Synchronous occurrence of gastrointestinal stromal tumor and acute myeloid leukemia: A case report and review of the literature

NA GAO[1,2], NONG-JIAN GUO[1], WEN-ZHENG YU[2], XUE-XIA WANG[2], JIAN-RONG SUN[2], NING YU[3], REN-TONG LIU[2], XIAO-DAN LIU[2], ZENG-YAN LIU[2] and RUI FENG[2]

[1]Department of Hematology, Central Hospital of Jinan, Shandong University School of Medicine, Jinan, Shandong 250013; Departments of [2]Hematology and [3]Pathology, Binzhou Medical University Hospital, Binzhou, Shandong 256603, P.R. China

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Abstract. Gastrointestinal stromal tumors (GISTs) originate from the mesenchymal tissue of the gastrointestinal tract. The pathogenesis of GIST is associated with the mutational activation of the receptor tyrosine kinase cluster of differentiation (CD)117 or platelet-derived growth factor receptor-α. Overall, ~60% of GISTs occur in the stomach. Clinically, GISTs may coexist with various types of cancer, including liver cancer, pancreatic tumors and lymphoma, either synchronously or metachronously. The present study reports the case of a patient with the synchronous occurrence of a CD117-positive GIST and acute myeloid leukemia. A 69-year-old man was hospitalized for heart palpitations and dizziness, and was diagnosed with acute myeloid leukemia (AML) by bone marrow aspiration and flow cytometry analysis. An abdominal computed tomograpy and gastroscopy revealed the presence of GIST. The patient received chemotherapy in combination with imatinib (400 mg/day), and the mass was removed 2 months later. To the best of our knowledge, the present study is the first reported case of the synchronous development of a CD117-positive GIST and AML. Additional studies are required in order to understand the association between GIST and hematological malignancies.

Introduction

Gastrointestinal stromal tumors (GISTs) are common mesenchymal tumors of the gastrointestinal tract that are categorized as being borderline benign and malignant tumors (1). GISTs arise predominantly in the stomach (60%), small intestine (30%) and colorectum (10%) (2). Previous studies have elucidated that the majority of GISTs are caused by a mutation of the receptor tyrosine kinase KIT [also known as cluster of differentiation (CD)117] or platelet-derived growth factor receptor-α (PDGFRA) (3-5). Immunohistochemistry demonstrates that the majority of GISTs express CD117 (6). In addition, 60-80% of GISTs diffusely express CD34 (7).

The synchronous or metachronous coexistence of GISTs and other malignancies, including liver cancer, pancreatic tumors and lymphoma, has been extensively reported (8-10). However, to the best of our knowledge, only 1 case of the synchronous development of GIST and acute myeloid leukemia (AML) has been reported in the literature (11). The present study reports the case of a patient diagnosed by GIST and AML. To the best of our knowledge, the present study is the first to report the synchronous development of a CD117-positive GIST and AML in China.

Case report

A 69-year-old man was admitted to the Binzhou Medical University Hospital (Binzhou, Shandong, China) in November 2013 due to heart palpitations, dizziness and general fatigue that had lasted for 2 months. The patient had suffered from hypertension and diabetes mellitus for ~10 years. A physical examination on admission revealed that the patient had anemia. Neither multiple superficial lymphadenopathies nor hepatosplenomegaly were evident. Preliminary investigations revealed a hemoglobin level of 76 g/dl (normal range, 110-160 g/dl), platelet count of 237,000 platelets/μl (normal range, 100,000-300,000 platelets), white blood cell count of 32,400 cells/μl (normal range, 4,000-10,000 cells/μl) and myeloblast level of 10%. No abnormalities in the liver function or routine blood biochemical examination were evident. The results of the blood coagulation tests and urine analysis were not notable. The patient did not express the human immunodeficiency virus antibody.

Bone marrow aspiration revealed that blasts comprised 92.5% of the myeloid cells. The blasts were small in size and possessed pseudopodia and processes. Bone marrow biopsy

Correspondence to: Dr Na Gao, Department of Hematology, Central Hospital of Jinan, Shandong University School of Medicine, 44 Wenhua Xi Road, Jinan, Shandong 250013, P.R. China
E-mail: gn2882155@163.com

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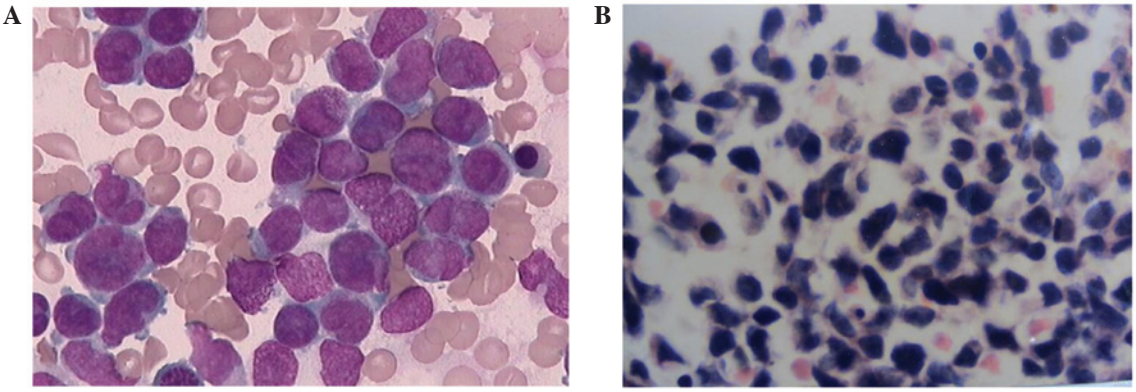

Figure 1. (A) Bone marrow aspiration (Wright-Giemsa staining; magnification, x1,000). (B) Bone marrow biopsy (hepatocyte growth factor staining; magnification, x400).

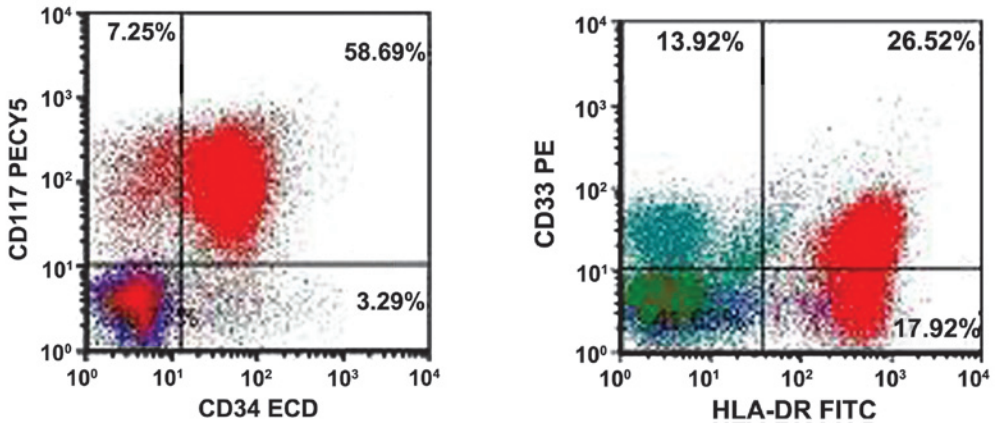

Figure 2. Flow cytometric analysis revealed that abnormal bone marrow cells expressed CD117, CD34, HLA-DR and CD33. The red signals indicate the abnormal cells. CD, cluster of differentiation; PECYS, phycoerythrin-cyanine 5; ECD, phycoerythrin-Texas Red conjugate; PE, phycoerythrin; HLA-DR, major histocompatibility complex, class II, DR; FITC, fluorescein isothiocyanate.

revealed that the patient had AML (Fig. 1). Flow cytometry analysis of the bone marrow revealed that the cellular characteristics were as follows: $CD34^+$; $CD117^+$; human leukocyte antigen-DR^+; and $CD33^+$ (Fig. 2). Cytogenetic analysis revealed an abnormal karyotype 47,XY,+8[2]/46,XY[18] (Fig. 3). The promyelocytic leukemia (PML)/retinoic acid receptor α and the AML/eight-twenty one fusion gene were not expressed. From the aforementioned data, a diagnosis of AML was eventually made.

A comprehensive physical examination of the patient was conducted prior to the implementation of chemotherapy. A computed tomography scan of the abdomen revealed a lesion measuring ~10x9x8 cm in size that was located in the lesser curvature of the stomach and was suspected to be a GIST (Fig. 4A). Gastroscopy revealed the presence of GISTs and bleeding in the digestive tract (Fig. 4B).

The patient received the CAG chemotherapy regimen (20 mg aclacinomycin, intravenous drip, days 1-4; 25 mg cytosine arabinoside, administered subcutaneously, days 1-14; 300 μg granulocyte-colony stimulating factor, administered subcutaneously, days 1-14) in combination with imatinib (400 mg, oral, days 1-14) to treat the AML, as the CAG scheme is the first choice of treatment for the elderly in China (12). The patient demonstrated complete remission following 2 courses of the Confidentiality Advisory Group scheme. In order to avoid a severe digestive tract massive hemorrhage, a subtotal gastrectomy was implemented and the patient recovered well from the procedure. The postoperative pathology suggested that the mass was a GIST lesion. The immunohistochemical staining revealed CD117, CD34 and discovered on GIST-1 (DOG1) expression, therefore also indicating that the lesion was a GIST (Fig. 5).

The patient was prescribed imatinib (400 mg, oral, continuous) for consolidation chemotherapy, and has regularly received blood routine and liver function tests. On the basis of the follow-up results, a reduction or temporary discontinuation of the chemotherapy may be decided in the future.

Discussion

GISTs account for the majority of gastrointestinal mesenchymal tumors, which are hypothesized to originate from the interstitial cells of Cajal (13). GISTs mainly occur in older patients and there is no significant difference in the incidence of GISTs between males and females (14). The malignant risk of a GIST may be determined based on the mitotic index, size and location of the lesion (15). Previous studies indicate that certain GISTs that are small in size and possess a low

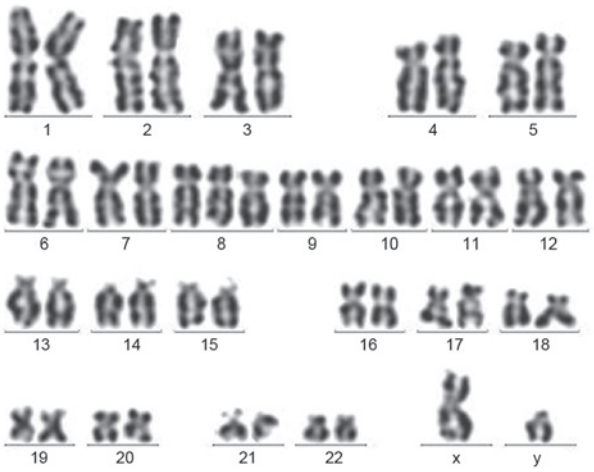

Figure 3. Cytogenetic analysis of bone marrow cells obtained from the patient revealed an abnormal karyotype of 47,XY,+8[2]/46,XY[18].

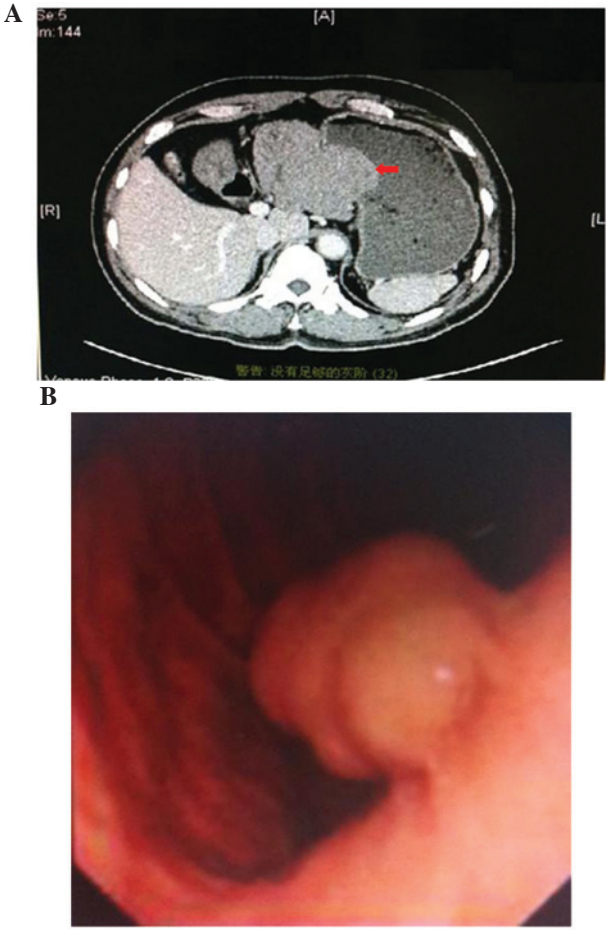

Figure 4. (A) Computed tomography revealed a giant mass (arrows) located in the lesser curvature of the stomach. (B) Macroscopic fingings of the gastroscopy revealed a giant mass.

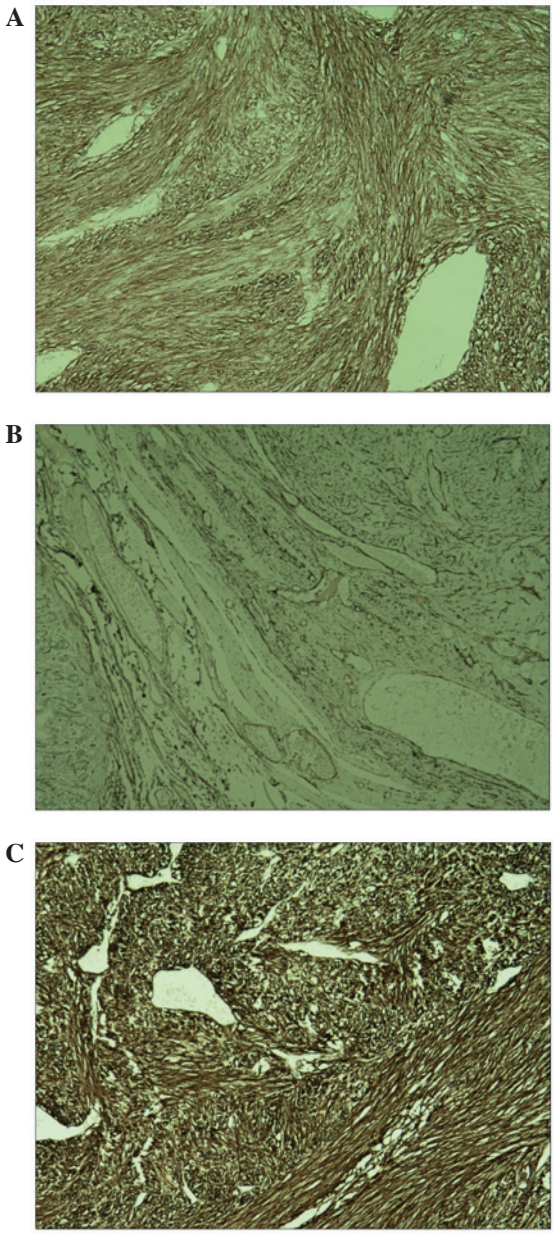

Figure 5. Immunohistochemical features revealed that the tumor expressed certain marker proteins: (A) Cluster of differentiation (CD)117, magnification, x10; (B) CD34, magnification, x4; and (C) discovered on GIST-1, magnification, x10.

mitotic index may adopt the features of metastasis; therefore, the concept of benign GISTs should be abandoned, as GISTs demonstrate malignant potential (16,17).

The coexistence of GISTs with other malignancies has been widely reported in the literature (10). However, the synchronous occurrence of GISTs and AML has rarely been reported. Yoshioka *et al* reported a case of acute PML that was diagnosed following a jejunal GIST (18). PML was considered to be the second malignancy in this study, and developed subsequent to chemotherapy or radiotherapy for GIST. In the present study, the case of a patient with synchronous occurrence of AML and GIST has been reported. To the best of our knowledge, the present study is the first to report the case of a patient that demonstrated the synchronous development of CD117-positive GIST and AML in China.

The pathogenesis of GISTs is hypothesized to be associated with the mutational activation of CD117 or PDGFRA (6). CD117, also termed KIT, has been highly conserved throughout evolution. Previous studies have indicated that the abnormal expression of genes and products caused by CD117 mutations is the major cause of GIST development (3,19-21). Imatinib

mesylate is important for the treatment of GIST, as it may alleviate symptoms, decrease post-surgery recurrence rates and prolong survival periods (1).

The immunohistochemical features of GISTs include the expression of CD117, which is widely expressed in the cytoplasm and cytomembrane of tumor cells (95%). CD117 is widely distributed in hematopoietic cells and other tissue cells. The detection of CD117 expression is an effective method to distinguish between GISTs and other mesenchymal tumors. CD117 is recognized as a highly sensitive and specific marker for GISTs, and is also an important pathogenetic factor in AML. Similarly to GISTs, hematopoietic progenitor cells are dependent on the CD117-signaling pathway, and numerous myeloid leukemias, including AML, with t(8,21) and inv(16) also have CD117-activating mutations. In the present study, t(8,21) was detected using conventional cytogenetic analysis. CD117 signaling is important for the regulation of red blood cell production, lymphocyte proliferation and mast cell development and function. Previous studies have demonstrated that CD117 is expressed in 68% of patients with AML and 80% of patients with chronic myelogenous leukemia in the blast phase, but in only 2% of patients with acute lymphoid leukemia (22). Additional studies indicate that AML patients demonstrating CD117 expression have lower complete remission rates and poorer prognoses compared with AML patients that do not express CD117 (23). Common types of CD117 receptor gene mutation include exon 9 (73%), exon 11 (10%), exon 13 (3%) and exon 17 (1%) (24). CD117 receptor gene mutations in exon 17 are closely associated with a poor prognosis. Therefore, the CD117 receptor is important for AML complete remission and recurrence. Stem cell factor, the ligand for CD117, is a hematopoietic cytokine that has been detected in GIST patients, and is important for maintaining the survival of hematopoietic cells, which may lead to myeloproliferation (25), differentiation and ultimately to the occurrence of leukemia. In addition, the primitive hematopoietic tissue differentiation antigen CD34 is diffusely expressed in 60-80% GISTs. CD117 and CD34 are important in GISTs and AML. In addition to CD117 and CD34, DOG1 is often expressed in GIST patients and is particularly important in the diagnosis of patients without CD117 expression.

The results of an epidemiological analysis in a previous study indicated a significant association between AML and GIST (26). This study indicated that AML developed 1.7-21.0 years subsequent to GIST (median interval, 6 years), and that the risk of AML was significantly higher for female patients with GIST compared to male patients with GIST. The frequency of this non-random association and the spectrum of neoplasms involved have not been sufficiently analyzed at present. The potential for a non-random and causal association between GIST and other neoplasms remains to be investigated.

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