. Meanwhile, genetic analyses can be recommended for patients and family members to predict disease risks.

**CONCLUSION**

Considerable publications have revealed that \textit{CDH1} mutations can promote the occurrence of malignant comorbidity, especially hereditary diffuse gastric carcinoma. However, the connection between \textit{CDH1} mutations and SMPC in the gastrointestinal tract is unclear. We report the first gastrointestinal SMPC case with two \textit{CDH1} alterations C.57T>G and C.1418A>T. The WNT/β-catenin signaling pathway was involved in the tumorigenesis. Further work is required to explore the underlying
Figure 3 Morphology and immunophenotype of the lesion. A: H&E staining showed poorly differentiated signet ring carcinoma; B: Tumor cells were negative for E-cadherin; C: β-catenin was translocated from the membrane to the cytoplasm and nucleus in malignant cells; D: Periodic acid Schiff (PAS) staining revealed the presence of mucin in the cytoplasm of signet ring cells. Original magnification, ×400.
Two base substitutions were confirmed in the CDH1 gene: C.57 T>G and C.1418 A>T.

**REFERENCES**

1. Kim SH, Park BS, Kim HS, Kim JH. Synchronous quintuple primary gastrointestinal tract malignancies: a case report. *World J Gastroenterol* 2017; 23: 173-177 [PMID: 28104991 DOI: 10.3748/wjg.v23.i1.177]

2. Maruyama T, Nakaseo T, Maruyama N, Matayoshi A, Arasaki A. Synchronous quadruple primary cancers of the tongue, bilateral breasts, and kidney in a female patient with a disease-free survival time of more than 5 years: a case report. *World J Surg Oncol* 2015; 13: 263 [PMID: 26310238 DOI: 10.1186/s12957-015-0684-5]

3. Oh SJ, Bae DS, Sub BH. Synchronous triple primary cancers occurring in the stomach, kidney, and thyroid. *Ann Surg Treat Res* 2015; 88: 345-348 [PMID: 26029681 DOI: 10.4174/astr.2015.88.6.345]

4. Cybulski C, Nazarali S, Narod SA. Multiple primary cancers as a guide to heritability. *Int J Cancer* 2014; 135: 1767-1763 [PMID: 24945890 DOI: 10.1002/ijc.28988]

5. Chen HY, Yuan K, Xie N, Wang K, Huang Z, Chen Y, Dou Q, Wu M, Nice EC, Zhou ZG, Huang C. PDLIM1 Stabilizes the E-Cadherin/β-Catenin Complex to Prevent Epithelial-Mesenchymal Transition and Metastatic Potential of Colorectal Cancer Cells. *Cancer Res* 2016; 76: 1122-1134 [PMID: 26701804 DOI: 10.1158/0008-5472.CAN-15-1662]

6. Hansford S, Kaurath P, Li-Chang H, Woo M, Senz J, Pinheiro H, Schrader KA, Schaeffler DF, Shumansky K, Zogopoulos G, Santos TA, Claro I, Carvalho J, Nielsen C, Padilla S, Lumi A, Talhouni A, Baker-Lange K, Richardson S, Lewis I, Lindor NM, Pennell E, MacMillan A, Fernandez B, Keller G, Lynch H, Shah SP, Guillford P, Gallinger S, Corso G, Roviello F, Caldas C, Oliveira C, Pharoah PD, Huntsman DG. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. *JAMA Oncol* 2015; 1: 23-32 [PMID: 26182300 DOI: 10.1001/jamaoncol.2014.168]

7. Mir E, Mir Eiz, di Pietro M, O’Donovan M, Hardwick RH, Richardson S, Ziauddeen H, Fletcher PC, Caldas C, Tischkowitz M, Ragunath K, Fitzgerald RC. Comparative study of endoscopic surveillance in hereditary diffuse gastric cancer according to CDH1 mutation status. *Gastrointest Endosc* 2018; 87: 408-418 [PMID: 28689383 DOI: 10.1016/j.gie.2017.06.028]

8. Liu X, Chu KM. E-cadherin and gastric cancer: cause, consequence, and applications. *Biomed Res Int* 2014; 2014: 637308 [PMID: 25184143 DOI: 10.1155/2014/637308]

9. St Croix B, Sheehan C, Rak JW, Floresen VA, Slingerland JM, Kerbel RS. E-Cadherin-dependent growth suppression is mediated by the cyclin-dependent kinase inhibitor p27(KIP1). *J Cell Biol* 1998; 142: 557-571 [PMID: 9679152 DOI: 10.1083/jcb.142.2.557]

10. Petrova YI, Schecterson LM, Gumbiner BM. Roles for E-cadherin cell surface regulation in cancer. *Mol Biol Cell* 2016; 27: 3233-3244 [PMID: 27582386 DOI: 10.1091/mbc.E16-01-0053]

11. Kim NG, Koh E, Chen X, Gumbiner BM. E-cadherin mediates contact inhibition of proliferation through Hippo signaling-pathway components. *Proc Natl Acad Sci USA* 2011; 108: 11930-11935 [PMID: 21730131 DOI: 10.1073/pnas.1103345108]

12. Bers G, Cleaton-Jansen AM, Noller F, de Leeuw MF, van de Vijver MJ, Cornelisse C, van Roy F. E-Cadherin is a tumour/invasion suppressor gene mutated in human lobular breast cancers. *EMBO J* 1995; 14: 6107-6115 [PMID: 8557030 DOI: 10.1002/j.1460-2075.1995.tb0301.x]

13. Moertel CG, Dockerty MB, Baggenstoss AH. Multiple primary malignant neoplasms. I. Introduction and presentation of data. *Cancer* 1961; 14: 221-230 [PMID: 13771652 DOI: 10.1002/1097-0142(196103)14:1<221::AID-CNCR2820140104>3.0.CO;2-6]

14. Nysted J, Persson F, Parris TZ, Helou K, Persson F, Kaurah P, Li-Chang H, Woo M, Szenz J, Pinheiro H, Schrader KA, Schaeffler DF, Shumansky K, Zogopoulos G, Santos TA, Claro I, Carvalho J, Nielsen C, Padilla S, Lumi A, Talhouni A, Baker-Lange K, Richardson S, Lewis I, Lindor NM, Pennell E, MacMillan A, Fernandez B, Keller G, Lynch H, Shah SP, Guillford P, Gallinger S, Corso G, Roviello F, Caldas C, Oliveira C, Pharoah PD, Huntsman DG. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. *JAMA Oncol* 2015; 1: 23-32 [PMID: 26182300 DOI: 10.1001/jamaoncol.2014.168]

15. Oh SJ, Bae DS, Sub BH. Synchronous triple primary cancers occurring in the stomach, kidney, and thyroid. *Ann Surg Treat Res* 2015; 88: 345-348 [PMID: 26029681 DOI: 10.4174/astr.2015.88.6.345]

16. Liu X, Chu KM. E-cadherin and gastric cancer: cause, consequence, and applications. *Biomed Res Int* 2014; 2014: 637308 [PMID: 25184143 DOI: 10.1155/2014/637308]
Hu MN et al. Synchronous multiple primary gastrointestinal cancers

17 Benusiglio PR, Malka D, Rouleau E, De Pauw A, Buecher B, Noguès C, Fourme E, Colas C, Coudet F, Warcoin M, Grandjouan S, Sezeur A, Laurent-Puig P, Molière D, Tlemsani C, Di Maria M, Byrde V, Delaloge S, Blayau M, Caron O. CDH1 germline mutations and the hereditary diffuse gastric and lobular breast cancer syndrome: a multicentre study. J Med Genet 2013; 50: 486-489 [PMID: 23709761 DOI: 10.1136/jmedgenet-2012-101472]

18 Pharoah PD, Guilford P, Caldas C; International Gastric Cancer Linkage Consortium. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology 2001; 121: 1348-1353 [PMID: 1172914 DOI: 10.1053/gast.2001.29611]

19 Kim HC, Wheeler JM, Kim JC, Ilyas M, Beck NE, Kim BS, Park KC, Bodmer WF. The E-cadherin gene (CDH1) variants T340A and L599V in gastric and colorectal cancer patients in Korea. Gut 2000; 47: 262-267 [PMID: 10896919 DOI: 10.1136/gut.47.2.262]

20 Hamilton LE, Jones K, Church N, Medlicott S. Synchronous appendiceal and intramucosal gastric signet ring cell carcinomas in an individual with CDH1-associated hereditary diffuse gastric carcinoma: a case report of a novel association and review of the literature. BMC Gastroenterol 2013; 13: [PMID: 23849133 DOI: 10.1186/1471-230X-13-114]

21 Mohammed MK, Shao C, Wang J, Wei Q, Wang X, Collier Z, Tang S, Liu H, Zhang F, Huang J, Guo D, Lu M, Liu F, Liu J, Ma C, Shi LL, Atthiviraham A, He TC, Lee MJ. Wnt/β-catenin signaling plays an ever-expanding role in stem cell self-renewal, tumorigenesis and cancer chemoresistance. Genes Dis 2016; 3: 11-40 [PMID: 27077077 DOI: 10.1016/j.gendis.2015.12.004]

22 Wong SHM, Fang CM, Chuah LH, Leong CO, Ngai SC. E-cadherin: Its dysregulation in carcinogenesis and clinical implications. Crit Rev Oncol Hematol 2018; 121: 11-22 [PMID: 29279096 DOI: 10.1016/j.critrevonc.2017.11.010]

23 Jang M, Ko H, Lee JE, Lim JY, Cheong JH, Kim P. Increased extracellular matrix density disrupts E-cadherin/β-catenin complex in gastric cancer cells. Biomater Sci 2018; 6: 2704-2713 [PMID: 30151505 DOI: 10.1039/c8bm00843d]
