Review Article: Pathology



# Hereditary gastric and breast cancer syndromes with lung metastasis: narrative review of molecular and clinical insights

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**Background and Objective:** CDH1 germline variants have been linked to hereditability in diffuse gastric (DGC) and lobular breast cancer (LBC). Although the incidence rate of these cases is relatively low, it is expected that there will be a concomitant increase in the diagnosis of germline pathogenic variants due to more frequent genetic testing. Hence, precise and selectively targeted clinical management is needed. Hereditary DGC and breast cancer syndromes are emerging entities linked to *CDH1* gene germline mutations where molecular and cellular pathways are yet to be studied and described. In our review, we aimed to narrate the current state of the problem to enhance the understanding and emphasize the urging need for future investigations for identification, stratification, and management of the patients with subsequent prognosis improvement.

**Methods:** We conducted an ample literature review from ultimate reliable online library sources to provide a summary on the contemporary syndrome understanding, where the key role in tumorigenesis belongs to *CDH1* mutations and main metastatic pathways are triggered by the epithelial-to-mesenchymal transition.

**Key Content and Findings:** E-cadherin is nowadays regarded as a tumor suppressor and its loss is related to tumor progression and metastasis formation. Other genes mutations may be involved in cell proliferation and motility enhancement. Here, we observed that one of the most common tumor patterns was signet-ring cell carcinoma, and one of common, yet insufficiently described in the literature, metastatic sites were lung. Screening guidelines and preventive surgery is proposed as an actual management trend.

**Conclusions:** Further investigations in molecular mechanisms involved should be conducted to create precise and fulfilling molecular and genetic testing panels to identify and stratify the affected patients.

**Keywords:** Hereditary gastric cancer; hereditary breast cancer; CDH-1; E-cadherin; lung metastasis

Received: 06 February 2022; Accepted: 09 May 2022; Published online: 13 May 2022.
doi: 10.21037/asj-22-9
**View this article at:** https://dx.doi.org/10.21037/asj-22-9

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## Introduction

Hereditary diffuse gastric cancer (HDGC) is a rare cancer syndrome characterized by a high prevalence of diffuse gastric cancer (DGC) and invasive lobular breast cancer (LBC) (1,2).

This syndrome has been mainly related to germline variants in the *CDH1* gene, located on the 16q22.1 chromosome (3). *CDH1* germline mutation is known as a crucial target for cancer initiation, yet, by itself, not sufficient for invasive gastric cancer (GC) development (4). This gene encodes a cell-to-cell adhesion molecule, E-cadherin, where its loss is linked to increased infiltrative and metastatic potential (1). The loss of E-cadherin expression is associated with familial cancer syndrome, HDGC, DGC signet-ring cell type, LBC, and other breast cancers progression (5-11). The major feature of recurrence in GC is intra-abdominal spread with the most common site of metastasis of the liver (in 48% of metastatic cancer patients) (12). Among the metastatic sites, a relatively rare incidence of pulmonary metastasis could be present in GC patients (13,14). One of the major LBC metastatic sites indeed is the lung and overlap of these two entities in HGDC prompted us to analyze possible correlations between DGC and LBC (15). We present this article in accordance with the Narrative Review reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-22-9/rc).

## Methods

We conducted literature research on the topic, including English articles published in the years 1996–2022, where all authors contributed equally reaching a final consensus before the article submission. The search strategy is described in *Table 1*.

## Discussion

### *Role of CDH1 in hereditary cancers and relationship with histological features*

*CDH1* encodes for E-cadherin, an epithelial marker, considered as a tumor suppressor which interacts with β-catenin as an effector of the WNT signaling pathway. Loss of *CDH1* is linked to increased infiltrative and metastatic potential (15). The translocation of β-catenin also represses the expression of phosphatase and tensin homolog (PTEN) , which is a tumor suppressor. *CDH1* loss has also been associated with epidermal growth factor receptor (EGFR) activation through pro-tumorigenic RAS/RAF/MEK, FAK/c-Src and PI3K/AKT/mTOR pathways, which enhance cell proliferation and motility (5-10). It is known that loss of E-cadherin (CDH1), Smad4, and p53 has an important role in breast and GCs formation (16). CDH1 hypermethylation is present in LBC and other breast cancer types, associated with reduced estrogen receptor (ER) and progesterone receptor (PR) expression, accompanied by lung, bone, brain and lymph node metastasis (15,17,18). Frequently, LBC and DGC patients carrying *CDH1* germline mutations present similar histological appearance with highly dispersive infiltrative cancer cells and signet-ring cell components, often followed by loss of E-cadherin on immunohistochemical staining (19). In CDH1 mutation carriers, two patterns of signet ring cells distribution have been described: *in situ* (confined to the basal membrane) and pagetoid spread below the preserved epithelium (5,6,19,20).

## CDH1 and hereditary cancers metastasis

The loss of CDH1 is known to promote cancer metastasis by disrupting cell-cell adhesion and transcriptional changes induction (21). The role of E-cadherin in metastasis has been sought through a prism of epithelial to mesenchymal transition (EMT), which is regarded as an important event in various cancer metastases (7). The process of EMT, occurring both in physiological and pathological conditions may downregulate E-cadherin, promoting epithelial cells inhibition with fibroblast phenotype acquisition. These cells start being invasive, expressing Snail family transcription factors and suppressing E-cadherin (22). Molecularly, the loss of E-cadherin may happen due to germline mutations with transcription inhibitors overexpression—Snail, Slug, Twist, ZEB1, ZEB2 that are known to be related to tumor differentiation and metastasis, induced by TGF-β causing E-cadherin suppression (*Figure 1*) (7,23-25).

It is known that one of the common HGDC-syndrome metastatic sites is the lung (12). Several lines of evidence have described the metastatic pattern of intestinal and diffuse-type GC so far (26). On the whole, intestinal-type carcinomas more often metastasize to the liver and lungs and have a better prognosis compared to diffuse GC that metastasizes more frequently to the peritoneum and bones (26). A Dutch national cohort including 8,231 metastatic GC cases reported a 13% rate of lung metastases for intestinal and 7% for diffuse GC (P<0.0001) (26). Another Northern European series included 7,559 patients, with

**Table 1** Narrative review methods description—hereditary gastric and breast cancer syndromes with lung metastasis: molecular insights and clinical management search strategy

| Items | Specification |
|---|---|
| Date of search | 24–28/01/2022 |
| Databases and other sources searched | PubMed, Wiley, Springer, *AME Surgical Journal* |
| Search terms used | Hereditary gastric cancer (HGC), hereditary diffuse gastric cancer (HGDC), hereditary breast cancer (HBC), CDH-1, E-cadherin, lung metastasis |
| Timeframe | 1996–2022 |
| Inclusion and exclusion criteria | Language restrictions: English only |
| Selection process | Selection process was conducted independently and consensus obtained by all authors before submission |

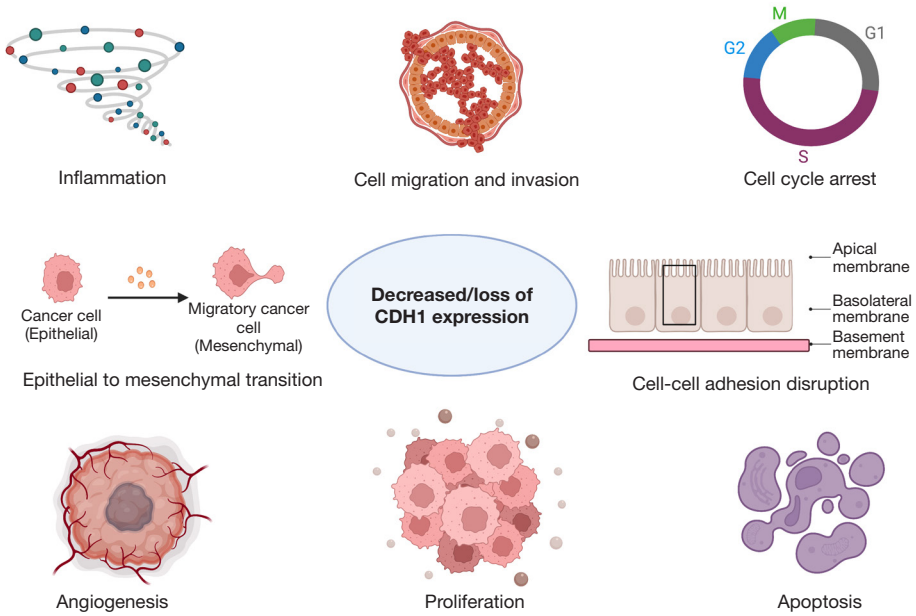


**Figure 1** Schematic overview of the events promoted by the decrease or loss of CDH1 expression.

5% of adenocarcinomas and 2% of signet ring carcinomas harboring lung metastases (12). A similar trend has been described in the Eastern series. Indeed, a Chinese cohort of 7,792 patients reported a 6.5% frequency of lung metastases for adenocarcinomas and 4.4% for signet ring cell cancers (14). Similarly, a large Korean cohort of 20,187 patients recorded a prevalence of lung metastases of 0.196% (193 patients). Most of these patients had a diagnosis of adenocarcinoma (71.4%), while only 16.6% of patients had a signet ring cell histology and 11.9% other rare histologies (13). Moreover, further confirmation of this data comes from a retrospective evaluation of the Surveillance, Epidemiology and End Result (SEER) database of the National Cancer Institute. A total of 1,104 patients with GC and lung metastases were identified, representing 6.02% of the cohort of patients with a new diagnosis of GC from 2010 to 2014. Of them, 21% had diffuse-type histology, while 72.6% had intestinal-type GC and the remaining portion had different and rare histologies (27).

Signet-ring cell GC metastasis to the lung has already been previously described in the literature (12,28). Biological differences between two GC histotypes may

justify the different patterns of metastasis in GC. Firstly, loss of E-cadherin expression that is typical of diffuse GC was associated with increased recurrence to the peritoneum (P<0.01) and distant lymph nodes (P<0.01), though GC with liver metastases had relatively positive E-cadherin expression (29). Another biological evidence supporting the different patterns of metastasis is given by the different expressions of adhesion molecules. Adhesion of neoplastic cells to the mesothelium is favored by the presence of molecules such as CD44, whose expression is higher in poorly differentiated tumors such as signet ring cell carcinoma (30). Moreover, signet ring cell carcinomas produce mucin, which may infiltrate the surrounding stroma and help the tumor become invasive, thus facilitating spread to the serosa and peritoneum (12). Additionally, the proliferative activity in diffuse GC is increased in the deeper layers, resulting in a greater propensity for peritoneal seeding and metastasis to female reproductive organs (31,32).

Experimental models of CHD1 loss/alterations in DGS showed a diffuse morphology with signet-ring cells and lung metastasis with peritoneal carcinomatosis and it has confirmed that signet-ring cell morphology is overall more frequently observed in CDH1 mutations (33,34).

In breast cancer, lung metastases were specifically attributed to the triple-negative breast cancers (TNBC) phenotype, by activation of breast cancer stem cells via β-catenin/WNT signaling (35,36). One study demonstrated lung metastasis developing after 12 weeks of primary breast cancer, where both primary and metastatic tumor cells expressed E-cadherin and lacked Vimentin which indeed indicates no EMT occurrence (37). These data were supported by EMT markers panel assessment in 148 LBC cases, where only 2% demonstrated downregulation of E-cadherin and upregulation of mesenchymal markers (38). Additional findings suggest that E-cadherin is suppressing metastasis in invasive LBC (39). Signet-ring cell carcinoma was also the most common histologic pattern in TNBC and pathogenic variants of CDH1, detected in patients with DGC and resulted in extensive or metastatic disease in 24% of patients and its mutations are overall associated with distant metastases (34,40,41).

Given that loss of E-cadherin expression in carcinoma development is regarded as a sign of EMT and tumor progression, numerous studies aimed to investigate its pathways. Experimental loss of E-cadherin and Smad4 in cooperation display promotion of DGC development and metastatic progression. Knock-out of one CDH1 allele with both p53 and Smad4 alleles lead to lung metastasis of gastric carcinomas formation, suggesting that loss of E-cadherin and Smad4 expression promote lung metastasis through β-catenin activation (16), while activation of oncogenic KRAS accelerates this process. The transduction of normal gastric epithelial cells with KRAS had significantly decreased the expression of E-cadherin and increased the expression of Vimentin, which is another proof of EMT role in tumorigenesis and metastasis. Interestingly, KRAS inhibition in gastric adenocarcinomas led to the loss of infiltrative tumor border and fewer lung metastases (42). In addition to this data, there is also a report about the role of intermediate filaments KRT17, where their downregulation induces E-cadherin loss and EMT, leading to metastasis of DGC and worse prognosis (43).

The main issue nowadays is that the timeframe of HDGC and DGC progression to metastatic disease is yet to be studied, as most patients with DGC have advanced disease at the time of presentation and this emphasizes the importance of early identification of these patients to develop effective surveillance techniques (41).

## CDH1 screening and management strategies

The patients with a family history of HDGC may use genetic testing for CDH1 mutations for individual risk assessment and consideration of prophylactic gastrectomy, while some studies confirm that all individuals with identified CDH1 mutation had a personal or family history of HDGC and shorter survival compared to those without abovementioned mutation (1-3,5,6,9,44,45). Increased availability and adoption of cancer gene panels have led to increased identification of variants of CDH1 gene mutations in patients with a family history of breast cancer (1). The patients with breast cancer history and confirmed CDH1 mutation found via genetic testing are at a higher risk of LBC and are at higher risk of DGC. However, there are numerous reports in patients with CDH1 mutations affecting exclusively LBC without any evidence of gastric tumors (46,47). Indeed the latest data demonstrate that carriers of CDH1 pathogenic or likely pathogenic variants and LBC have high rates of occult signet ring cell GC incidence (48).

The International Gastric Cancer Linkage Consortium (IGCLC) developed criteria to facilitate the screening of CDH1 mutation carriers, which have been proven to have excellent sensitivity and specificity (9). According to ultimate guidelines, the breast surveillance for HDCG starts

at age of 30 with an annual magnetic resonance imaging (MRI) as a reporter of elevated risk of LBC incidence. If LBC is detected, CDH1 mutation carriers usually undergo breast-conserving surgery with reconstruction. Patients with DGC with ascertained CDH1 mutation are recommended to undertake total gastrectomy, where the latter could be also considered as a prophylactic procedure in the presence of known HGDC family history and confirmed CDH1 mutation (1,6,44,49). The oncogene role of CDH1 overexpression has been also demonstrated in lung adenocarcinoma, which can be a common site of metastasis in HGDC (50).

## Conclusions

In conclusion, hereditary diffuse GC is a rare entity and, as opposed to LBC, lung metastases from this histologic subtype are very infrequent compared to intestinal GC. Many biological differences between signet ring and intestinal cancer cells explain the distinct pattern of metastasis for these two GC histological subtypes. Identification of a higher number of patients, affected by HGDC may somewhat shift our perception of this complex entity and provide a better understanding of the disease's nature. There are still numerous questions to be answered in molecular and cellular events in CDH1 mutations carriers disease progression. A multidisciplinary approach in CDH1 mutations assessment is needed to accurately estimate its roles in HDGC and LBC familial syndromes, examining the risk for other cancers and conducting effective prevention and screening strategies with the probable establishment of susceptible genes testing panel (1,2,5,10,24,45,51).

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the Guest Editors (Davide Tosi, Alessandro Palleschi and Paolo Mendogni) for the series "Management and Treatment of Lung Metastases" published in *AME Surgical Journal*. The article has undergone external peer review.

*Reporting Checklist:* The authors have completed the Narrative Review reporting checklist. Available at https://asj.amegroups.com/article/view/10.21037/asj-22-9/rc

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://asj.amegroups.com/article/view/10.21037/asj-22-9/coif). The series "Management and Treatment of Lung Metastases" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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doi: 10.21037/asj-22-9
**Cite this article as:** Ivanova M, Evangelista J, Venetis K, Sajjadi E, Lococo F, Corso G, Ghidini M, Fusco N. Hereditary gastric and breast cancer syndromes with lung metastasis: narrative review of molecular and clinical insights. AME Surg J 2023;3:39.

 