Emerging Concepts in Gastric Neoplasia

Heritable Gastric Cancers and Polyposis Disorders

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KEYWORDS

• Hereditary gastric cancer • Signet ring cell • Stomach • E-cadherin • CDH1 • CTNNA1 • GAPPS • Gastric polyposis

Key points

- Hereditary diffuse gastric cancer results from germline mutations in *CDH1* (40% of families) and *CTNNA1* (few families reported).
- Small intramucosal foci of signet ring cell carcinoma, in situ signet ring cell carcinoma, and pagetoid lesions can be observed in *CDH1* mutation carriers.
- Gastric adenocarcinoma and proximal polyposis displays fundic gland polyposis, dysplasia, and intestinal-type or mixed-type adenocarcinoma.
- Fundic gland polyposis occurs in familial adenomatous polyposis (FAP), attenuated FAP, and MUTYH-associated polyposis syndromes.
- Gastric polyps in juvenile, Peutz-Jeghers, and Cowden polyposis cannot be reliably distinguished from each other or sporadic hyperplastic polyps.

ABSTRACT

Hereditary gastric cancer is a relatively rare disease with specific clinical and histopathologic characteristics. Hereditary gastric cancer of the diffuse type is predominantly caused by germline mutations in *CDH1*. The inherited cause of familial intestinal gastric cancer is unknown. Gastric adenocarcinoma and proximal polyposis of the stomach is a hereditary cancer syndrome caused by germline mutations in promoter 1B of *APC*. Other well-defined cancer syndromes, such as Lynch, Li-Fraumeni, and hereditary breast or ovarian cancer syndromes, are associated with increased risk of gastric cancer. This article reviews important histopathologic features and emerging concepts regarding gastric carcinogenesis in these syndromes.

OVERVIEW

Most (>80%) gastric carcinomas are sporadic; familial aggregation occurs in 10% to 20% of patients and fewer than 3% of cases can be attributed to known inherited causes.[1] Gastric

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carcinomas diagnosed at advanced stage have a poor prognosis; every effort should be made to prevent or detect it at early stages when potentially curable.

Familial gastric carcinoma can be classified as hereditary diffuse gastric cancer, familial intestinal gastric cancer, and familial gastric cancer when the histologic subtype is unknown.[2] Advanced gastric cancers are often classified as "poorly differentiated adenocarcinoma" at the time of biopsy, although an attempt should be made to categorized them according to the World Health Organization or Laurén schemes. The latter classifies tumors as intestinal and diffuse types; tumors that cannot be placed in one of these categories are considered indeterminate and mixed type.[3]

The purpose of this review was to describe the histologic and clinical characteristics of several gastric cancer syndromes, including other primary malignancies and types of gastrointestinal polyps. This article focuses on important histopathologic features and emerging concepts in (1) hereditary diffuse gastric cancer, (2) familial intestinal gastric cancer, (3) gastric adenocarcinoma and proximal polyposis of the stomach and similar polyposis syndromes, as well as (4) other hereditary cancer syndromes, as enumerated in **Tables 1** and **2**.

HEREDITARY DIFFUSE GASTRIC CANCER

CDH1 GERMLINE MUTATION

Identification of *CDH1* germline mutations in the Maori population defined a newly recognized autosomal dominant cancer-susceptibility syndrome termed "hereditary diffuse gastric cancer."[4] Following this discovery, many families around the world with clustering of gastric cancer have been tested to identify novel *CDH1* germline mutations. *CDH1* encodes E-cadherin, a transmembrane calcium-dependent protein with important roles in cell-cell adhesion at the *adherens* junctions.[5,6]

Germline *CDH1* alterations can affect the entire coding sequence and include small frameshifts, splice-site, nonsense, and missense mutations, as well as large rearrangements.[7] Most truncating mutations are pathogenic and several missense mutations have a deleterious effect on E-cadherin function.[8] Individuals with germline *CDH1* mutations have a single functional *CDH1* allele. Inactivation of the wild-type allele by a somatic second-hit molecular mechanism (ie, promoter hypermethylation, loss of heterozygosity) leads to biallelic inactivation and development of diffuse gastric cancer.[9–12] Biallelic *CDH1* inactivation leads to loss of E-cadherin function and abnormal immunohistochemical staining for E-cadherin compared with complete membranous staining in normal epithelium.[11–14] Aberrant E-cadherin staining patterns include absence of immunoreactivity, weak membranous staining, "dotlike" staining, and cytoplasmic staining.[15]

Individuals with a pathogenic germline *CDH1* mutation are at 60% to 70% increased risk for diffuse gastric cancer and women are at risk for lobular breast cancer (40%).[1,16] There is no evidence that individuals with *CDH1* mutations are at significantly increased risk for other cancer types. Testing for germline *CDH1* mutations is recommended in families that fulfill 1 of the following 3 criteria[1]:

1. Two or more documented cases of gastric cancer at any age in first-degree or second-degree relatives, with at least 1 confirmed diffuse gastric cancer.
2. Personal history of diffuse gastric cancer before the age of 40 years.
3. Personal or family history (first-degree or second-degree relatives) of diffuse gastric cancer and lobular breast cancer, 1 diagnosed before the age of 50 years.

Genetic testing also can be considered in patients with bilateral lobular breast cancer before the age of 50 years, families with multiple cases of lobular breast cancer, families with clustering of diffuse gastric cancer and cleft lip/cleft palate, and any patient diagnosed with in situ or pagetoid spread of signet ring cells in the gastric mucosa.[1]

Prophylactic total gastrectomy is advised for individuals with a proven pathogenic germline *CDH1* mutation.[1] These resection specimens generally show no specific gross abnormalities, but multiple invasive intramucosal cancers (pT1a) are almost always detected when the entire stomach is processed for histology (**Fig. 1**A).[13,17,18] In most cases, these tiny (<0.1–10 mm) foci are restricted to the superficial mucosa. They are composed of relatively small signet ring cells at the neck-zone level that enlarge toward the mucosal surface.[14] Foci are found throughout the stomach and even in gastric metaplasia beyond the pylorus.[1]

Two typical precursor lesions of intraepithelial signet ring cell carcinoma include signet ring cell carcinoma in situ (Tis) and pagetoid spread of signet ring cell carcinoma. The former is defined as a disorganized proliferation of signet ring cells that replaces normal glandular epithelial cells, but is confined by the basement membrane. Pagetoid spread of signet ring cells appears as a linear proliferation of signet ring cells between normal epithelial cells and the