CASE REPORTS

Gastrointestinal stromal tumors

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Abstract

A case of gastrointestinal stromal tumors (GIST) in the Third Affiliated Hospital of Inner Mongolia Medical University was collected and analyzed on the basis of diagnosis, physical examination and treatment. Misdiagnosis of GIST is very common since it is a rare disease. So this paper aims to enhance the doctors' awareness of GIST during clinical practice.

Key Words: Gastrointestinal stromal tumors, Gastrointestinal diseases, Tumors

1 Medical record

1.1 General information

A 60-year-old female patient was admitted to our hospital due to repeated epigastric discomfort for five years, black stools for half month, and emesis for an hour on October 3, 2011. The patient complained of epigastric discomfort of 5 years' duration, without abdominal pain, distension nor acid reflux, heartburn, anorexia, and significant weight loss. No treatment regarding the disease was received. She passed black stool, an average of one time per day about 50 grams, and had a sense of fatigue during the past half month. She vomited brown and dark red blood once, a total of about 200 ml, one hour before admission, and felt flu dizziness, palpitations without sign of chest tightness, shortness of breath. The patient had oral administration of Chinese traditional medicine (specific condition unknown) due to knee pain for nearly one week prior to her admission. There was no reported history regarding hypertension, diabetes and coronary artery heart disease. Both medicine and food allergy were denied. No contact history of hepatitis, tuberculosis. Clinic ECG showed: sinus tachycardia, heart rate of 105 beats per minute.

1.2 Physical examination

The physical examination results are: T 36.6°C, P 105 beats per minute, R 20/min, blood pressure 120/80 mmHg, conscious and anemic appearance. No yellow of skin and sclera was included. Superficial lymph nodes were not found to be enlarged. Double lung breath sounds resonance. The heart rate is 105 beats/min, showing regularity in the force and rhythm of the heartbeat. Abdomen soft, mild epigastric tenderness, without rebound tenderness and muscle tension. No enlargement of liver, spleen and kidneys beneath the rib was found, nor edema of lower limbs. Murphy's sign was negative, shifting dullness was positive, bowl sound was normal, without vessel murmur.

1.3 Auxiliary examination

Blood biochemical test showed that K^+ 3.10 mmol/L, Na^+ 135 mmol/L, Ca^{2+} 1.77 mmol/L, Glu 7.05 mmol/L, blood urea nitrogen 5.52 mmol/L, serum creatinine 50.4 mmol/L. Four blood coagulation indexes: PT 12.7 s, PTA 83.2%, APTT 18.3 s. HBV, HCVAb, HIVAb and Anti-TP were negative. Blood Rt: WBC 9.1×10^9/L, GR% 74.3%, Hb 50.0 g/L, PLT 130×10^9/L. Blood gas analysis: PH 7.473,

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PCO_2 28.2 mmHg, PO_2 68.6 mmHg, BE -3.2 mmol/L. Stool routine test: tarry stools, fecal occult blood test (++). Liver function test showed that ALT 12 U/L, TP 53.9 g/L, ALB 35.2 g/L, TBIL 25.3 μmol/L, DBIL 9.4 μmol/L, IBIL 15.9 μmol/L. Tumor indexes: AFP, CEA, CA50, CA125, CA153, CA199, CA724, CA242 were negative. ECG: sinus tachycardia. Abdominal ultrasound showed that the gallbladder wall was rough, gallstones (multiple). Gastroscopy examination revealed that elevated lesions mass of 3.0 cm $\times$2.0 cm was visible near greater curvature of the gastric body, the central depression with erosion, the surrounding mucosa and gastric mucosal color were the same, a sense of volatility depression could be felt. Endoscopy reexamination showed that a bulge mass of 3.0 cm $\times$4.0 cm was visible at the posterior wall of greater curvature of the cardia, with irregular depression on top, surrounding mucosa bulged like a dam, covered by white fur mucus, biopsy of five block confirmed that tissue elasticity was poor, hard texture, soft touch of easy bleeding. Pathology demonstrated that (Gastric body) mucosa chronic inflammation, hyperplasia of fibrous tissueunder local mucosa (see Figures 1,2). Abdominal CT exhibited that stomach cancer at the greater curvature was suspended, with left adrenal gland and left fourth intercostal transfer (see Figure 3).

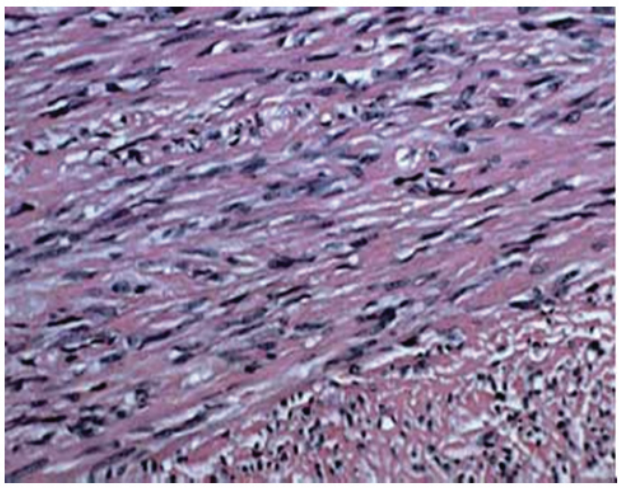

Figure 1: Histopathology of GIST ($\times$200)

1.4 Primary diagnosis

(1) Gastrointestinal stromal tumors?
(2) Peptic ulcer?
(3) Lymphoma?
(4) Stomach cancer?

1.5 Diagnosis and treatment

The patient received venous inflow of Omeprazole Sodium-for 40 mg and Hemocoagulase 3U, packed red blood cells 800 ml. No vomiting blood and black stools were reoccurred after admission. Hemoglobin was examined to be 84 g/L the first two days after admission. She was discharged after nine days when the condition was better.

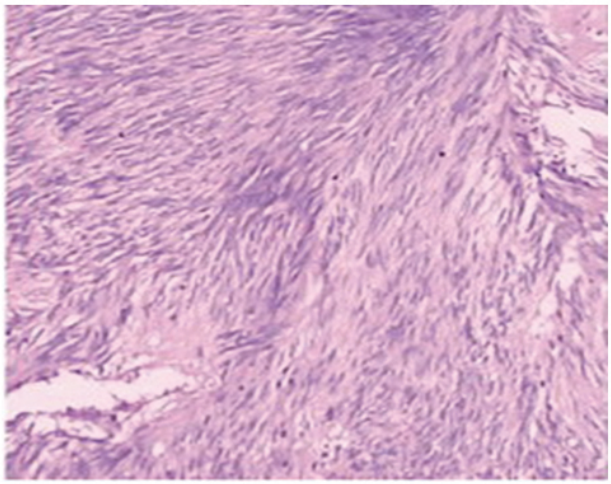

Figure 2: Histopathology of GIST ($\times$100)

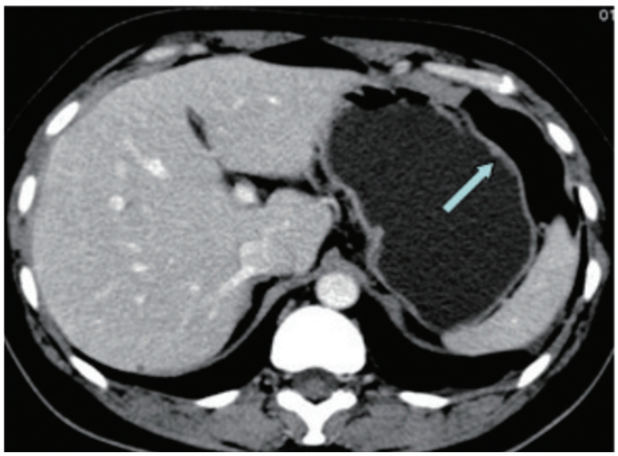

Figure 3: Abdominal CT

2 Discussion

2.1 Dr. Meili Gao

Dr. Meili Gao is the director of Digestive Department at the Third Affiliated Hospital of Inner Mongolia Medical University, specializing in diagnosis and treat gastrointestinal diseases.

Gastrointestinal stromal tumors (GIST) are the most common mesenchymalneoplasms of the gastrointestinal tract, which arise in the smooth musclepacemaker interstitial cell of Cajal or similar cells. Stromal tumor includes the previously so-called "gastrointestinal smooth muscle tumor"

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or "gastrointestinal leiomyosarcoma." As a tumor of mesenchymal tissue, the gastrointestinal smooth muscle tumors or gastrointestinal leiomyosarcoma concept has not been ruled out, and accounts for only a small part of gastrointestinal mesenchymal tumors in the current clinical and pathological diagnosis. Gastric stromal tumors are different sizes, ranging from 0.2 cm-44 cm, originated in the gastrointestinal tract wall inherent muscle, and grow inside and outside the chamber. The growth path of inside chamber forms ulcers. It can be classified into intramural, dumbbell, gastrointestinal tract, extraabdominal cavity type according to the location of the tumor. Most tumors show expansive growth, clear boundary, hard brittle, whose planes of section are fish-shaped, gray-red and hemorrhage, necrosis, cystic degeneration would be seen in the center. The number of tumors may be more than one. Gastric stromal tumors mainly compose of spindle cells and epithelial cells, two cells could be simultaneously in different tumors, and their morphological changes vary greatly. It can be divided into spindle cells, epithelioid cell type and mixed spindle and epithelial cells according to the amount of the cells. Arrangement of tumor cells also diversifies, in which bundles and flaky arrangement are the majority type.

The majority of GISTs present at older individuals. Across most of the age spectrum, the incidence of GIST is similar in men and women. This makes GIST the most common form (1%-3%) of sarcoma. Most (50%-70%) occur in the stomach, 20%-30% in the small intestine and less than 6% in the esophagus. It is rare in mesenteric, omental and abdominal cavity. There is no particularity in GIST as its symptoms largely depend on the size and site of tumor. GISTs may present with trouble swallowing, gastrointestinal hemorrhage. Some patients may involuntarily increase the risk of local recurrence and peritoneal implantation due to intestinal perforation treatment. Approximately 11%-47% metastasis, mainly in the liver and abdominal cavity, was to be checked for patients with gastric stromal tumors at the first visit. Lymph nodes and extraabdominal metastasis are even rare in more advanced patients. The malignancy level of intestinal stromal tumors and lymph node metastasis ranks the top, while esophageal stromal tumor carries low malignancy. Strictly speaking, the stromal tumor, therefore, could not be benign at all.

The patient was presented with abdominal discomfort, blood in the stool, anemia, abdominal soft, mild tenderness in the upper abdomen. Gastroscopy examination revealed that: elevated lesions mass of 3.0 cm × 2.0 cm was visible near greater curvature of the gastric body, the central depression with erosion, the surrounding mucosa and gastric mucosal color were the same, a sense of volatility depression could be felt. Endoscopy reexamination showed that a bulge mass of 3.0 cm × 4.0 cm was visible at the posterior wall of greater curvature of the cardia, with irregular depression on top, surrounding mucosa bulged like a dam, covered by white fur mucus, biopsy of fivec block confirmed that tissue elasticity was poor, hard texture, soft touch of easy bleeding. Pathology demonstrated that (Gastric body) mucosa chronic inflammation, hyperplasia of fibrous tissueunder local mucosa. Abdominal CT exhibited that stomach cancer at the greater curvature was suspended, with left adrenal gland and left fourth intercostal transfer. Therefore, the probable diagnosis of gastric stromal tumor, adenoma and gastric cancer should be included.

2.2 Dr. Qifen Qu

Dr. Qifen Qu is the deputy director of Department of Internal Medicine at The Third Affiliated Hospital of Inner Mongolia Medical University, specializing in stomach, liver disease.

2.2.1 The origin and definition of GIST

It is a non directional differential, original or immature mesenchymal tumor that originates from gastrointestinal mesenchymal stem cell, which was diagnosed as a tumor of gastrointestinal smooth muscle tumors or nerve source in the past. Mazur and Clark brought the concept of GIST[1] to public in 1983 by electron microscope and immunohisto chemical methods to reevaluate the tissues of gastrointestinal mesenchymal tumors. Relatively recently, *i.e.* in 1998, this neoplasm was distinguished from a group of other gastrointestinal tract sarcomas after prof. Hirota had discovered a mutation in c-kit[2] protooncogene, which is crucial for the development of this tumor. Since then, the expression of c-kit protein (CD117 antigen) with tyro-sine kinase activity on the surface of the tumor cells has become the main diagnostic criterion. Mutations in the exons 11, 9 and rarely 13 of the c-kit gene are known to occur in GIST. GISTs are generally defined as[3] tumors whose behavior is driven by frequent mutations in the c-kit gene, stain positively for CD117, arise from spindle cells and epithelioid cells.

2.2.2 Clinical behavior and medical imaging of GIST

The incidence of GIST is lack of exact data in our country. The estimated incidence of GIST in Spain and Hong Kong is approximately 1.09/1,000,000 and 1.68-1.96/1,000,000 respectively.[4,5] It most occurs in the stomach (60%-70%), followed by small intestine (20%-30%), rectum, colon and esophagus (together 10%), extra-gastrointestinal tract is rare site.[6]

Clinical manifestation of GIST is generally non-specific, and there is no clinical symptom among 1/3 of the patients. Abdominal pain, abdominal distension and palpable abdominal mass are the primary clinical manifestations of GIST, followed by gastrointestinal bleeding induced by the tumor or anemia.[7] GIST carries high recurrence rate to be 40%-80%, even after radical operation excision. It is also characterized by local invasion and metastases, usually to the liver

and peritoneum. However, cases of metastases to lymph nodes around are rare.

The diagnostic imaging of GIST. CT and MRI scanning are of great value in the diagnosis and treatment of GIST as they could precisely locate the lesion with high resolution and clear presentation of connection between tumor and adjacent tissue. The role of CT and MRI usually comes down to staging and determining whether the lesions found through other diagnostic modalities are suitable for excision and provides precise diagnostic imaging of the tumor for the surgery.[8] The typical CT performance of primary GIST lies in the fact that it is soft tissue mass with clear boundary and uneven density. It could grow both inside and outside the chamber, supplied by rich blood. Some GIST intratumoral hemorrhage and necrosis form large irregular liquefaction necrosis foci. Enhanced scan reveals the lesions to be inhomogeneous enhancement. Endoscopic ultrasound (EUS) displays the gastrointestinal wall structure, corresponding histology. The changes of these hierarchies carry high sensitivity and reliability in the diagnosis of gastrointestinal submucosal tumor. Doppler ultrasound examination of tumor blood supply, on the other hand, serves as a supporting role in treatment options and prognosis assessment.[9] EUS examination combined with fine needle aspiration (EUS-FNA) of gastric mucosa underlying tissue and immunohistochemistry is highly accurate in detecting GIST. Digital subtraction angiography embodies its strength in detecting GIST of small volume (< 3 cm). GIST is shown to be hyperplasia twisted blood vessels and tumor staining, tumor staining, round lesions with clear boundary. The contrast medium dispersed with a delay and showed rich blood vessels in tumor, the artery thickening, and large draining vein.[10]

2.2.3 Pathological and immunohistochemical diagnosis of GIST (see Figures 2,3)

A precise diagnosis of GIST is heavily depended on pathological characteristics and immunohistochemistry. The diameter of the tumor can range from 1 cm to more than 20 cm with distinct border, occasionally pseudocapsule, plane of tumor section is gray or gray-red. Sometimes, the second changes of mucoid degeneration or necrosis, hemorrhage, cystic degeneration, *etc* may occur in tumors of larger sizes. Endoscopic manifestations of GIST vary as the gross patterns are diverse. It can also be divided into histologic subgroups including: spindle cell and epithelioid variants. Therefore, it can be classified as spindle cell type (70%), epithelioid cell type (20%), spindle and epithelioid cell mixed type (10%). The clinical manifestation of spindle cell type includes: spindle shaped or rod-shaped, with the presence of sparse chromatin, vacuoles at the end of nuclear and obvious nucleolus, cytoplasmic slightly eosinophilic or basophilic. In addition to this, spindle cell has similar morphology with leiomyoma cells of other parts. The clinical manifestation of epithelial tumor cells includes: larger size, different forms, rounded, polygon or star-shaped, the cytoplasm was pale and the cytoplasm was obviously vacuole, the nucleus is round, the surrounded area forms the empty bright nucleus, the nucleus to the side is sickle shaped, forming signet ring cells. As for arrangement aspect, GIST tumor cells arranged in various structures, spindle tumor cells was bundle cross, swirling, fence-like, *etc*, while epithelioid tumor cells often has filled nest on a sheet or cord-like arrangement histology. Histologically, GIST is different from the real leiomyoma and leiomyosarcoma Schwann tumor, it is sometimes difficult to distinguish between the two, especially spindle cell GIST, based on HE form alone.[11, 12] CD117 is the most characteristic immune marker of GIST, whose positive rate of expression may be as high as 98% to 100%. Its advantage is of high specificity, not affected by histological type and parts of the occurrence. CD117, expression product of the proto-oncogene c-kit, should be distinguished from its role as normal gastrointestinal mast cells expression. CD34, another expression product of GIST, shows high expression. It is generally expressed in vascular endothelial cells and the tumor. Whose positive rate reaches 60%-70%.[13] CD34 may have expressed in many mesenchymal cells, while its diagnosis specificity and sensitivity are not prominent. When CD117 is positive, SMA together with S-100 is suggested for combined detection as supplementary reference. The diagnosis of GIST is confirmed when the clinical and histological features are consistent with GIST. KIT/CD117, therefore, plays in important role in establishing the diagnosis. CD117 is not expressed in all GIST. Studies have shown that,[14] a percentage of 35 could still be found by detecting c-kit and mutation on exons PDGFRA. Hence, many factors are imperative to ensure precise diagnosis. The best technology to detect gene mutation remains to be determined. Currently, the polymerase chain reaction (PCR) amplification and direct sequencing method are mostly employed for detecting c-kit and PDGFRA mutations.

Gastroscopy examination revealed that elevated lesions mass of 3.0 cm ×2.0 cm was visible near greater curvature of the gastric body, the central depression with erosion, the surrounding mucosa and gastric mucosal color were the same, a sense of volatility depression could be felt. Endoscopy reexamination showed that a bulge mass of 3.0 cm ×4.0 cm was visible at the posterior wall of greater curvature of the cardia, with irregular depression on top, surrounding mucosa bulged like a dam, covered by white fur mucus, biopsy of 5 block confirmed that tissue elasticity was poor, hard texture, soft touch of easy bleeding. Pathology demonstrated that (Gastric body) mucosa chronic inflammation, hyperplasia of fibrous tissueunder local mucosa. Abdominal CT exhibited that stomach cancer at the greater curvature was suspended, with left adrenal gland and left fourth intercostal transfer. The bumps were more likely to be gastrointestinal stromal tumors so that further immuno-

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histochemical examination is needed for a more accurate diagnosis.

2.3 Dr. Ridong Shi

Dr. Ridong Shi is a resident doctor of Gastroenterology Department at The Third Affiliated Hospital of Inner Mongolia Medical University, specializing in digestive disease.

The neoplasm should be distinguished from the following group of other gastrointestinal tract sarcomas: (1) The gastrointestinal leiomyoma/sarcoma: the expression of CD117 and CD34 in GIST is negative, expression of SMA is diffuse positive. (2) Gastrointestinal schwannomas: the expression of CD117 and CD34 in GIST is negative, expression of S-100 diffuse is positive, and S-100 is less expressed in GIST. (3) Gastrointestinal autonomic nerve tumor: neurosecretory granules are present under electron microscopecan. The expression of CD117, CD34, S-100 and SMA is negative.

2.4 Dr. Hong Cui

Dr. Hong Cui is the deputy director of Department of Internal Medicine at The Third Affiliated Hospital of Inner Mongolia Medical University, specializing in endoscopic diagnosis and treatment of digestive diseases.

Surgical excision is the primary treatment of choice. Professor Hassan *et al.*[15] discovered that more than half of GIST is likely to reoccur after complete resection of tumor, with survival rate in 5 years to be 50%. The complete surgical excision, in theory, is suggested to perform when lesions are confined to the tumor, maximum diameters to be 2 cm. The surgery is attainable for solitary recurrence or metastatic disease without affecting other organ's function after a thorough estimate of the surgery was made. It remains to be a feasible method for unresectable GIST when the tumor is shrunk by the molecular targeting therapy. En bloc tumor excision could be obtained in 70% of the first and non-metastatic GIST. Preventing tumor rupture and keeping complete capsule become particularly important during the surgery due to the fact that GIST tumors are of crumbly texture, often associated with hemorrhage and necrosis, inclined to grow in the abdominal cavity.[16,17] Although metastasis and local recurrence rate ranges from 50% to 60% among GIST patients, 24%-46% of the patients are suitable for the surgery.[18,19] Currently, there are less materials regarding the tumor whose size is less than 2 cm, unified the diagnosis and treatment, therefore, have yet to be determined. The following theory is suggested for reference: the extent of surgical trauma was required when the surgery trauma is not severe, with little effect on the relevant organ function.

Endoscopic technique pushes forward the development of minimally invasive surgery treatment for the disease. To locate the lesion, evaluate for signs of invasion, detect metastasis, demonstrate whether the surgery is available for the case,[20] for example, the tumor is less than 5 cm, distinct border in stomach or intestines without invasion or metastasis, before the operation are required.

Radiotherapy and chemotherapy. Radiotherapy used to be much preferred to the treatment of GIST. 10 cases of small intestinal GIST with metastasis treated with radiology are reported to reoccur, among which 6 cases of recurrence were outside radiation area.[21] The authors, therefore, concluded that six cases were under decentralized control by radiotherapy. Intraperitoneal perfusion chemotherapy is potential curative for the cases of peritoneal metastasis underwent palliative resection, postoperative peritoneal recurrence or metastasis. Intraperitoneal chemotherapy, however, neither poses effect on liver metastasis nor prolongs the survival time of patients. Malignant GIST metastases are mostly like to occur on liver. Surgery is feasible for a single lesion or multiple lesions but is still confined to the range. Tumor resection along the edge is advisable when the tumor is with clear boundary. Hepatic resection is referred on the condition that all the multiple metastases were confined to one leaf alone. Catheterization of hepatic artery and portal vein chemotherapy are used for unresectable liver metastases. The hepatic artery embolization is believed to be a more effective palliative treatment of all the therapies.[22] 14 cases of GIST with liver metastases were treated with hepatic arterial embolization with gelfoam and cisplatin powder, followed by the perfusion of vinorelbine, and received an average interventional therapy twice. 70% of the cases were reported to achieve partial remission (PR). Interventional treatment proves to have advantage over chemotherapy upon its continuous use for the following 10 months.[23]

Molecular targeting therapy. Combined with imatinib mesylate therapy. Radiotherapy has not historically been effective for GIST and GIST does not respond to most chemotherapy medications. The median survival period of GIST patients is only 18 to 24 months before molecular targeting therapy was introduced.[24] The tyrosine kinase inhibitor imatinib used in clinical treatment of GIST prolongs the survival period to be 4.8 years.[25]

3 Conclusion

GIST is a kind of submucosal lesion, whose imaging modalities in the evaluation of GISTs are CT and MRI, immunohistochemical investigation of CD117, CD34, endoscopic ultrasound and pathological examination. The majority of GIST tumors are cured by surgery, molecular targeting therapy is alternative method in need. Hemostatic theory is required when elderly patients are presented with abdominal discomfort and gastrointestinal hemorrhage. Endoscopy and CT examination are suggested to be undertaken when they are in stable condition, followed by pathological and immunochemical examination for early diagnosis, treatment and higher survival rate.

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