Multiple Gastrointestinal Cancers in a Single Patient—a Rare Clinical Entity

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Abstract

Multiple gastrointestinal cancers in a single patient is a rare entity. In our study, we are showing the clinical presentation and management of these patients. A fifty-nine-year-old asthenic male (already treated case of metachronous colorectal cancer in 2008 and 2011) presented with complaints of generalized weakness and fatigue. Strong family history was present with two of his first-degree relatives having diagnosed with gastrointestinal cancer at the age < 50 years with one of them having stomach carcinoma and another with GEJ tumors. On evaluation, upper GI endoscopy revealed growth at cardia and endoscopic biopsy revealed adenocarcinoma. Radiological evaluation with PET-CT scan revealed proximal stomach growth with regional lymphadenopathy. Patient was optimized for surgery and underwent D2 total gastrectomy, distal pancreatectomy and splenectomy with Roux-en-Y oesophago-jejunal anastomosis. Pathological stage revealed pT4N2M0, moderately differentiated adenocarcinoma of proximal stomach, both distal and proximal cut margins negative for tumor, LVI present with no perineural invasion, and 5/18 lymph nodes dissected were positive for malignancy. Genetic testing needs to be considered in this patient (modified Bethesda guidelines and IGCLC criteria). Familial gastric cancer are of two types: (a) hereditary diffuse gastric cancer syndrome, (b) familial intestinal type gastric cancer. Approximately 5% of patients have germ-line mutations—AD LYNCH syndrome, hereditary breast-ovarian cancer, and polyposis and non-polyposis syndrome. Once diagnosed in localized advanced stage, the best treatment is R0 resection though overall prognosis in these patients is very poor. So it is rationale to find such families with elevated risk and to do active surveillance for early diagnosis and providing prophylactic gastrectomies to them as it has proven to be beneficial in hereditary form of gastric cancer.

Keywords MSI · Multiple gastrointestinal tract cancer · HDGS

Introduction

Clinically apparent second primary cancers in different organs or tissues were observed at an average annual incidence rate of 10.9 per 1000. Genetic instability may play an important role in the development of multiple gastrointestinal cancers but there may be different genetic

alterations between multiple gastrointestinal cancers of the same and different organs. Almost 5% of gastric and colorectal cancer patients develop other primary gastrointestinal cancers either synchronously or metachronously [1, 2]. Genetic markers help to identify high-risk patients with multiple primary gastrointestinal tract cancers and the clinical management which may lead to better prognosis. Hereditary non-polyposis colorectal cancer (HNPCC) syndrome is characterized clinically by early onset, more of right-sided colorectal cancers, multiple colorectal cancer and extracolonic cancers including stomach, urinary tract, uterus and ovary. While MSI has been seen in approximately 15–30% of single sporadic gastric cancers [3, 4] and in 10–15% of single sporadic colorectal cancers [5, 6] but is associated with 90% of hereditary cases. Little is known about MSI or other genetic alterations in multiple primaries of the gastrointestinal tract. We hypothesized that MSI would be found frequently in

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multiple gastrointestinal cancers as this is one of the features of HNPCC.

If MSI is observed frequently in these individuals, it may be a useful screening marker to detect high-risk patients of multiple gastrointestinal cancers and to rule out hereditary predisposition which requires genetic testing of complete three-generation family history.

We are presenting a case of multiple gastrointestinal cancers in a single patient and how we managed it.

Materials and Methods

A fifty-nine-year-old male without any comorbidity (already treated case of metachronous colorectal cancer in 2008 and 2011) presented to us with complaints of generalized weakness and fatigue. He also gave a strong family history with two of his first-degree relatives having diagnosed with gastrointestinal cancer at the age < 50 years with one of them having stomach carcinoma and other with oesophagus carcinoma (GEJ tumor). On examination, he had pallor with no supraclavicular lymphadenopathy. On per abdominal examination—a vertical midline abdominal 10-cm hypertrophied scar was present, abdomen was soft and non-tender with no organomegaly, and bowel sounds were present. On evaluation, his blood haemoglobin was 6.5 g/dl and liver and kidney function tests were normal. Chest X-ray was normal. On upper GI endoscopy, an ulceroproliferative growth was present at gastric cardia with active ooze, with normal first and second part of duodenum. Scope was negotiable. Endoscopic biopsy was taken which revealed well to moderately differentiated adenocarcinoma. Radiological evaluation with whole-body PET-CT scan revealed a metabolically active soft tissue thickening with asymmetric polypoidal mass with increased FDG uptake involving cardia and lesser curvature of stomach measuring 6×2.9 cm with a metabolically active gastrohepatic lymph node measuring $2.2 \text{ cm} \times 1.9 \text{ cm}$. Patient was optimized for surgery after transfusing 6 units of packed blood cells to correct anaemia and i/v fluids to correct the hydration status of the patient. He underwent D2 total gastrectomy, distal pancreatectomy, and splenectomy with Roux-en-Y esophagojejunal anastomosis under general anaesthesia on 29/08/16. Operative findings revealed an irregular mass in the proximal stomach involving cardia and lesser curvature of the stomach measuring 8×6 cm with infiltration to body of pancreas at places. Grossly, tumor was seen to be 2 cm below the GE junction with multiple enlarged lymph nodes in the gastrohepatic ligament largest measuring $2 \text{ cm} \times 2 \text{ cm}$. No evidence of liver metastasis/peritoneal deposits and ascites was present (Fig. 1). Postoperative period was uneventful. He was

Fig. 1 No evidence of liver metastasis/peritoneal deposits and ascites

started on feeding jejunostomy feed on postoperative day 3 and was discharged on postoperative day 7 with advice regarding feeding, medications and follow-up.

Results

Histopathological stage revealed pT4N2MO and moderately differentiated adenocarcinoma of proximal stomach; both distal and proximal cut margins were 5 cm away from tumor margins. Lymphovascular invasion was present with no perineural invasion; 5/18 lymph nodes were positive for tumor. He has completed six cycles of adjuvant chemotherapy and is on regular follow-up to us.

Discussion

Gastric cancer is now the fourth most common malignancy worldwide. India stands in low-risk region statistically with 5.3/100,000 persons suffering from gastric cancer [1]. The peculiarity of this case is the presence of strong family history and association with multiple cancers like colorectal cancer. This patient needs to be considered for genetic testing but patient did not comply for it. MSI testing and CDH1 testing are required in this case as the patient is fulfilling both revised Bethesda guidelines and IGCLC criteria which are as follows:

Revised Bethesda guidelines (for identification of patients with colorectal tumor who should undergo testing for MSI) state:

1. Colorectal cancer diagnosed in a patient below 45 years of age;
2. Right-sided colorectal cancer with an undifferentiated pattern on histopathology before the age of 45 years;
3. Signet ring cell type of colorectal cancer before the age of 45 years;

4. The presence of synchronous, metachronous colorectal or other HNPCC-associated tumor regardless of age.

HNPCC-related tumors include colorectal cancer, urogynaecological malignancies, and gastric cancer (seen in 6 to 13%) [3].

The international gastric cancer linkage consortium (IGCLC) criteria for CDH1 testing include the following [5]:

Two gastric cancer cases in the family, one confirmed diffuse type (his brother had this type of cancer) and one diagnosed at age of less than 50 years, three confirmed diffuse gastric cancers in first- or second-degree relatives independent of age, diffuse gastric cancer diagnosed at age less than 40 years (no additional family history needed), and personal or family history (1st or 2nd degree) of diffuse gastric cancer and lobular breast cancer, and one diagnosed at age of less than 50 years.

In this particular case, he had history of metachronous colorectal cancer who now presented with locally advanced gastric cancer. Also, two of his first-degree relatives suffered from diffuse gastric cancer below 50 years of age. MSI and CDH1 testing is recommended in this case. But our patient did not comply for it. But through this study, we emphasize that MSI testing is mandatory in all colorectal cancer specimens. And those found to have MSI in tumor need genetic clinic referral for counselling and blood testing for germ-line mutation.

Even if the gene is not found but there is strong family history, we strongly recommend colonoscopy at an age 5 years before an index case. Also, the need to take good family history in cancer patients and the need for every oncology centre to have a genetic clinic if feasible would help these patients.

Also, prophylactic gastrectomies should be offered to the carriers of germ-line CDH1 mutations [6] as there are high chances of false negative rate in endoscopic findings as mucosal abnormalities tend to occur late in these patients and there is lifetime risk of developing diffuse gastric cancer in 80% of the carriers. Therefore, rigorous surveillance using improved chromoendoscopic-aided methods for directed biopsies to diagnose the early diffuse lesions may prove beneficial. The optimal timing of prophylactic gastrectomy is generally recommended when the unaffected carrier is 5 years younger than the youngest family member who developed gastric cancer. The impact and long-term outcomes of prophylactic gastrectomy on carrier lifestyle and health are significant as most of the patients experience some level of morbidity, including diarrhea, weight loss and eating difficulties though there are no reports of cancer recurrence in these patients post surgery. But prophylactic gastrectomies provide the best chance for curative resection and hence the improved survival rate as different studies [7] have shown it although it clearly

comes at the cost of high morbidity. Owing to very poor prognosis for most gastric cancer patients, early diagnosis and prophylactic surgery improve cure, so it should be strongly recommended to these patients.

Conclusion

Genetic instability may play an important role in the development of multiple gastrointestinal cancers but there may be different genetic alterations between multiple gastrointestinal cancers of the same and different organs. We hypothesized that MSI testing should be done in patients with multiple gastrointestinal cancers as this form of cancer is one of the features of HNPCC. Also, hereditary gastric cancer is a relatively unusual disease with a poor prognosis. Our aim through this study is to emphasize on the effort that should be made to find individuals from inherited colorectal and gastric cancer syndrome families by active surveillance and also do get genetic testing in all colorectal cancer specimens. It would help the individuals whose family members can get benefit of active surveillance and colonoscopy at an appropriate age. Also, prophylactic surgical gastrectomies have shown to be beneficial in HDGS if diagnosed early as it is still curable. And this requires the need to take good family history in cancer patients and the need for every oncology centre to have a genetic clinic or an easy access to the genetic clinics.

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