Gastrointestinal Stromal Tumors: A Rare Neoplasm Presenting with Gastrointestinal Bleeding

Fardah Akil, HAM Akil*, Tajuddin Tjambolang**, NK Sungowati***, M Adnan****, Bachtiar Murtala****, Junus Alkatiri*****, Santa Jota******

* Division of Gastroentero-Hepatology, Department of Internal Medicine, Faculty of Medicine University of Hasanuddin Dr. Wahidin Sudirohusodo General Hospital, Makassar
**Division of Digestive Surgery, Department of Surgery, Faculty of Medicine University of Hasanuddin Dr. Wahidin Sudirohusodo General Hospital, Makassar
*** Department of Pathology Anatomy, Faculty of Medicine University of Hasanuddin Dr. Wahidin Sudirohusodo General Hospital, Makassar
**** Department of Radiology, Faculty of Medicine, University of Hasanuddin Dr. Wahidin Sudirohusodo General Hospital, Makassar
***** Division of Cardiology, Department of Internal Medicine, Faculty of Medicine University of Hasanuddin Dr. Wahidin Sudirohusodo General Hospital, Makassar

ABSTRACT

Gastrointestinal stromal tumors (GIST) are rare tumors of the gastrointestinal (GI) tract that arise from primitive mesenchymal cells. GISTs occur throughout the GI tract but are usually located in the stomach and small intestine. GISTs are known with myoid, neural or mixed features of differentiation. Clinical findings are gastrointestinal bleeding, abdominal pain, and weight loss. GISTs express a heterogeneous clinical course not easily predicted. The histologic features that correlate best with development of recurrence and metastasis are mitotic activity, tumor size and the presence of tumor necrosis and most recently, mutation in the c-kit gene. Some authors specifically use the term GIST to refer to only those mesenchymal tumors that express CD117, whereas others believe that the diagnosis can be made in the absence of CD117 positivity based on clinical and morphologic features. Surgical resection remains the treatment of choice, since chemotherapy and radiation are ineffective. Long-term follow-up is imperative and recurrence rates are high.

We report the case of a 60 years old female patient who presented with intermittent melena, chronic dyspepsia, and anemia. Upper digestive tract endoscopy showed a submucosal tumor, broad-based, centrally ulcerated, projection of >5 cm in the gastric corpus-antral wall as the cause of the upper gastrointestinal bleeding. Endoscopic biopsies were negative for neoplastic changes. After triple eradication therapy of Helicobacter pylori and treatment continued with proton pump inhibitor agent, the patient underwent distal gastrectomy with Billroth-I reconstruction. Histopatological studies on the surgical resection specimen revealed a GIST of smooth muscle with spindle cell, no evidence of mitotic activity but of uncertain biological behavior. One year after surgery the patient is was improved with no signs of residual malignancy. However, metastases were found later in the liver in the next two year.

Keywords: *GIST, stromal tumor, surgery, C-kit.*

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are a rare neoplasms arising from connective tissue elements of the gastrointestinal wall. They show a great heterogenity with respect to their histogenetic, morphologic and prognostic characteristics.[1]

GISTs account for approximately 80% of gastrointestinal (GI) mesenchymal tumors, in benign or malignant form. These tumors predominantly affect middle-aged and older patients with a median age of 50-60 years, with an equal sex incidence. About 60-70% of GISTs occur in the stomach, 20-30% in the small intestine and 10% or less in the oesophagus.[2,3]

The annual incidence of clinically detected new cases of GIST in the United States have increased from perhaps 300-500 per year to 5,000-6,000 per year due to renewed interest and better diagnosis. In Finnland suggest that the annual incidence of all GISTs is approximately 10-20/million and that of malignant GISTs is about 4 cases per million of population.[2]

The immunophenotypic and ultra-structural resemblance of GISTs to the interstitial cells of Cajal, gastrointestinal pacemaker cells which control gut motility, suggests a histogenesis from the latter cells.[2,3,4]

The term of GISTs was introduced and used in 1983, most tumors described as leiomyomas and leiomyosarcomas in the older medical literature actually refer to GISTs. Only with tumors in the esophagus does the term leiomyoma/ leiomyosarcomas remain accurate.[3,5,6]

These tumors have a wide clinical spectrum at presentation. They range from incidentally detected, asymptomatic, benign GISTs to large malignant tumors and if symptomatic, GISTs usually cause symptoms as a result of their size or tendency to ulcerate and bleed. The most common presenting signs and symptoms include abdominal pain, GI bleeding manifested by hematemesis or melena, and a palpable mass with weight loss.[7,8,9]

Microscopically, there are two principal histological patterns: spindle cell (70-80% of cases) or epithelioid (30-40% of cases) character, or a combination of both in variable proportions. GISTs are immunohistochemically positive for c-kit protein (CD117) and/or CD34.[6,10]

The expression of CD117 (a proto-oncogene protein) has emerged as the most important defining feature and probably the gold standard for diagnosing GISTs.[6,9,11]

Complete surgical excision is the treatment of choice for localized GISTs. Inoperable and metastasis targeted therapy using imatinib mesylate is a synthetic tyrosine kinase inhibitor, which now has been confirmed by larger trials in America and in Europe. This drug has effect as proapoptotic and antiproliferation. The role of radiother-apy is limited by the potential toxicity to surrounding struc-tures, especially the intestines. In the other hand conventional chemotherapy is usually not responsive.[2,5,12]

The histologic features that correlate best with development of recurrence and metastasis include mitotic activity, tumor size and the presence of tumor necrosis and most recently, mutation in the c-kit gene. Long-term follow-up is imperative, as recurrence rates are high.[3,13,14]

We report a case diagnosed as GIST a rare neoplasm presenting with gastrointestinal bleeding.

CASE REPORT

Mrs. A, 60 years old, with chief complaint intermittent melena for 5 years and received blood transfusion for several times. She have visited many physicians before, and being diagnosed gastric ulcer. She was treated with antacid. Beside that, she always felt abdominal fullness, sometimes with nausea and vomiting, pain in epigastrium, anorexia, and weight loss 15 kg of body weight five years period. The patient frequently feelt weak and dizziness. There was no history of taking NSAID, jaundice, and malignancy in family. She had hypertension for 5 years and taking antihypertensive medicine regularly.

Physical examination on admission revealed the general condition was moderately ill with poor nutritional status (weight 50kg with height 166 cm). Blood pressure was 120/80 mmHg, respiration 20, pulse 90, temperature 37.4^{o}C. The conjunctiva were pale, no jaundice on sclera. No lymph nodes enlargement. Jugular venous pressure (JVP) within normal range. There was systolic murmur grade I/II. Lung was within normal range and no sign of cirrhosis. Abdomen examination revealed palpation of tumor mass in epigastrium to left hypocondrium region, hand boxer with oval-rounded shape, slight cysteus-elastic, mobile with clear margin and no pain. No hepatomegaly or splenomegaly was found. Extremities revealed pale, no palmar erythema. Rectal touché examination showed black stools.

The laboratory examination on admission showed hemoglobin 6.2 g/dl, hematocrit 25.1%, leukocyte 7,700/ mm^3, platelet 253,000/mm^3, LED 35/80, BT 2'3" and CT 8'45". Peripheral blood result hypochrom micrositic anemia, AST 38.2 U/L, ALT 16.7U/L, AP 200.8 U/L and kidney function and amylase level in normal range.

Working diagnosis were epigastric tumor. Melena had caused hypochrom micrositic anemia in this patient. Clinical differential diagnosis:

1. Gastric tumor with ulceration
2. Left lobe liver abscess

Therapies were given such as octreotide, proton pump inhibitor and blood transfusion.

Upper digestive tract endoscopy showed a submucosal tumor, broad-based, centrally ulcerated, projection of > 8 cm in the gastric corpus-antral wall with erosive in LES esophagus (figure 1). Endoscopic biopsies were negative for neoplastic changes, *H. pylori* negative with serology IgG antiHp positive.

Abdominal ultrasound showed inhomogeneous hypoechoic mass, clear margin, enlarge to the left with size 11.7 x 6.2 cm; CT scan abdomen with contrast was performed and showed large mass in epigastrium to left hipochondrium, filling defect with soft tissue density round/oval shape. There was no liver or spleen enlargement. Conclusion of CT scan abdomen was large gastric tumor (figure 2).

Figure 1. Upper digestive tract endoscopy showed a submucosal tumor, centrally ulcerated, projection of > 5 cm in the gastric corpus-antral wall with erosive in LES esophagus.

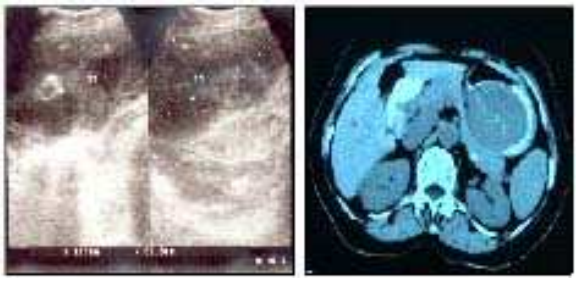

Figure 2 (A). Abdominal ultrasound showed inhomogeneous hypoechoic mass, clear margin enlarge to the left with size 11.7 x 6.2 cm (B). CT scan abdomen with contrast was performed and showed large mass in epigastrium to left hipochondrium, filling defect with soft tissue density round/oval shape

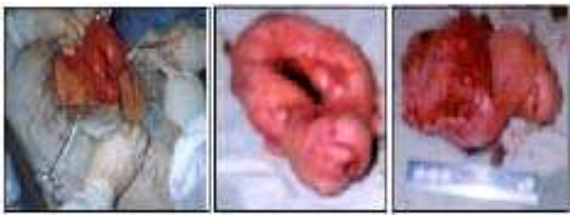

Figure 3. Resection specimen of a case of GIST shows a large bulging tumor with surface erosion at posterior wall corpus, mobile, intact mucosa around tumor

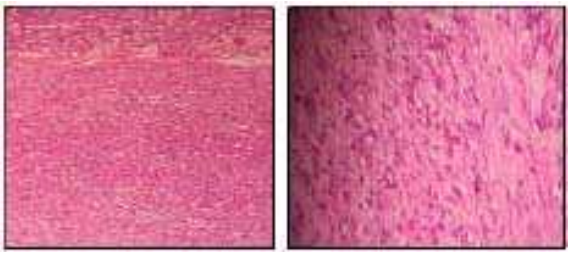

Figure 4. Histologically, the tumor consist of densely packed spindle cell, atypia, pleomorfik with no evidence of mitotic activity

The clinical diagnoses for the patient were submucosal gastric tumor suspect GIST with GERD grade B and peptic ulcer caused by *H. pylori*. Triple eradication therapy of *Helicobacter pylori* and followed by proton pump inhibitor agent.

Consultation to digestive surgery and radiology department suggested to make distal gastrectomy with Billroth-I reconstruction.

At surgery, a large bulging tumor with surface erosion at posterior wall corpus was found. It was mobile and surounding mucosal tumor was still intact. No lymph node enlargement nor infiltration in the liver or spleen. Diagnostic surgery revealed gastric leiomyoma.

Histolopatological studies on the surgical resection specimen revealed a gastrointestinal stromal tumour (GIST) of smooth muscle with spindle cell, atypia, pleomorfik with no evidence of mitotic activity.

One year after surgery the patient was improved with no signs of residual malignancy. However, metastases were later found in the liver in the next two years. The died due to metastatic cancer.

DISCUSSION

On admission, the patient had 5 years melena intermittent with history of chronic dyspepsia. Physical findings that showed the patient appears very pale with palpable of tumor mass in epigastric to the left hypochondrium.

Blood transfusion was given to correct the anemia. The bleeding was minimized by given octreotide and Proton Pump Inhibitor agent. Upper digestive tract endoscopy showed a sub mucosal tumor, broad-based, centrally ulcerated, projection of > 5 cm in the gastric corpus-antral wall with erosive in LES esophagus. Biopsy specimen was negative for neoplastic changes and serology test for IgG antiHp was positive. Abdominal ultrasound and CT showed a large mass tumor enlarge to the left with size of 11.7 x 6.2 cm.

The source of bleeding for long period and intermittent originally from peptic ulcer where was active before due to *H. pylori* infection. The mucosal erosion at the base of the tumor because of tumor overgrowth had made pressure resulting necrosis and chronic bleeding.

Grossly, GISTs are well-demarcated spherical masses that appear to arise from the muscularis propria layer of the GI wall. Intramural in origin, they often project exophytically and/or intraluminally, and they may have overlying mucosal ulceration. Larger GISTs nearly always outgrow their vascular supply, leading to extensive areas of necrosis and hemorrhage.[6,9]

Submucosal tumor that found at Upper gastrointestinal endoscopy probably was a mesenchymal tumor from GISTs group, where is differential diagnosis was tumor from smooth-muscle or neurogenic origin. GISTs account for approximately 80% of GI mesenchymal tumors, which the stomach is the most common site (60-70%).[2,8,15]

The understanding of mesenchymal neoplasms of the gastrointestinal tract has evolved dramatically over the last two decades since gastrointestinal stromal

tumor (GIST) was described as the most common stromal tumor arising anywhere from the esophagus to the ano-rectum. GISTs differ clinically and pathogenetically from true leiomyosarcomas (very rare in the GI tract) and leiomyomas. There was indicated the majority that previosly diagnosed smooth muscle tumors (SMT) actually belong to GIST.[5,6,13,16]

GISTs express more than 80% of the KIT protein, gain-of-function mutations in the KIT or *Platelet-Derived Growth Factor Receptor alpha* (PDGFRα) gene is involved in oncogenesis and growth of GISTs.[10,17,18,19]

Because of the uncertain biological behavior of the GISTs an early surgical intervention is recommended as well as therapeutic. *Helicobacter pylori* eradication and cardiac condition was treated to maintain optimal condition before surgery. Technique gastrectomy Billroth-I showed large gastric leiomyoma without metastases changes in accordance with USG abdomen/CT Scan.

CT scan examination is being used with increasing frequency in an attempt to diagnose primary and/or metastasis GISTs before surgery. Double contrast barium and CT Scan demonstrated an abnormality in 80% and 87-90% cases respectively.[9,13]

The most specific criterion for a diagnosis of GIST by immunohistochemical examination of c-KIT (CD117) and presently account for 90% cases, unfortunately the material not available in our institution.

As noted previously, some authors specifically use the term GIST to refer to only those mesenchymal tumors that express CD117, whereas others believe that the diagnosis can be made in the absence of CD117 positivity based on clinical and morphologic features.[3,6,8]

According to clinical manifestation and morphologic features, diagnosis GIST of this case was made based on:

- the patient's age was 60 years old (typically present in older individuals)
- occur in the stomach as gastric submucosal tumor (60-70% cases)
- histological identified as highly cellular spindle cell (70-80% cases)

The sign of high-risk malignant degeneration for this patient were occurred because the size of the tumor > 5 cm (size 11.7 x 6.2 cm). Necrotic area might cause hemorrhage; although no metastases was found.

Condition of the patient 1 year after surgery was improved, but the next two years liver metastases ocurred and caused the patient die.

Regardless of the presentation, the disease-specific survival rates with malignant GISTs are 69% at 1 year, 38-44% at 3 years, and 29-35% at 5 years.[3]

Surgical resection remains the mainstay of treatment, as chemotherapy and radiation are ineffective. In patients who had malignant primary disease and who underwent complete gross resection of the tumor, 40% had recurrence; 91% of the patients died from the disease during the course of one study. The disease-specific survival rate in this group of patients was 88% at 1 year, 54-65% at 3 years, and 42-54% at 5 years. Recurrence is typical, and the rate has been reported to be as high as 90% at long-term follow-up.[15]

REFERENCES

1. Fenton RG, Longo DL. Cell biology of cancer. In: Harrison's principles of internal medicine, ed by Fauci AS, Braunwald E, et al. 15th ed. McGraw-Hill Inc, New York 2001.p. 509-17.
2. de Silva MVC, Reid R. Gastrointestinal stromal tumors (GIST): C-kit mutations, CD117 expression, differential diagnosis and targeted cancer therapy with imatinib. Pathol Onco Res 2003;9:13-9.
3. Nguyen V, Taylor A. Gastrointestinal stromal Tumors-leiomyoma/leiomyosarcoma. In: Abeloff. Clinical Oncology, ed by Dipiro P, Coombs B, Schmeidel U, et al. 2nd ed. BC Decker Inc., Hamilton London 2000.p.237-51.
4. Tornoczky T, Kover E, Pajor L. Frequent occurrence of low-grade cases among metastasis gastrointestinal stromal tumors. J Clin Pathol 2003;56:363-7.
5. Collins CG, O'Sullivan G, Shanahan F. Effective therapy for advanced gastrointestinal stromal tumors. Gastroenterology 2003;124:1150-58.
6. Miettinen M, Majidi M, Lasota J. Pathology and diagnosis criteria of gastrointestinal stromal tumors (GISTs): a review. Eur J Cancer 2002;38(5):S39-51.
7. Grady WM. GISTs: The revolution continues. Gastroenterology 2003;125:967-78.
8. Nishida T, Hirota S. Biological and clinical review of stromal tumors in the gastrointestinal tract. Histol Histopathol 2000;5(4):1293-301.
9. Pidhorecky I, Cheney RT, Kraybill WG, et al. Review gastrointestinal stromal tumors: current diagnosis, biologic behavior, and management. Ann Surg Oncol 2000;9:705-12.
10. Van Roggen JFG, Van Velthusyen MLF, Hogendoorn PCW. The histopathological differential diagnosis of gastro intestinal stromal tumors. J Clin Pathol 2001;54:96-102.
11. Richter JE, Zuccaro G. Esophageal disease. In: Gastroenterological Endoscopy. Ed by Classen M, Tytgat GNJ, Lightdale CJ, Thieme Stuttgart. New York 2002.p. 457-58.
12. Demetri GD, Mehren M, Blanke CD, et al. Efficacy & safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472-80.
13. Ho SB. Tumors of the stomach and small intestine. In: Current Diagnosis & Treatment in Gastroenterology. Friedman SL, McQuaid KR, Grendell JH editors. 2nd ed. Large Medical Books. McGraw-Hill Inc, New York 2003.p.389-402.
14. Kuan SF. Pathology of gastric neoplasms. In: Atlas of Cancer of the Upper Gastrointestinal Tract. Posner MC, Vokes EE, Weichselbaum RR, editors. BC Decker Inc. Hamilton London 2002.p.218-36.
15. Logrono R, Jones DV, Faruqi S, et al. Recent advances in cell biology, diagnosis, and therapy of gastrointestinal stromal tumor. Cancer Biol Ther 2004;3:86-98.
16. Wang X, Mori I, Tang W, et al. Gastrointestinal stromaltumors: are they of cajal cell origin? Exp Mol Pathol 2002;72(2):172-7.

17. Corless CL, McGreevey L, Haley A, et al. KIT Mutations are common in incidental gastrointestinal stromal tumors one centimeter or less in size. Am J Pathol 2002;160:11567-72.
18. Duensing A, Heinrich MC, Fletcher CD, Fletcher JA. Biology of gastrointestinal stromal tumors: KIT mutations and beyond. Cancer Invest 2004;22(1):106-16.
19. Hirota S, Ohasi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor á gene in gastrointestinal stromal tumors. Gastroenterology 2003;125:660-7.