Letter to Editor

The First *CDH1* Gene Mutation Gastric Cancer Case in Kazakhstan: Implications for Genetic Screening; A Letter to the Editor

Dear Editor

Despite significant advances in medicine, food preservation methods, and *Helicobacter pylori* (*H. pylori*) treatment, gastric cancer remains the fifth most common type of cancer and the fourth leading cause of cancer-related deaths worldwide, accounting for over a million new cases and nearly 770,000 deaths in 2020.[1] The majority of gastric cancer cases are sporadic. Approximately, 1-3% are associated with inherited cancer predisposition syndromes, the most frequent of which is hereditary diffuse gastric cancer (HDGC), caused by mutations in the *CDH1* (E-cadherin) gene.[2]

HDGC is characterized by the early onset of diffuse gastric cancer in affected individuals. *CDH1* mutations occur in up to 40% of HDGC cases, significantly increasing the lifetime risk of developing gastric cancer. Furthermore, gastric cancer in younger patients frequently presents at an advanced stage and is associated with poor survival outcomes, even after intensive treatment.[3] Herein, we present the first reported case of *CDH1* mutation-associated gastric cancer in a young patient from Kazakhstan.

A 25-year-old Kazakh man presented with epigastric pain, nausea, vomiting, heartburn, reduced appetite, and 30 Kg weight loss over 3 months. Initial treatment for suspected gastric ulcers failed to alleviate his symptoms, prompting his admission to the Emergency Hospital (Aktobe, Kazakhstan) for laparoscopic repair of a perforated gastric ulcer on August 21, 2023. During the procedure, a cytological examination revealed undifferentiated gastric cancer, which was later confirmed by histological analysis as poorly differentiated adenocarcinoma with signet-ring cell differentiation (figure 1). Abdominal computed tomography (CT) showed the presence of ascites and gallbladder polyps (figure 2). Esophagogastroduodenoscopy (EGD) revealed a gastric ulcer, which was suspicious of malignancy. Based on these findings, the patient was diagnosed with stage III gastric cancer (T3NxM0).

Surgical management involved cytoreductive, extended, combined spleen-preserving gastrectomy with D2 lymphadenectomy. Histological analysis confirmed poorly differentiated adenocarcinoma infiltrating all layers of the gastric wall and surrounding tissues, with evidence of lymph node metastases and vascular invasion. No tumor tissue was detected at the resection margins, indicating complete surgical excision. Afterward, the case was discussed at a multidisciplinary conference, and adjuvant chemotherapy with six cycles of sunitinib was initiated. During chemotherapy, the patient experienced leukopenia, which was managed conservatively.

Given the patient's young age and the aggressive nature of the malignancy, genetic testing for *CDH1* mutations was recommended. After obtaining informed consent, a peripheral blood sample was collected and sent for analysis to Biogen Technopark Center (Astana, Kazakhstan). The genetic analysis was performed using the 3730xl DNA Analyzer (Applied Biosystems, USA). The findings revealed a heterozygous G/A nucleotide substitution at position 69560 in exon 3 of the *CDH1* gene (*rs1801023*).

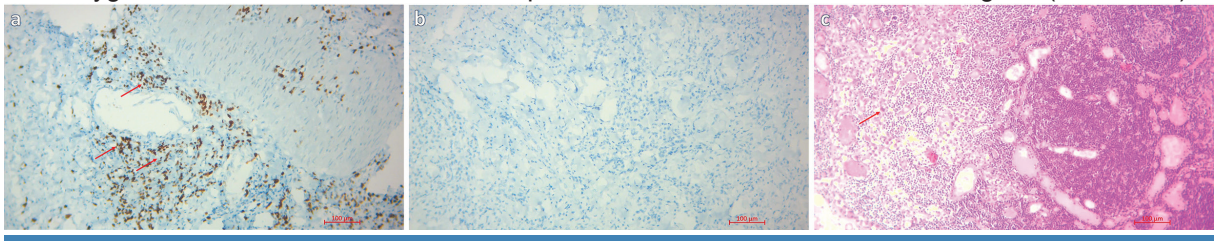

Figure 1: a) Stomach tissue shows Ki-67 positivity in 25% of cells. Red arrows highlight regions with Ki-67-positive cells, indicating areas of proliferative activity in moderately differentiated adenocarcinoma with signet-ring cell differentiation (magnification 100x). b) The stomach tissue shows HER2-negative expression; c) A histological section of the lymph node shows moderately differentiated adenocarcinoma with signet-ring cell differentiation. The arrow highlights signet-ring cell morphology.

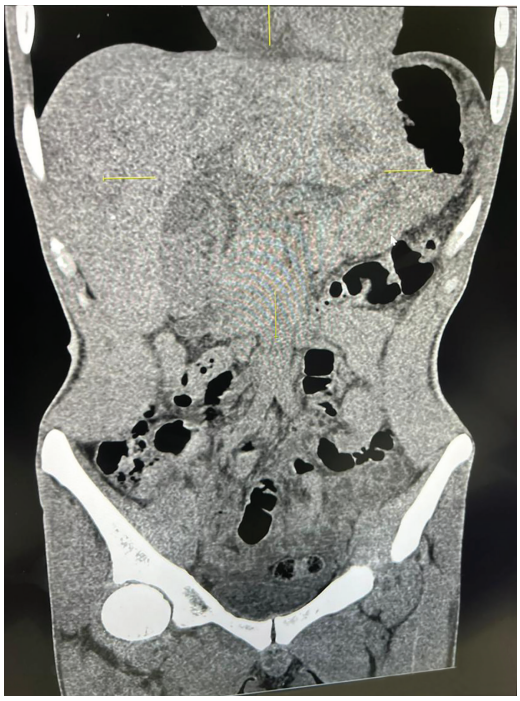

Figure 2: The CT scans reveal the presence of gastric cancer located on the lesser curvature.

To confirm familial inheritance, molecular genetic testing using Sanger sequencing was performed on close relatives, including his father, mother, and sister. The father was found to carry the same heterozygous mutation (G/A at position 69560), while the mother and sister tested negative for this mutation. Additionally, the father exhibited a T/C substitution in exon 13 of the *CDH1* gene (*rs1801552*). Based on the information provided by the patient, a pedigree was constructed (figure 3). Informed consent was obtained from the patient to publish his case details.

This case represents the first documented instance of a *CDH1* mutation associated with gastric cancer in Kazakhstan, highlighting the significance of genetic factors in the etiology of HDGC in this region. Mutations in the *CDH1* gene, responsible for the synthesis of the E-cadherin protein, are the most common genetic abnormality identified in HDGC which are associated with aggressive tumor biology and poor prognosis. Patients with germline *CDH1* mutations exhibited lower one-year and five-year survival rates than those without such mutations, underscoring the importance of early genetic testing and timely clinical intervention.[4]

Familial gastric cancer accounts for approximately 10% of all cases, with hereditary variants such as HDGC contributing to less than 3% of cases.[2] However, *CDH1* mutations have high penetrance and individuals with these mutations have a lifetime risk of acquiring gastric cancer of up to 80%.[5] The International Gastric Cancer Consortium has established screening criteria to identify individuals at risk, such as early-onset diffuse gastric cancer or a family history of gastric or lobular breast cancer.

To the best of our knowledge, this is the first reported case of a *CDH1* gene mutation associated with gastric cancer in Kazakhstan, underscoring an urgent need for increased awareness of hereditary cancer syndromes among healthcare practitioners. Early detection through genetic testing allows for timely intervention, potentially improving outcomes for at-risk families. This case highlighted the significance of establishing genetic screening programs in Kazakhstan to promote early diagnosis and targeted surveillance in families predisposed to gastric cancer. Further research on the genetic foundations of gastric cancer in Central Asia is required to better understand regional risks and improve preventive strategies.

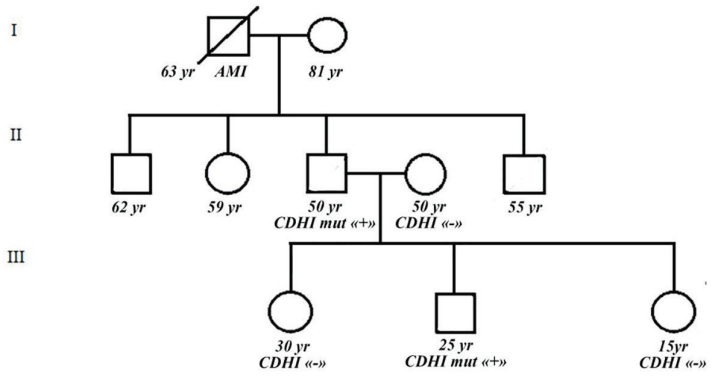

Figure 3: This pedigree chart illustrates the familial inheritance pattern, showing individuals across three generations along with their ages and *CDH1* gene mutation status.

Authors' Contribution

M.A: Conceptualization, data interpretation, and drafting; A.T: Conceptualization, data collection, supervision, drafting, reviewing, and editing; A.K: Data collection, supervision, drafting, reviewing, and editing;

E.Zh: Data interpretation, drafting, reviewing, and editing; S.B: Data interpretation, drafting, reviewing, and editing; N.K: Data collection, drafting, reviewing, and editing; D.Zh: Data collection, drafting, reviewing, and editing; N.A: Conceptualization, data interpretation, and drafting. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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Keywords ● E-cadherin ● Gastric carcinoma ● Heredity ● Genetic predisposition

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