By the Pricking of My Thumbs, Something Wicked This Way Comes*: Sporadic Cancers Versus Eponymous Hereditary Cancer Predisposition Syndromes

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Key Words

Eponymous single-gene cancer predisposition syndromes, hereditary diffuse gastric cancer, genetic testing, genetic counseling, hereditary gastric cancer syndromes, hereditary breast cancer syndromes, hereditary colorectal cancer syndromes

Abstract

Advances in cancer genomics have led to the recognition of a growing number of high-penetrance single-gene cancer predisposition syndromes. Frequently, the suspicion for a hereditary syndrome is raised by a strongly positive family history. However, other features, such as younger-than-usual age at diagnosis and rare histology should also prompt consideration of a genetic syndrome. Common malignancies frequently show a positive family history without an eponymous syndrome being recognized. This article reports on a case with an unusual constellation of malignancies with distinctive pathologies, which raised suspicion for an eponymous cancer predisposition syndrome. Absent a positive family history, a de novo mutation—an alteration in a gene that is present for the first time in a family member as a result of a mutation in a germ cell of one of the parents or in the fertilized ovum—was suspected. The authors discuss indications for genetic counseling and testing, limitations, and the evidence that supports the recommendations as formulated by working groups and the NCCN. Most frequently, these recommendations are reasonable statements based on the natural history of the disease, but without population-based studies for many rare syndromes, the actual penetrance, variable expressivity, and actual associated cancer risk are unknown. (*JNCCN* 2012;10:7–13)

Macbeth, William Shakespeare, Act IV, scene 1.

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As genetic testing becomes increasingly available in contemporary oncology and as more germline mutations associated with a high risk of cancer are discovered, the clinician's responsibility increases to recognize the small but growing minority of patients with hereditary cancer predisposition syndromes. Experts estimate that these patients constitute approximately 5% to 10% of all patients with cancer.[1] Most frequently, suspicion of a hereditary syndrome is raised by a family history of multiple family members affected by the same or similar diagnoses across consecutive generations. This report presents the case of a patient without significant family history but with an unusual constellation of malignancies and pathologies, which prompted further investigation for an eponymous syndrome—a high-penetrance cancer predisposition syndrome associated with a well-defined genetic alteration. We discuss the diagnostic process, the indications for genetic consultation, and the limitations of evidence-based recommendations.

Case Report

A 51-year-old woman of Hispanic descent was in her usual state of health when she underwent a screening colonoscopy. The colonoscopy showed at least 4 sessile polyps in the descending colon and rectum. One polyp

excised from the descending colon was tubular adenoma, and the other 3 were poorly differentiated adenocarcinomas with signet-ring cell features. Although imaging studies were not consistent with distant metastases, a sharply circumscribed lytic lesion in the left iliac wing was noted. In the context of investigating the incidental findings, the patient underwent upper endoscopy, which revealed multiple nodules, primarily involving the proximal third of the stomach. The distal stomach and antrum were spared. Biopsy results of these nodules were consistent with poorly differentiated adenocarcinoma with signet-ring cell features, similar to the pathology of the colonic lesions (Figure 1).

The patient underwent further staging using PET. No lymphatic or hepatic metastases were identified, but the osteolytic lesion in the left iliac wing was hypermetabolic, and new right axillary lymphadenopathy was seen. In the context of investigating for a breast primary malignancy, an area of architectural distortion and suspicious enhancement was found on MRI of the right breast. On pathology, this lesion was consistent with infiltrating mammary carcinoma with predominantly lobular features and lobular carcinoma in situ (Figure 2). The specimen was positive for estrogen and progesterone receptors on immunohistochemistry; *Her2* was nonamplified. In addition to the different histologic appearances of the gastric and breast biopsies, the absence of staining for mammaglobin, and estrogen and progesterone receptors on the gastric specimen confirmed them to be distinct primary cancers.

Clinically, aside from skeletal pain that developed later, a striking contradiction was noted between the extent of disease and the patient's minimal symptom burden. Physical examination was negative for abnormal findings. A thorough family history was unrevealing. She had one brother, who was diagnosed with colonic polyps on routine screening colonoscopy and was fine. Her grandparents on both sides lived to 98 to 100 years. After her father was diagnosed with a benign colonic tumor in his 60s, the patient underwent a screening colonoscopy in her 30s; the results were normal.

Considering that surgery for her primary breast tumor would not be curative in the context of skeletal metastases and the high morbidity and mortality of a combined gastrectomy and colectomy, the patient was placed on anastrozole and zoledronic acid while considering chemotherapy when her gastrointestinal malignancies become symptomatic or metastatic. Early-stage signet-ring cell gastric carcinoma usually has a favorable prognosis (5-year survival rate of 94.3%),[2] but the inability to perform gastrectomy, advanced-stage disease, and coexistent malignancies in this case altered her prognosis significantly. Her disease remains stable on PET, with at least mild improvement of the primary breast lesion 9 months after the original diagnosis. The patient was offered genetic counseling and testing.

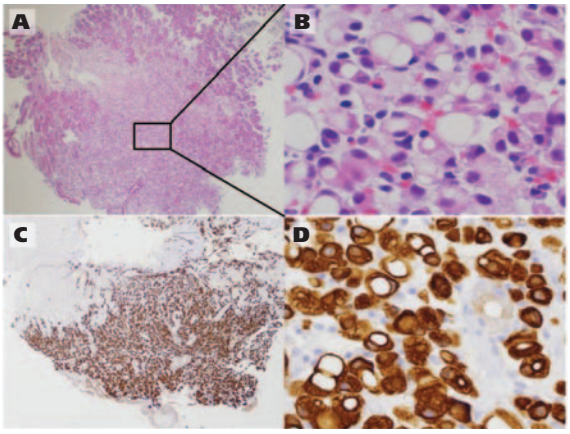

Figure 1 Gastric biopsies. (A) Low-power magnification (hematoxylin-eosin, original magnification ×4) of the gastric biopsy specimen. The histologic findings are consistent with poorly differentiated adenocarcinoma with signet-ring cell features. (B) High-power magnification (hematoxylin-eosin, original magnification ×40) of the gastric biopsy specimen. (C) Immunohistochemistry for cytokeratin 7 (×4); the neoplastic cells were strongly positive for cytokeratin 7. (D) Immunohistochemistry for cytokeratin 7; higher magnification (×40) shows the sheets of discohesive cells with abundant vacuolated cytoplasm and eccentrically placed nuclei.

Discussion

Sporadic Cancer Versus Hereditary Syndromes

Several features in this case support the consideration of genetic counseling despite the negative family history: multiple and multifocal primary tumors in the same organ, concurrent primary tumors in different organs, rare histology,[3] and phenotype that "fits" an eponymous genetic syndrome. Other features that should raise the suspicion of a hereditary syndrome include a younger-than-usual age at diagnosis, bilateral occurrence in paired organs, and the presence of rare diseases, congenital defects, traits, or precursor lesions known to be associated with hereditary syndromes.[3]

Despite the increasing recognition of hereditary syndromes, most cancers are sporadic. Frequently, a positive family history is seen, but no hereditary syndrome is recognized. In lieu of available genetic testing and in view of available risk-modifying interventions, cancer risk estimates may rely on prediction models, such as those developed for breast cancer,[4] and risk stratification, such as that used in colorectal cancer risk assessment.[5]

Absent a single-gene high-penetrance syndrome (as is the case for most patients), the magnitude of effect of a positive family history on cancer risk is more accurately assessed by population-based registry studies.[6–8] Studies based on the Utah Population Database and Swedish Family-Cancer Database have been useful in providing a global view of the familial relative risk of cancer[8] and have shown that, for common cancers, a substantial proportion of risk is attributable to familial factors.[9,10] Data analyzed by cancer site yielded familial relative risks greater than 1 for all sites,[6–8] indicating that family history of cancer in first-degree relatives is uniformly a risk factor for cancer.

Indications for Genetic Testing

Incorporating advances in cancer genomics, NCCN issued Clinical Practice Guidelines in Oncology (NCCN Guidelines) on diagnosis, treatment, and preventive interventions for eponymous cancer susceptibility syndromes.[5,11,12] The NCCN Guidelines serve as an open resource for clinicians who are still responsible for recognizing these syndromes and referring patients appropriately for genetic counseling. Given the rarity of these syndromes and the inherent difficulty in conducting prospective clinical studies, the evidence supporting these guidelines is primarily reasonable consensus statements based on the natural history of the syndromes. Nonetheless, the need for high-level evidence cannot be underestimated.

Recommendations for preventive interventions in these syndromes build on cancer risk estimates that, without population-based data on penetrance and variable expressivity, often include ascertainment bias. This sampling bias emanates from initial clinical studies that are conducted in rare familial clusters with high expression of the disease, leading to overestimation of penetrance and underestimation of the variable expressivity of the syndrome. This is illustrated in the case of

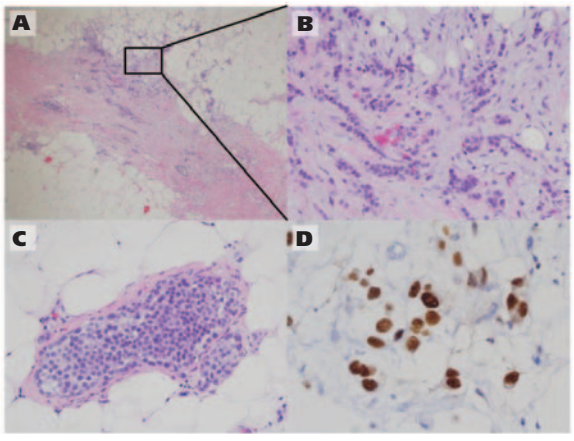

Figure 2 Breast biopsies. (A) Low-power magnification (hematoxylin-eosin, original magnification ×4) of the breast biopsy specimen consistent with infiltrating mammary carcinoma with predominately lobular features. (B) High-power magnification (hematoxylin-eosin, original magnification ×40) of the breast biopsy at the site of invasive growth. (C) Lobular carcinoma in situ (hematoxylin-eosin, original magnification ×40). (D) Immunohistochemistry for estrogen receptors (×40). Cancer cells stained strongly positive for estrogen (shown) and progesterone receptors. *Her2* was not amplified.

BRCA1 mutations. Although the lifetime cumulative risk of breast cancer was initially estimated at 87%,[13] a probably more accurate assessment (65%) is provided by a pooled analysis of 22 studies involving patients unselected for family history.[14] Single nucleotide polymorphisms[15] and nongenetic factors such as parity[16] can modify cancer risk and may account for this discrepancy in estimates. Nonetheless, familial breast-ovarian cancer constitutes one of the few cancer predisposition syndromes in which an invasive risk-reducing intervention is supported by prospective studies.[17]

Because the performance characteristics of genetic testing can be poor if the pretest probability for a specific mutation is low, the NCCN Guidelines incorporate diagnostic criteria from many syndrome-specific working groups that must be fulfilled before referring for genetic consultation. Previous investigation of likely diagnoses is necessary to guide consultation and eliminate unnecessary testing and cost.

Hereditary Syndromes Associated With Breast, Gastric, and Colorectal Malignancies

A list of hereditary syndromes associated with breast, gastric, and colorectal cancer is provided in Table 1. For many syndromes, clinical phenotypes have not been subjected to rigorous statistical analysis.[3] The spectrum of malignancies can be broad in some instances, as in Bloom syndrome, in which every cell capable of division is susceptible to malignant transformation.[3]

Many genetic syndromes outlined in Table 1 can be eliminated based on the absence of distinctive defects, traits, or lesions. In ataxia-telangiectasia, non-Hodgkin's lymphomas and leukemias are the most frequent malignancies; however, an excess risk for breast, gastric, and colorectal cancer in heterozygous mutation carriers in the absence of other features of the syndrome has also been reported.[18] The patient had none of the nonmalignant manifestations of the syndrome, and the distinctive histologic features of her malignancies made this diagnosis less likely. Cowden syndrome is associated with breast cancer, but the association with gastrointestinal malignancies is unclear, and the patient did not have pathognomonic mucocutaneous lesions. The absence of mucocutaneous pigmentations and lesions such as neurofibromas and café-au-lait macules eliminated Peutz-Jeghers syndrome and neurofibromatosis type I, respectively.

Colorectal cancer arising from adenomatous and hamartomatous polyps constitutes the principal malignancy of familial adenomatous polyposis and juvenile familial polyposis, respectively. Colon cancer is also the hallmark of Lynch syndrome (hereditary nonpolyposis colorectal cancer) and MYH-associated polyposis. In Lynch syndrome, colon cancer typically involves the right colon and is usually diagnosed in the patient's mid-40s. In MYH-associated polyposis, biallelic mutations in *MYH* (a base excision repair gene) lead to somatic mutations in *APC* and, thus, a usually attenuated familial adenomatous polyposis phenotype. Although these syndromes have been associated with gastric cancer, breast cancer is not a typical feature.

Increased risk for gastric and colon cancers has been reported in familial breast-ovarian cancer 1,[19] but breast (typically triple-negative) and ovarian cancer are its defining features.[3] Breast cancer is also seen in Li-Fraumeni syndrome; however, usually the onset is earlier, and malignancies such as sarcoma, adrenocortical carcinoma, and brain tumors are more typical. Other syndromes that may be considered include heterozygosity for *NBS1* mutations[20] and familial breast-ovarian cancer 2. However, this particular constellation of malignancies and their distinctive pathologic features are highly consistent with the phenotype of hereditary diffuse gastric cancer syndrome (HDGC).

HDGC

Significant advancement in understanding the genetic pathophysiology of gastric cancer has been made with the discovery of inactivating germline mutations of the E-cadherin gene *CDH1* in families with multiple cases of early-onset diffuse gastric cancer.[21] Mutations of *CDH1* have been identified in patients of diverse ethnic backgrounds, and an association with breast (primarily lobular) and possibly colorectal (characteristically signet-ring cell) cancers has been recognized.[22] *CDH1* mutations are inherited in an autosomal-dominant pattern, with incomplete but high penetrance.[22] The causative mutations are typically truncating, whereas the pathogenicity of missense mutations requires in vitro or in silico confirmation.[23,24] Genetic testing of the proband requires sequencing of the entire gene, because the pathogenic mutations are distributed throughout the gene and few recurring mutations have been identified.[23,25]

Although the patient did not meet the clinical criteria for HDGC of the International Gastric Cancer Linkage Consortium,[23] the description of de novo

Table 1 Hereditary Cancer Predisposition Syndromes* (Cont. on page 12)

Syndrome	Gene (locus) Transmission	Malignancies	Other Features
Ataxia-telangiectasia (AT)	*ATM* (11q22.3); autosomal recessive	Neoplasms of the lymphoreticular tissue, especially NHL and leukemias (85% of AT-associated malignancies); gastric cancer (especially in adult males with IgA deficiency); susceptibility to breast cancer	Cerebellar ataxia; oculomotor apraxia; telangiectasias of the sun-exposed skin and conjunctivae; variable immune deficiencies; interstitial lung disease; pulmonary fibrosis
Bloom syndrome	*BLM* (15q26.1); autosomal recessive	Heterogeneous malignancies: in patients aged < 25 y: acute leukemias, lymphomas, Wilms' tumor; in patients aged > 20 y: cancers of the upper respiratory tract, colon, skin, breast, esophagus	Growth deficiency (pre- and postnatal); infantile diarrhea and vomiting; sun-sensitive erythema and telangiectasias; characteristic facies; immune deficiency; diabetes mellitus; hypogonadism; premature menopause
Cowden syndrome (multiple hamartoma syndrome)	*PTEN* (10q23.3); autosomal dominant	Breast (usually ductal); uterine; nonmedullary thyroid (especially follicular); possibly renal cancer; male breast cancer; gangliogliocytoma of the cerebellum (Lhermitte-Duclos disease)	Hamartomas of the skin, oral mucosa, breast, and intestine; papillomas of the lips and mucous membranes; acral skin keratoses; megalencephaly; facial trichilemmomas
Familial adenomatous polyposis	*APC* (5q22.2); autosomal dominant	Colorectal adenocarcinoma; ampullary and nonmedullary thyroid carcinoma; childhood hepatoblastoma; brain tumors (medulloblastoma, Turcot syndrome†); gastric cancer (more common in Korean patients)	Desmoids tumors; adenomatous ampullary and colonic polyps; hamartomatous and adenomatous gastric polyps; dental abnormalities; osteomas; sebaceous and epidermoid cysts; lipomas; CHRPE
Familial breast-ovarian cancer 1	*BRCA1* (17q21); autosomal dominant	Premenopausal triple-negative/basal-like breast cancer, ovarian, and fallopian tube carcinoma; smaller risk for papillary serous peritoneal carcinoma, prostate cancer, pancreatic cancer, male breast cancer	None syndrome-specific
Familial breast-ovarian cancer 2	*BRCA2* (13q12.3); autosomal dominant	Breast cancer (usually luminal; can be ER-positive); ovarian and fallopian tube carcinoma; papillary serous peritoneal carcinoma; male breast and prostate cancer	None syndrome-specific
Hereditary diffuse gastric cancer	*CDH1* (16q22.1) autosomal dominant	Diffuse gastric cancer; breast cancer (typically lobular); signet-ring cell colon cancer	None syndrome-specific
Hereditary nonpolyposis colorectal cancer/Lynch syndrome	*MLH1*(3p22.2); *MSH2* (2p21); *PMS1* (2q32.2); *PMS2* (7q22.1); *MSH6* (2p16.3); *MSH3* (5q14.1); autosomal dominant	Colorectal cancer (typically right colon); endometrial cancer; small intestinal cancer; gastric cancer; ovarian cancer; cancers of the biliary and urinary tract; glioblastomas (Turcot syndrome†)	Sebaceous neoplasms of the skin (Muir-Torre syndrome); sebaceous adenomas; Fordyce granules (intraoral sebaceous glands)
Juvenile familial polyposis	*BMPR1A* (10q23.2); *MADH4* (18q21.2); *ENG* (9q34.1); autosomal dominant	Colorectal cancer	Hamartomatous polyps throughout the GI tract; may overlap with hereditary hemorrhagic telangiectasia

Abbreviations: CHRPE, congenital hypertrophy of the retinal pigment epithelium; ER, estrogen receptor; GI, gastrointestinal; NHL, non-Hodgkin's lymphoma.

*These syndromes may be associated with breast, gastric, or colorectal cancer. For many genetic syndromes, the clinical phenotypes have not been subjected to vigorous statistical testing, and the association with certain malignancies may be inconsistent or weak.

†Turcot syndrome refers to combination multiple adenomatous colonic polyps and brain tumor. This combination can be seen with Lynch syndrome and familial adenomatous polyposis.

Table 1 Hereditary Cancer Predisposition Syndromes* (Cont.)

Syndrome	Gene (locus) Transmission	Malignancies	Other Features
Li-Fraumeni syndrome	*TP53* (17p13.1); autosomal dominant	Multiple cancers, including soft tissue sarcomas, osteosarcomas, leukemias, adrenocortical cancer, brain tumors (especially glioblastomas), breast cancer (most commonly < 45 y); gastric and colorectal cancer reported	None syndrome-specific
Li-Fraumeni syndrome 2	*CHEK2* (22p12.1); autosomal dominant	Early-onset breast cancer; whether *CHEK2* mutations truly cause Li-Fraumeni syndrome is debatable	None syndrome-specific
MYH-associated polyposis	*MYH* (1p34.1); autosomal recessive	Colon and duodenal cancer; increased risk of breast cancer	None syndrome-specific
Neuro-fibromatosis I	*NF1* (17q11.2); autosomal dominant	Malignant peripheral nerve sheath tumors; moderately increased risk of breast cancer	Café-au-lait macules, neurofibromas, axillary and inguinal freckles, hamartomas of the iris (Lisch nodules), skeletal abnormalities, learning disabilities
Nijmegen breakage syndrome	*NBS1* (8q21.3); autosomal recessive	Heterozygotes have increased risk for breast, prostate, colorectal cancer; NHL; lymphoblastic leukemia; homozygotes very high risk for malignancy, typically hematopoietic	Heterozygotes are phenotypically normal; homozygotes can have microcephaly, growth retardation, mild cognitive impairment, and immunodeficiencies
Peutz-Jeghers syndrome	*STK11* (19p13.3); autosomal dominant	Cancers throughout the GI tract; breast cancer; lung cancer; pancreatic cancer; uterine, ovarian (especially granulosa cell subtype), cervical (especially adenoma malignum), Sertoli cell testicular cancers	Hamartomatous polyps throughout the GI tract, sometimes involving other luminal organs; mucocutaneous pigmentations, menorrhagia, precocity in females from hyperestrogenism from sex cord tumors with annular tubules

Abbreviations: GI, gastrointestinal; NHL, non-Hodgkin's lymphoma.
*These syndromes may be associated with breast, gastric, or colorectal cancer. For many genetic syndromes, the clinical phenotypes have not been subjected to vigorous statistical testing, and the association with certain malignancies may be inconsistent or weak.

CDH1 mutations in sporadic early-onset gastric cancer[24] and the significant implications for her children justified genetic consultation and testing for HDGC. If a deleterious *CDH1* mutation is identified in the proband, testing of other family members for the identified mutation should be recommended. Given the syndrome's high penetrance, the aggressive phenotype of gastric cancer, and the absence of effective clinical screening, prophylactic gastrectomy in *CDH1* mutation carriers should be offered. This recommendation is further justified by the high frequency of occult gastric cancer found in surgical specimens of asymptomatic patients,[25] despite the high mortality and nearly 100% morbidity associated with gastrectomy.

Genetic testing also has limitations, and the detection rate of *CDH1* mutations, even among carefully selected patients, does not exceed 50%.[23] In this case, genetic testing of family members will not be informative; however, intensive endoscopic surveillance and breast cancer screening are recommended.

Conclusions

Advances in cancer genomics have led to the increasing recognition of hereditary cancer predisposition syndromes. Referral for genetic counseling and appropriate genetic testing should be considered in patients with a strong family history, even if an eponymous syndrome cannot be recognized, or in patients with unusual presentations. Recommended risk-reducing interventions in hereditary syndromes

are most commonly based on the natural history of the disease, but population-based studies are needed to more accurately assess cancer risk.

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