Multiple Gastrointestinal Stromal Tumors (GISTs) of Stomach in a Healthy 13 year-old Girl

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Abstract

Gastrointestinal stromal tumors (GISTs) are uncommon tumors of the gastrointestinal (GI) tract that occur predominantly in adults. These tumors originated from Cajal cells have positive mutations for KIT (CD117) or platelet-derived growth factor receptor (PDGFRA). GIST especially multiple GISTs are very rare in children and lacking mutations in KIT. We present a previously healthy 13 year- old girl with history of hematemesis and melena for two months which has caused severe anemia requiring ICU admission with final diagnosis of KIT positive multiple GISTs in stomach.

Key Words: Gastrointestinal stromal tumors, Gastrointestinal neoplasm's, GIST tumor, Children

Introduction

Gastrointestinal stromal tumors (GISTs) are one of the most common mesenchymal tumors in the gastrointestinal tract,(1) but they stand for only 1% of GI cancers.(2, 3) They originate from the interstitial cells of Cajal. For diagnosis of These tumors, a positive C-kit (CD117) or platelet-derived growth factor receptor (PDGFRA) on immunohistochemistry is required.(4) Mutations in these receptor tyrosine kinases lead to dysregulation of downstream signaling pathways that contribute to GIST pathogenesis.(5) GISTs typically occur late in life,(6, 7) and approximately 95% of GISTs are positive for KIT (CD117) by immunohistochemistry.(1) But pediatric gastrointestinal stromal tumors (GIST) are rare(8-10) and occur preferentially in females as multifocal gastric tumors, typically lacking mutations in KIT.(11) Approximately 85% of pediatric GISTs do not have mutations in KIT or in PDGFRA (platelet-derived growth factor receptor) (PDGFRA).(5) The occurrence of multiple GIST's lesion is considered an extraordinary event restricted to pediatric,(12) familial GISTs and rare hereditary conditions such as type 1 neurofibromatosis.(13, 14) We present a previously healthy 13 year old girl who had this uncommon condition and positive C-kit.

Case Report

A previously healthy 13-year-old girl presented with a 2-month history of hematemesis and melena with a 2-week history of fatigue. On physical exam, she was cooperative with pale appearance and normal vital signs except for tachycardia. The Rest of her physical examination was normal. Due to severe anemia; (hemoglobin= 6.5 gr/dl) and palpitation, she admitted to intensive care unit. Laboratory tests revealed white blood cell count of 6,800/mL, (74% neutrophils, 19% lymphocytes, 7% mixed cells), platelets 470,000/mm3, Na 142 mEq/L, K 4 mEq/L, and Cr 0.9 g/dL. Chest X-Ray was normal. Upper endoscopy revealed multiple submucosal lesions with various sizes, biopsies were taken, but the histological examination disclosed only mild chronic superficial gastritis. Abdominal CT scan demonstrated a solid lesion (4×3.8 cm), likely arising from the gastric fundus (figure 1). Thus after correction of anemia she underwent laparotomy. Intraoperative finding was

multiple tumoral lesions with various sizes and different locations in stomach, thus enucleations were impossible. A total gastrectomy and Roux-en-Y esophagojejunostomy was done. Postoperative period was eventless and she discharged in the7th post operative day. Macroscopic examination findings were numerous round masses in stomach, with sizes, ranging from 2- 7 cm. Two masses were so large that extended up to the external surface of stomach. In microscopic examination of sections from tumors, neoplastic proliferations composed of spindle shape cells with eosinophilic cytoplasm and mildly pleomorphic elongated to plump nuclei were seen. Indistinct to small nucleoli and occasionally mitotic figures were arranged in fascicles and sheets. (Figure- 2) Also tumors invading into the muscularis and serousa layer were reported. Immunohistochemistery staining was positive for CD117(C-kit) and CD34 and negative for S100, SMA and desmin.

Because positive mutation of C-kit and PDGF receptor lead to imatinib sensitivity,(15) Imatinib 300 mg/day was started as adjuvant therapy. After 2 years follow up the patient is doing well without any signs of tumors.

Discussion

Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal tumors of the gastrointestinal (GI) tract that occur predominantly in adults.(8) They originate from the interstitial cells of Cajal.(16) The National Institutes of Health (NIH) convened a GIST workshop in April 2001 with the goal of developing a consensus approach to diagnosis and morphologic prognostication. Key elements of the consensus are defining role of KIT immunopositivity in diagnosis and a proposed scheme for estimating metastatic risk in these lesions, based on tumor size and mitotic count.(17) GISTs are not regarded as benign tumors, and morphological risk assessment is generally recommended according to the NIH consensus.(16, 17) The histological diagnosis of GIST requires immunohistochemistry (CD117, PDGFR alpha).(16) Imaging examination plays an important role in preoperative diagnosis and postoperative evaluation. CT examination is helpful in risk prediction for GIST, but it is difficult to detect small lesions (<2 cm) Due to the infiltrative growth of GIST with neural differentiation (S100-positive). it is difficult to distinguish GIST from gastric cancer on CT images.(18) In our patient also abdominal CT scan showed one of the multiple lesions. The possible reason for missing others may be due to smaller size of other lesions or external surface budding of them. Gastrointestinal stromal tumors typically occur late in life; however, There is 56 cases reported with the same disease in pediatric and young adults.(8) Like our patient, most pediatric GIST patients are female., but most of them; inspite of our patient, lack the gain-of-function mutation in KIT (CD-117),(7) but have activating mutations in the CD-117 gene. This rare subset of GISTs which is not well characterized in children causes unavailable standard therapy in this group. Multiple gastrointestinal stromal tumors (GISTs) are extremely rare and usually associated with type 1 neurofibromatosis and familial GIST.(19)

The most frequent clinical feature of GISTs is anemia, in 86.4% symptomatic patients, either through acute or subacute gastrointestinal bleeding. Less common features are gastrointestinal obstruction, palpable mass, abdominal pain or vomiting.(9)

In 2003, Budzynski A. et al reported stomach GIST in a 14 y/o girl, presented with epigastric tumor, which underwent stomach resection without recurrence during follow up period.(20)

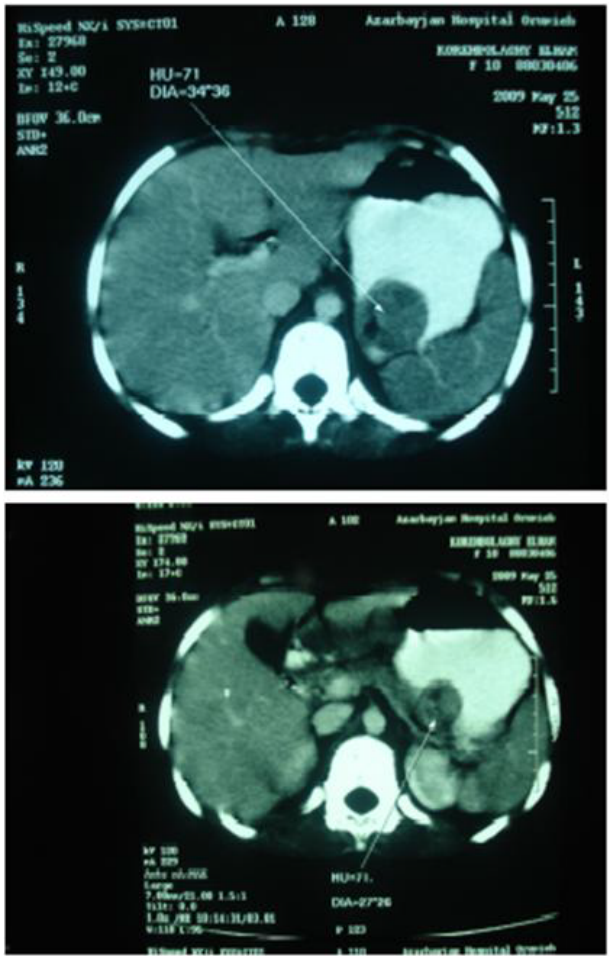

Figure-1: Abdominal CT scan demonstrated a solid lesion on gastric fundus.

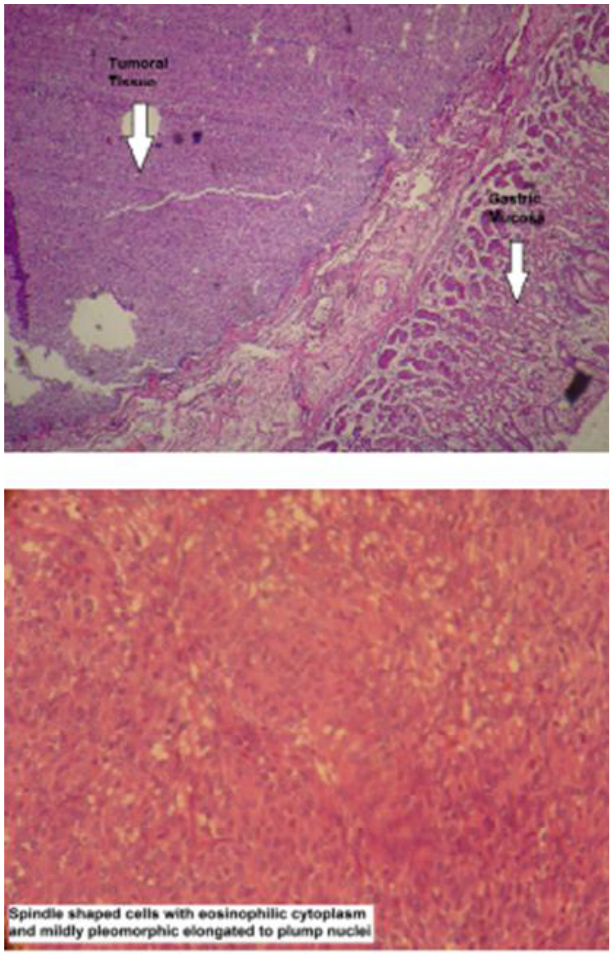

Figure- 2: Histology showing neoplastic proliferations composed of spindle shape cells and mitosis.

Durham M. M. et al in 2004 reported stomach GIST in 3 children, all of them presented with upper gastrointestinal bleeding and all of them underwent surgical resection.(21)

Chiarugi M. et al in 2007 reported GIST of duodenum in a 14 y/o boy, presented with recurrent upper GI bleeding and severe anemia.(22) Our patient also presents with subacute, painless GI bleeding and severe anemia. GISTs require resection and close observation for hepatic metastases. Our patient's repeated laboratory findings and abdominal CT scan were normal two years after tumors resection.

Imatinib mesylate is a small molecule which inhibits KIT and PDGF receptor tyrosine kinases in vitro and a new therapeutic agent for gastrointestinal stromal tumors.(23) It has been successfully used in the treatment of metastatic GISTs for more than 5 years.(24) Positive mutation of C-kit and PDGF receptor lead to imatinib sensitivity(15) and the imatinib resistance rate was lower in this group.(25) On the other hand current studies are ongoing for the potential role of imatinib mesylate for GISTs in children.(21) Thus in our patient imatinib was started 300 mg/day as adjuvant therapy after gastrectomy. After 2 years follow up the patient is doing well without any clinical symptoms or signs of tumors in later abdominal CT scans.

Conclusion

In children with gastrointestinal bleeding especially with severe anemia and without explaining endoscopic finding, an abdominal CT scan should be performed to rule out GISTs.

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