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Title: Synchronous gastric and colon cancers. Important to consider hereditary syndromes and chronic inflammatory disease associations.

Shenoy S. Synchronous gastric and colon cancers.

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Abstract

In this editorial we comment on the manuscript (87745) by Lin YJ *et al,* describing management and surveillance strategies in synchronous and metachronous, gastric and colon cancers. [1]

Synchronous or metachronous primary malignancies at different sites of the gastrointestinal tract pose a unique diagnostic and therapeutic challenge. Multidisciplinary services and strategies are required for the management of multiple site primary malignancies, to provide the best oncological outcomes. Although this study by Lin YJ *et al* highlights the dual cancers in 76 sporadic cases, the authors excluded 55 patients due to combination of factors which includes; incomplete clinical data, genetic syndrome, gastric stump cancers. In addition, the authors did not elaborate if any patients presented with signet ring cell morphology, E-cadherin mutations or presence of inflammatory bowel disease. Genetic and mutational errors and epithelial field defects from chronic inflammatory diseases of the gastrointestinal tract are important when considering synchronous gastric and colonic cancers. We will briefly discuss these in this editorial.

Key words: Synchronous gastric and colon cancers; gene mutation; chronic inflammation

Core tip: Certain genetic polyposis syndromes and inflammatory familial diseases are associated with increased risks for multiple site gastrointestinal cancer, specifically gastroduodenal and colon cancers. These include familial adenomatous polyposis (FAP), Lynch syndromes (LS), Hereditary diffuse gastric cancer (HDGC), Peutz-Jeghers syndrome, Crohn's disease (CD). Mutations in *APC* gene, Mismatch repair genes (MMR), E-Cadherin gene (*CDH1*) and *STK11* gene respectively. Generally, cancers associated with genetic mutations progress through adenoma carcinoma sequence while inflammatory bowel disease progress to malignancy through dysplasia -carcinoma sequence.

Introduction

Synchronous or metachronous primary cancers at different sites of gastrointestinal tract pose a unique diagnostic and therapeutic challenge. Multidisciplinary services and strategies are required for the management of multiple site primary malignancies to provide the best oncological outcomes.

This manuscript by Lin YJ *et al,* describes dual synchronous and metachronous gastric and colon cancer and highlights the management strategies and need for surveillance of colon and gastric cancers by surgeons and oncologists. [1]

Although this study highlights dual cancers in 76 sporadic cases, the authors excluded 55 patients due to combination of factors which includes; incomplete clinical data, genetic syndrome, gastric stump cancers. [1] In addition this study did not elaborate, if any patients presented with signet ring cell morphology, E-cadherin mutations or presence of inflammatory bowel disease.

Familial gastrointestinal polyposis syndromes and inflammatory bowel diseases increase the risks for multiple site gastrointestinal cancer, specifically gastroduodenal and colon cancers.

These include familial adenomatous polyposis (FAP), Lynch syndromes (LS), Peutz-Jeghers syndrome (PJ), Hereditary diffuse gastric cancer (HDGC) and Crohn's disease (CD) and H pylori infections. Associated gene mutations include adenomatosis polyposis coli (APC), mismatch repair (MMR), serine threonine kinase 11 (STK11) and E-Cadherin (CDH1) gene respectively. [2]

Mutational errors due to genetic syndromes and epithelial field defects from chronic inflammatory bowel diseases are important when considering synchronous gastric and colonic cancers. Generally, cancers associated with genetic mutations progress through adenoma carcinoma sequence while inflammatory bowel disease progress to malignancy through dysplasia -carcinoma sequence. [2]

We will briefly discuss these in this editorial.

Familial adenomatous polyposis (FAP)

FAP is an autosomal dominant genetic disorder with an incidence of 1:10000 in newborns and is due to mutation of APC gene located on the long arm of chromosome 5. Characteristic feature includes, multiple (>100) scattered colorectal polyps. The majority of patients develop these polyps in their teenage years with malignant transformation occurring by the fourth decade. The reported incidence of cancer is 15%, 75% and 90% by age of 10, 20 and 30 years respectively. [3] In addition, these patients are at a higher risk for gastric polyps (14% incidence) and small bowel adenocarcinoma. [4-6]

APC gene produces a tumor suppressor protein and is a negative regulator of Wnt signaling pathway. Absence of APC protein leads to upregulation of Wnt/β-catenin pathway with unopposed Wnt signaling. This causes excessive cell proliferation and poorly regulated cell cycle control resulting in multiple polyps. In addition, dysregulated Wnt/β-catenin pathway also activates epithelial mesenchymal transition (EMT) pathways and loss of apoptosis. Wnt

pathways also regulates cell-cell adhesion and therefore has an important physiological role in tissue formation, organogenesis in an embryo, and in post-natal growth and tissue renewal. [2,7]

Gastric cancers have been reported in FAP mutation carriers, although they are infrequent when compared to small bowel cancers. The incidence is 2–4% in Asian FAP patients and is higher compared to western FAP patients. In a large Japanese cohort of 303 FAP patients, the reported incidence was 4.2 percent. As sporadic gastric cancer is common in Japanese general population and increased in FAP, the authors from this study could not conclude if the incidence of gastric cancer is truly higher in Japanese FAP patients when compared to the general population. Similar incidence of approximately 4 percent was also reported from a Korean cohort. [8,9]

The role of upper gastrointestinal endoscopy for gastric tumors in FAP is unclear, although there is clear evidence of higher risk for small bowel cancers. In a large European gastric polyp registry, patients with gastric adenoma and carcinoma were followed from a prospective database. All patients underwent periodic upper endoscopy. The primary outcome was progression to gastric adenocarcinoma and secondary outcomes included presence of APC mutation, assessment of tumor stage, management and survival. Eight patients developed gastric cancer and 21 adenomas at median age of 52 and 44 years, respectively. This is in spite of regular esophagogastroduodenoscopy (EGD) surveillance which was performed in 6/8 patients who developed gastric cancer. The majority of patients presented with advanced T3/T4 stage tumors. 75% (6/8 cases) presented with lymph node or distant metastatic spread, at time of diagnosis. All cancer cases, died within a median of 13.5 months from diagnosis. Gastric adenomas were evenly distributed, 52% (11/21 cases) in the distal stomach and 48% (10/21 cases) in the proximal stomach respectively. The majority of cancers 63% (5/8 cases) were diagnosed in the proximal stomach. Another interesting finding from this study was an association of gastric tumor and desmoid tumors. It is well described, that FAP patients are predisposed to desmoid tumors. This was observed in 7/8 (88%) cancer and 11/21 (52%) adenoma cases. [10]

Therefore, gastroduodenal surveillance with upper endoscopy should be considered and repeated annually beginning after either colon polyps are detected or malignancy is diagnosed and FAP mutation is confirmed. [4-6,11]

Lynch syndrome (LS)

LS is an autosomal dominant disorder with germline mutations of mismatch repair genes (MMR): MLH1, MSH2, MSH6 and PMS2. These carriers are at an increased risk for gastrointestinal tract, hepatobiliary and genitourinary tract cancers. [12] Although uncommon, the overall lifetime cumulative risk for gastric cancer in LS has been estimated as high as 19%. [13,14]

Cancers with defective (MMR) genes are also known as microsatellite instability (MSI) tumors. These patients have a predilection for right sided colon cancers. The tumor histology is commonly poorly differentiated, mucin producing adenocarcinoma, with higher incidence of early lymph node metastases.

MMR genes, also known as DNA repair genes encode for proteins that rectify spontaneous small base insertions or deletions that may occur during normal cell division. Thus, these genes ensure the fidelity in DNA replication and maintain genomic integrity. MMR proofreads and repairs defects that were overlooked by DNA polymerase.[15]

The pathogenesis of cancers in LS includes, DNA methylation associated epigenetic silencing. This leads to secretion of abnormal peptides called neoantigens and is also referred as tumor mutational burden (TMB). These neoantigens are recognized by immune cells as non-self-antigens (foreign proteins). Neoantigens in tumors lead to infiltration by cytotoxic T lymphocytes (TIL) and express immune check point ligands such as CTLA4 and PD-1/PD-L1. These are hallmarks of solid malignancies such as colon, endometrial, gastric, melanoma and non-small cell lung cancers in LS. [15]

An increase in the cytotoxic T cells (TIL) in the tumor is considered as positive predictive biomarker for immunotherapy and is a favorable prognostic factor in gastric and colon cancer. The initial experiments on MMR deficient mice with colorectal cancer cells demonstrated a correlation between increased mutational load and improved survival due to immune surveillance by TILs. [16]

In a cohort of 2014 LS mutation carrier patients from Netherlands, gastric cancer was diagnosed in 32 (1.6%) subjects (male/female: 21/11), 22 (69%) of them had a negative family history of gastric cancer. The standardized incidence ratios of gastric cancer were 3.4 (95% confidence interval, 2.1–5.2). Lifetime risk of developing gastric cancer was 8.0% in male vs 5.3% in females (*P* = .02), and predominantly in 4.8% and 9% for MLH1 and MSH2 carriers, respectively. None of the 378 MSH6 carriers developed gastric cancer. [17]

Certain studies have mentioned a low incidence of gastric cancer in LS and therefore, have questioned the usefulness of endoscopic surveillance in patients with LS. However, these studies also identified H pylori infection as a risk factor and suggested that its eradication is more beneficial and reduces the incidence of gastric cancer by 35% in high-risk familial groups. [14]

In general, given the promising response to immunotherapy and relatively better prognosis of detecting and treatment of early gastric cancer, upper gastrointestinal endoscopic surveillance is recommended in patients with LS over the age of 30 years, in addition to colonoscopy. [12]

Hereditary diffuse gastric Cancer (HDGC)

HDGC due to CDH1 mutations could also predispose to both gastric and colon cancers. Some studies have reported small number of cases of colon cancers in CDH1 mutation carriers. CDH1 gene mutations are associated with hereditary diffuse gastric cancers (signet ring cell phenotype) also known as (HDGC) and lobular breast cancers. The incidence of HDGC due to germline CDH1 mutation ranges from 1% to 3%. [18,19]

The CDH1 is a tumor suppressor gene and located on chromosome 16q22.1 and transcribes a 120-kDa protein called E-cadherin. These are a family of highly conserved transmembrane glycoproteins, called cadherins and are one of the early necessary proteins in fetal development. The E-cadherin proteins forms a complex with another set of proteins called catenin's and function to cement cell-cell adhesion. In addition, it also transduces signal to the nucleus and cytoskeleton, through interplay with other pathways such as β-catenin, Rho-GTPase, NF-kB and EGFR signaling in an adhesion-independent manner. [20]

Loss of E-Cadherin (E-cad) promotes EMT (epithelial-mesenchymal transition) with loss of cell–cell adhesion capabilities and apical polarity. This contributes to invasion and metastases. [21]

Meta-analysis of a genome-wide association data identified the CDH1 gene locus as a susceptibility gene for developing colon cancers. Other studies have demonstrated CDH1 polymorphism and association of susceptibility loci of CDH1 gene with colon cancer associated with inflammatory bowel disease. [22-24]

The hazard ratio among sporadic gastric signet ring cancer patients for a secondary colorectal signet ring adenocarcinoma was three-fold higher, relative to conventional sporadic adenocarcinoma patients. Although the overall risk for colon cancers remains low all patients with a diagnosis of HDGC and high-risk family members should undergo screening and surveillance colonoscopy. [25]

Peutz-Jeghers syndrome (PJS)

PJS is an autosomal dominant disorder with mutation in the tumor suppressor, STK11 gene, located on the short arm of chromosome 19. The incidence of PJS is approximately 1 in 50000 to 200,000 live births. STK11 is primarily a tumor suppressor gene and modulates TP53-dependent apoptosis pathway and additionally has a role in cell metabolism and polarity. [26-27]

The characteristic phenotypic features of patients with PJS are melanin spots on the buccal mucosa and predilection to form multiple gastrointestinal hamartomas and polyps. Pediatric patients present with small bowel intussusception. There is an increased risk for GI tract (esophagus, stomach, colorectal, pancreas) and non-GI tract malignancies which include breast, ovaries, testicular and non-small cell lung cancers. Due to the rarity of this mutation in general population, the overall lifetime incidence of cancers in unclear. Adenocarcinoma can originate from both adenomas and hamartomas. Screening and surveillance endoscopy are recommended, beginning at age 18 and repeated every 2–3-years. [28]

Inflammation induced gastric and colon cancers.

Chronic inflammation of the stomach due to Helicobacter Pylori (H Pylori) infection, Crohn's disease and celiac disease of gastro-duodenum are well established risk factors for upper gastrointestinal tract cancers. Similarly chronic inflammatory bowel disease induced dysplasia is a risk factor for colon cancers. Factor common to both these sites is inflammation induced metaplasia and dysplasia through a process of field cancerization. These tumors present initially as dysplasia and progresses to carcinoma. Adenoma to carcinoma sequence is established in genetic mutation carriers and sporadic GI tract cancers. The exact mechanism still remains obscure but findings point to combination of genetic predisposition and additional environmental triggers leading to cumulative inflammatory burden. Some established mechanisms include activation of IL-23 target cells such as T helper 17 cells, innate lymphoid cells, granulocytes and natural killer cells with excessive production of proinflammatory cytokines. Alteration of the gut microbiota and abnormal metabolism of metabolites such as bile acids leads to imbalance in intraluminal and intramucosal cytokine activity causing chronic inflammation and is a risk factor for dysplasia and cancer. [29-30]

A recent multi-omics analysis, including single-cell RNA, whole-exome and microbiome sequencing, was performed to elaborate the tumor immune signature of synchronous primary gastric and colorectal cancers. These authors demonstrated that the mutational landscape and microbiome contributed to the distinct tumor microenvironment and inflammatory cellular

components which may contribute to different prognosis and drug responses in these cancers. [31]

Similarly, H pylori infection may be a strong promoter of colorectal carcinogenesis. A recent study on APC mutant mouse models with H pylori infection demonstrated accelerated tumor development in APC mutant mice. These authors identified a unique H. pylori-driven immune alteration signature characterized by a reduction in regulatory T cells and excessive inflammatory T cells. H pylori induced pro-carcinogenic STAT3 signaling and a loss of goblet cells in colonic epithelium. These changes with combination of pro-inflammatory cytokines and mucus degrading microbial signatures lead to carcinogenesis. Similar immune and epithelial alterations were described in human colon biopsies from H pylori-infected patients. [32]

An analysis of a cohort of patients with early gastric cancer from Japan demonstrated a high risk for adenomas in colon. Patients with early gastric cancers had a significant risk for colorectal cancer. Among these patients, high serum CEA level was an independent predictor for high-risk adenoma. [33]

Similarly, another study from South Korea comparing the colonoscopy findings in patients with gastric neoplasms in age and sex matched healthy subjects demonstrated higher incidence of both the number and size of colon polyps. The prevalence of advanced colon adenoma was significantly higher in the gastric neoplasm group (10.7% vs 3.8%, P < .001). [34]

A high index of suspicion should be maintained for malignancy with changes in abdominal pain, bowel habits, unexplained weight loss in patients with chronic inflammatory bowel disease of long-standing duration and should be evaluated with surveillance upper endoscopy and colonoscopy. [2]

Conclusion

Familial gastrointestinal polyposis syndromes and inflammatory bowel diseases increase the risks for multiple site gastrointestinal cancer, specifically gastroduodenal and colon cancers.

A multidisciplinary approach is required for diagnosis of genetic mutations, risk stratification and management of these patients and other family members for optimal outcomes.

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