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Is there an association between hereditary hemochromatosis and colon cancer in children?

ABSTRACT

Colon cancer is very rare in children and adolescents, so it remains in an advanced stage at diagnosis. Hereditary hemochromatosis (HH) is an autosomal recessive disease in which iron overload leads to dysfunction of several organs. Elevated body iron stores has association between HFE genotype and risk for some types of cancer. There are HFE gene mutations, including the C282Y and the H63D mutation in the majority of individuals with phenotypic hemochromatosis. The HFE gene mutations may predispose to an increasing risk of colon cancer. Careful clinical and colonoscopic evaluation in patients with these mutations may lead to detect cancer at an earlier stage. We report a case of adenocarcinoma of the colon in 17-year old male with HH and risk of gastrointestinal cancer in patients with hemochromatosis gene mutations.

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Key words: hemochromatosis, colon cancer, treatment, children

INTRODUCTION

Colon cancer is very rare in children and adolescents, so it remains in advanced stage at diagnosis. According to the literature gastrointestinal cancers constitute about 2% of neoplasms in children, and of this colorectal carcinoma (CRC) is the second most common cancer after primary liver cancer [1]. The etiology of this disease is multifactorial. It regards that iron overload can potential environmental risk factor for carcinogenesis. It is known that high iron levels induce oxidative stress and the production of reactive oxygen species which may induce lipid peroxidation and oxidative damage to DNA and target tumour suppressor genes. On the other hand, it regards the risk of colon cancer associated with mutations in the hemochromatosis (HFE) gene [1]. Hereditary hemochromatosis (HH) is an autosomal recessive genetic disease, characterized by an excessively increased absorption of dietary iron. Excess iron can be accumulated because of the lack of an effective excretory mechanism leading to toxic effects [2] in which iron overload leads to dysfunction of several organs [3]. In the HFE gene was identified two mutations leading to an

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exchange of cysteine to tyrosine at position 282 (C282Y) and histidine to aspartate at position 63 (H63D). In the U.S. about 15% population has at least one these mutations [4]. It is known the clinical influence of the C282Y mutation in patients with HH, with the C282Y homozygosity in 44-100% and C282Y heterozygosity in up to 11% [5]. It regards that it is the association between H63D and iron overload [6] but others conclude that the H63D mutation contributes to increase the risk for HH if inherited with the C282Y mutation [7].

Here, we report a case of adenocarcinoma of the colon in 17 year old male with HH and risk of gastrointestinal cancer in patients with hemochromatosis gene mutations.

CASE REPORT

A 17-year old boy who presented a 10-month history of abdominal pain, intermittent diarrhea with blood and nausea. These symptoms were accompanied by 3 kilos weight loss over 1 month. Family history was remarkable for a maternal aunt having been diagnosed with colon polyps. Ultrasonography of the abdomen revealed wall thickening of the sigmoid colon and it was suspicion of colitis. A colonoscopy was performed, which demonstrated an inflammatory concentric infiltration in the mucosa of the sigmoid colon. Endoscopy of the intestinal mucosa revealed mucinous adenocarcinoma. The patient had a contrast-enhanced computed tomography scan, which demonstrated a circumferential wall thickening in the sigmoid colon and upper rectum of approximately 22 mm in thickness and 60 mm in length. Then he underwent resection of sigmoid colon with upper rectum with regional lymph nodes. There was a polypoid mass lesion projecting into the lumen, which measured 5.5x6.5x1.3cm. There were no metastases to the liver. Resection margins were free from tumour. Pathologic specimens from tumour yielded mucinous adenocarcinoma grade 2 with histochemical stains negative for CD56, chromogranin and synaptophysin. Mitotic index (Ki 67) was huge — over 80% cancer cells. Resected lymph nodes showed complete replacement by metastatic deposit. Signet ring cells were discovered infiltrating through intestinal wall diffusely, lymphatic emboli from cancer cells in vessels and peritoneal invasion (pT3N2bMx – Duke C). Serum carcinoembryonic antigen (CEA) level before surgery and Ca 19.9 were very high, after surgery the level of CEA decreased but it still was high. Genetic testing was unknown and not available. He was subsequently treated with a chemotherapy regimen FOLFOX 4, which consisted of oxaliplatin (85 mg/m^2 *i.v.*), 5-FU (400 mg/m^2 bolus followed by 600 mg/m^2 *i.v.* day1–2 for 22 hours), folinic acid (200 mg/m^2 *i.v.* day 1–2) to be repeated every 2 weeks. Unfortunately, we observed myelosuppression after each cycle of chemotherapy so he required delayed of using therapy. Ten cycles of adjuvant chemotherapy were administered. No radiation therapy was given. After eleven months of treatment, the US of the abdomen, CEA level remained within normal limits, colonoscopy and CT of the abdomen showing no evidence of recurrence. Follow-up positron emission tomography imaging revealed no evidence of recurrent or metastatic disease. After treatment hepatosplenomegaly was observed. It was confirmed in scintigraphy. In laboratory exams the level of ferritin (1149.48 ng/ml; reference value: 21.81–274.66) and iron (232 ug/dl; reference value: 65–165) were elevated, Unsaturated Iron Binding Capacity was lower. HFE mutational testing for C282Y and H63D mutations were identified, so hereditary hemochromatosis was confirmed. Now, he is in clinical remission 8 years after finishing of oncological treatment with celiac disease.

DISCUSSION

Mutations in the HFE gene can weaken synthesis of hepcidin leading to increased release of iron from intestinal cells and macrophages, elevating plasma transferrin saturation and causing deposition of iron in the

Iron overload can potential environmental risk factor for carcinogenesis

liver and other tissues [8]. Intracellular iron may include oxidative DNA damage by iron-catalyzed free radical production, changes in gene expression in proliferating cells and decrease immune surveillance against cancer [9, 10]. Osborne et al. [11] proved that the 82% of men and 65% of women with C282Y homozygotes have elevated serum ferritin and 28% of male and 1 % of female C282Y homozygotes develop the iron overload-related disease in future. Patients with a single copy of both the C282Y and H63D mutations in HFE usually have higher serum ferritin and transferrin saturation levels than without HFE mutations. It regards that elevated body iron stores have the association between HFE genotype and risk for some types of cancer. There are HFE gene mutations, including the C282Y and the H63D mutation in the majority of individuals with phenotypic hemochromatosis [12]. In some studies, authors proved a positive association for homozygous C282Y or carriers of at least one mutation in C282Y or H63D for colorectal cancer [11–13]. In Shaheen et al. [12] study almost all of the patients with colon cancer were heterozygous for HFE mutation. Our patient had the C282Y and H63D mutations. It is difficult to say what may predispose patients to the development of colon cancer. On the one hand, chronic subclinical increases in total body iron stores may be the result of increased oxidative stress and induce DNA damage. On the other hand, the HFE gene encodes a transmembrane protein that has homology to the beta 2 microglobulin receptor. In this way, this protein may play a role in iron homeostasis [14]. In patients with a single copy of both the C282Y and H63D mutations in HFE confirmed higher serum ferritin and transferrin saturation levels than people without HFE mutation [15]. Etiology of CRC is still unknown. Weber et al. [16] regards that a genetic predisposition, immunological features, and early exposure to environmental factors promote CRC in pediatric patients. Our case patient present here, there were predisposing factors for CRC indicated, genetic and HFE. Polyposis syndromes, ulcerative colitis in a family are predisposing factors in about 10% of CRC in children [17]. Despite typical symptoms of CRC such as bloody stools, the pain of the abdomen, unexplained weight loss, vomiting, change in bowel habits initial colonoscopy is rare and often appendectomy or intestinal obstruction is performed before CRC is diagnosed [18]. Weber et al. [16] shown that the overall 5-year survival rate in pediatric cases with CRC in advanced disease and unfavorable histology was 65,6%. CRC is a rare tumour in children so therapy must be taken from adult guidelines [19]. Complete excision with lymph nodes examination should be the mainstay of treatment [18]. Our patient received multidrug chemotherapy and he is in clinical remission. CRC in children mucinous or signet ring is the most often in contrast to adults where tumour shows tubular differentiation [20].

Additionally, it seems that high dietary iron intake has an influence on CRC. It appears the intraluminal milieu may trigger oxidative — genotoxic changes in gut epithelial cell and it leads to gut tract cancers [21]. Osborne et al. [11] documented that patients homozygous for the C282Y variant of the HFE gene are at two-fold increased risk for colon cancer, and breast cancer, but not for prostate cancer in male. The association between HFE gene and risk of cancer may explain in this way that HFE is a non-classical major histocompatibility protein and has an immunological function and people with HH have an abnormal expression of MHC class I molecules and an impaired class I antigen presentation pathway and having an altered CD4/CD8 ratios [22]. Chang et al. [23] suggest that either heme iron intake or serum iron levels have associated with breast cancer risk in women. Similar observations were described in patients with colorectal cancer [24–26]. Authors regard that the catalytic effects of heme iron on endogenous N-nitrosation and

The HFE gene mutations may predispose to can increased risk of colon cancer

lipid peroxidation, and then subsequent oxidative damage to cellular biomolecules may contribute to the development of breast and colon cancer.

CONCLUSION

The HFE gene mutations may predispose to an increased risk of colon cancer. Careful clinical and colonoscopic evaluation in patients with these mutations may lead to detecting cancer at an earlier stage. Pediatric patients with CRC should be registered in national base rare tumours e.g. the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT), to improve management strategy of treatment.

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