A Case Report of Classical Gastrointestinal Stromal Tumor with an Undifferentiated Pleomorphic Sarcoma Component

YiFan Hu

Affiliated Hospital of North Sichuan Medical College <https://orcid.org/0000-0001-7069-451X>

SHUNHAI JIAN (✉ 2051084695@qq.com)

Affiliated Hospital of North Sichuan Medical College <https://orcid.org/0000-0002-5940-1365>

bin wen

Affiliated Hospital of North Sichuan Medical College

linli he

Affiliated Hospital of North Sichuan Medical College

yifan huang

Affiliated Hospital of North Sichuan Medical College

Case Report

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Abstract

Background: Gastrointestinal stromal tumor (GIST) is the most common primary mesenchymal neoplasm of the gastrointestinal tract.a small number of GIST patients showed morphologic and immunohistochemical phenotypes change after taking the selective tyrosine kinase inhibitor imatinib.

Case presentation :A 64-year-old Asian man was referred to a hospital for dizziness and anemia. Then the patient received imatinib for 11 months after the discovery of a gastric stromal tumor, and had the tumor surgically removed. We found that the classical GIST region was juxtaposed to a undifferentiated component of pleomorphic sarcoma. The genetic test results of the patient showed that the 11 exon of C-Kit gene was homozygous deletion, and the 567 codon of the 12 exon of PDGFR α was homozygous mutation. We infer that the patient showed rare dedifferentiation change after taking the tyrosine kinase inhibitors (TKIs) imatinib(IM).

Conclusions: Together with reported cases, awareness of this rare clinical entity and its potential occurrence following Tyrosine kinase inhibitor (TKI)treatment could prevent a diagnostic pitfall. The case report reminds us of the diagnosis in GIST that the possibility of dedifferentiation in GISTs should always be considered when an undifferentiated sarcoma component is identified in the gastrointestinal tract.

1. Background

Gastrointestinal stromal tumor is the most common mesenchymal tumor of the gastrointestinal tract. It originates from the gastrointestinal mesenchymal cells of Cajal and can occur in any part of the whole digestive tract, mainly in the stomach, small intestine, colorectal and esophagus.[1]Epidemiological studies show that the age of onset of gastrointestinal stromal tumors ranges from 66 to 69 years old, but 75% of patients with symptoms of GIST are over 50 years old. There is no obvious boundary between benign and malignant gastrointestinal stromal tumors, and the degree of benign and malignant is different .At present, the KIT gene and PDGFR α gene mutations in the patients with somatic cell is considered to be its main driving factors in the development of GISTs[2].

Clinically, a small number of GIST patients showed morphologic and immunohistochemical phenotypes alteration after taking the selective tyrosine kinase inhibitor imatinib, and the tumor underwent dedifferentiation process. The current reports include rhabdomyosarcoma, angiosarcoma and undifferentiated pleomorphic sarcoma. The dedifferentiated component, which is rarely seen in GISTs, is morphologically distinct from the classical GIST. The dedifferentiated component presents anaplastic/pleomorphic appearance,high nuclear atypia, high mitotic activity, and necrosis[3,4].The unusual histological and immunohistochemical characteristics of these tumors are challenging to diagnose. Therefore, pathologists must recognize GIST that has an abnormal shape and be aware of the process of dedifferentiation.

The most common symptoms of patients are bleeding, anemia, and abdominal pain. Other symptoms are also common, such as indigestion, nausea or vomiting, constipation, or diarrhea.[14,15,16]At first, our

patient was hospitalized for anemia. We report a patient who received imatinib for 11 months after the discovery of a gastric stromal tumor by biopsy firstly and then had the tumor surgically removed. In the excised tumor specimens, we found that the classical mixed epithelioid and spindle cell GIST region was accompanied by a undifferentiated component of pleomorphic sarcoma. The genetic test results of the patients showed that the 11 exon of C-Kit gene was homozygous deletion, and the 567 codon of the 12 exon of PDGFR was homozygous mutation.

2. Case Presentation

The patient is a 64 - year - old Asian man, he was admitted to a local hospital for dizziness and anemia the past year ,Computed tomography scan disclosed one large tumor at the bottom of the stomach (FIG1A,1B). Subsequently, the endoscopic biopsy was performed, and the pathological diagnosis was "Gastrointestinal stromal tumors". The little tumor tissue was positive for CD117 and Dog-1 by immunohistochemical (IHC) stains but negative for S100, SMA, Desmin, PCK, CK5/6, P63, P40, CK20 and CDX-2. Due to the large size of the tumor, the patient did not receive immediate surgical treatment, but began taking imatinib(400mg,qd), 11 months later, the patient was admitted to the local hospital for dizziness and fever, and then transferred to our hospital for further diagnosis and treatment. The outpatient diagnosis was "gastric stromal tumor with hemorrhage and anemia". Computed tomography scan disclosed the gastric wall of the fundus was significantly thickened, and a large mass with a size of 11.7cm×0.7cm was seen inside. The shape of the lesion was irregular, the edges of enhanced scanning were significantly enhanced, and large flaked areas of unenhanced liquefaction necrosis could be seen in the center (FIG2A,B). Then he underwent surgical treatment in our hospital, During the operation, the primary tumor was found to be located at the bottom of the stomach and grew out of the luminal cavity, involving the diaphragm and the tail of the pancreas. the gastric tumor, spleen and pancreas were removed, and the postoperative pathological diagnosis and genetic testing were performed. After the pathological diagnosis, imatinib administration was initiated (400 mg/d) at a few days after the operation, two months after the operation, the patient is alive with an outpatient status. At present, there are no serious postoperative complications.

2.1 Materials and methods

2.1.1 Immunohistochemical analysis

The surgical specimen was examined grossly and fixed in 10% neutral formalin. The representative specimen was embedded in paraffin and submitted for permanent histological examination. Four-micron thick hematoxylin and eosin (H&E) stained sections were prepared.

Immunohistochemical stains for CD117 (mouse monoclonal, Abcam), CD34 (mouse monoclonal, Ventana), DOG-1 (rabbit monoclonal, Ventana), smooth muscle actin (SMA) (clone 1A4, mouse

monoclonal, Ventana), CD68(mouse monoclonal[Abcam]),S-100[mouse monoclonal[Abcam]]and Ki-67(mouse monoclonal[Abcam]) were performed by an automated immunostainer .

2.1.2 Sequence analysis of the c-kit and PDGFR α gene

For mutational analysis,the paraffin-embedded sections of the patients' tumors were sent to guangzhou microread medical laboratory for detection of gene mutations associated with individualized treatment of tumors,the tissues examined included typical gastric stromal tumor and dedifferentiated pleomorphic sarcoma.The genomic DNA was extracted from paraffin-embedded sections of tumor tissue by using sureselect human all exon V6(Agilent,America),Genes (exons) analyzed include the following [Gene(exon)]:C-kit(9,11,13,17)and PDGFR α (12,18),The test was performed with the patient's informed consent.

2.2 Results

2.2.1 Histopathology and immunohistochemistry

The resection specimens showed that the tumor had separated from the gastric tissue. The size of the tumor was 15×11×4.5cm.The cut surface was grayish white and the local area was gray-red localized bleeding and necrosis can be seen on the incised surface.The tumor affected the spleen and pancreatic tissues. The gastric wall thickened to 1.1 cm immediately adjacent to the resection margin of esophagus, and the gastric mucosal surface at the thickening point is slightly rough. Microscopically, the tumor is composed of two distinct demarcated areas; one conventional GIST area and the other dedifferentiated area. The classic area consists mostly of epithelioid cells and spindle cells of uniform size, abundant cytoplasm, and rare nuclear pleomorphism. The tumor cells in classic GIST area was positive for CD117 (Fig. 3A),CD34 (Fig. 3B) and Dog-1(focally,Fig. 3C) by immunohistochemical (IHC) stains. In particular, the dedifferentiated pleomorphic sarcoma component was found locally in the tumor, abruptly adjacent to the classical GIST. These pleomorphic cells are of various sizes, with large, hyperchromatic nuclei and prominent nucleoli, among which are bizarre multinucleated giant cells[FIG,4). At higher magnification abnormal mitosis are easy to find. The undifferentiated pleomorphic sarcoma of the tumor was positive for SMA[not shown]but negative for CD117 (Fig. 5A), CD34(Fig5B), DOG-1 (Fig. 5C), desmin (not shown), CD68(not shown),andS-100[not shown]by IHC stains. Notably, there was a loss of CD117and CD34 expression in the undifferentiated component of the tumor.

The resected pancreas, spleen and adrenal gland were involved by the tumor cells, and the live tumor showed a highly cellular and aggressive growth pattern.

Additionally, sarcomatoid tumor cells had higher mitotic activity by immunostain for proliferative index Ki-67 compared to adjacent classic epithelioid GIST tumor cells[FIG6],indicating higher mitotic activity.

The resection margins were negative. After imatinib treatment, some areas of hyaline degeneration are seen in the tumor tissue (Fig. 7A).

2.2.2 Mutational status of the patient

We detected the exon 9/11/13/17 of c-kit and the exon 12/18 of PDGFR α gene, the patient's genetic test results showed that the exon 11 of c-kit gene was homozygous deficient [FIG8], and the codon 567 at the exon 12 of PDGFR α homozygous mutation [Pro567=CCA>CCG] [Fig9]. There was no gastric stromal tumor in the immediate family. C-kit gene mutation is related to the efficacy of targeted therapy with imatinib, this test detected the 11 exon deletion mutation of c-kit gene. Patients with this mutation were more sensitive to imatinib treatment than patients with 9 exon mutation, and the treatment effect was the best.

3. Discussion And Conclusions

We encountered a case of gastric stromal tumor involving other abdominal organs, including spleen, pancreas and adrenal gland. His pathological diagnosis was classic GIST with undifferentiated pleomorphic sarcoma. Generally speaking, KIT and PDGFRA mutations are mutually exclusive [13], but the patient's genetic test results showed that the exon 11 of c-kit gene was homozygous deficient, and the codon 567 at the exon 12 of PDGFR α was homozygous mutation. The exon 12 of PDGFR α is a synonymous variant. It is most likely a germline mutation. In this case, the significance of the mutation is unclear. The patient was given imatinib orally for 11 months (400mg, QD) prior to surgical treatment.

Until recently, dedifferentiated anaplastic variants of GISTs were mostly reported in patients who had received long-term treatment with the tyrosine kinase inhibitor imatinib mesylate [5,6,7]. As in our case, in all other reported cases of dedifferentiation transformation of GIST, the prevalence of KIT (exon 11) and PDGFR α activating mutations was preserved in each tumor's dedifferentiated component. However, KIT protein expression (CD117) was either completely lost or significantly reduced with transformation [7, 8]. In this case, after taking imatinib for 11 months, the resected specimen showed obvious degeneration of tumor tissue. Although the abrupt transition from CD117-positive classic GIST to CD117-negative undifferentiated pleomorphic sarcoma is striking, the underlying molecular mechanism remains uncertain. New dedifferentiated GISTs have only been reported in a handful of cases. It has been shown that dedifferentiation can occur through KIT-independent mechanisms with loss of KIT expression and altered morphology [9,10,11]. In addition to gross chromosomal rearrangements, potential alterations could include mutations and/or small insertions/deletions that disrupt the open reading frame of the KIT gene or the splicing and processing of the KIT mRNA. Additionally, mutations within the KIT promoter may prevent transcription of the gene, preventing KIT protein expression [12].

It is clinically significant to note that dedifferentiation mostly occurred in metastatic or recurrent lesions [5,7,10]. Antonescu et al. investigated the underlying molecular mechanism of tumor progression in three imatinib-resistant and five imatinib-naïve tumors. Molecular characterization of the tumors

showed that half of them had wild type KIT, PDGFRA, and BRAF genes in both conventional and dedifferentiated components in contrast to KIT-mutant GIST. These findings suggest that dedifferentiation can be triggered through alternative escape mechanisms besides activating mutations. Loss of a KIT gene copy due to haplo-insufficiency was found in the dedifferentiated components of the three KIT-negative imatinib-resistant GISTs. Two imatinib-resistant tumors showed co-existence of KIT mutations in exons 11 and 13[10] .

In this case, the patient's initial pathological diagnosis showed no dedifferentiated components, but it may also be caused by limited sampling. We prefer patients with dedifferentiation changes after imatinib administration, and the genetic changes are consistent with those reported in other cases. The mechanism of this change is still unclear. Related research shows that the dedifferentiation of GISTs can occur after a long time treatment with Imatinib and presents with different morphologies, or rhabdomyosarcoma, angiosarcoma, or undifferentiated pleomorphic sarcoma.

In summary, the case shows morphologic and immunophenotypic pleomorphic sarcoma dedifferentiation of a treatment refractory GIST ,with hyaline changes of tumor cells after IM therapy. Together with reported cases, awareness of this rare clinical entity and its potential occurrence following Tyrosine kinase inhibitor (TKI)treatment could prevent a diagnostic pitfall. The case report reminds us of the diagnosis in GIST that the possibility of dedifferentiation in GISTs should always be considered when an undifferentiated sarcoma component is identified in the gastrointestinal tract. Molecular analysis provides valuable information exploring tumor origin and tumor progression and may assist with optimal treatment strategies in the future.

Declarations

- **Ethics approval and consent to participate**

The article did not disclose any patient's personal privacy, and was written with the patient's informed consent, without any ethical issues.

- **Consent for publication**

No conflict of interest exists in the submission of this manuscript, and the manuscript is approved by all authors for publication.

- **Availability of data and materials**

Not applicable

- **Competing interests**

The authors declare that they have no competing interests

• Funding

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• Authors' contributions

Yifanhu analyzed and explained the patient's diagnosis, medical history and other relevant data, and was the main author of the paper. Shunhaijian, who conducted histological examinations of patient tissue, was a major contributor to the manuscript and provided guidance on editing and writing articles. All authors read and approve the final manuscript.

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Figures

Figure 1

Ct scan of gastrointestinal stromal tumors (GIST) before imatinib administration: A Ordinary scanning B enhanced scanning

Figure 2

2CT-scan of Gastrointestinal Stromal Tumor (GIST) Prior to Surgery: A enhanced scanning B Ordinary scanning

Figure 3

Microscopic view of gastric tumors A:Immunohistochemical staining for CD117.Proliferating Epithelioid cells were positive for CD117B:Immunohistochemical staining for CD34. Proliferating Epithelioid cells were positive for CD34,C:Immunohistochemical staining forDog-1. Proliferating Epithelioid cells were FOCALLY positive for Dog-1.

Figure 4

Microscopic view of resected tumor,Hematoxylin-eosin staining—the undifferentiated pleomorphic sarcoma component was found locally in the tumor, abruptly adjacent to the classical epithelioid GIST— These pleomorphic cells are of various sizes, with large, hyperchromatic nuclei and prominent nucleoli, among which are bizarre multinucleated giant cells.

Figure 5

Microscopic view of gastric tumor,A:Immunohistochemical staining for CD117,the undifferentiated component of the tumorwere negative for CD117,B:Immunohistochemical staining for CD34,the undifferentiated component of the tumorwere negative for CD34,C:Immunohistochemical staining for Dog-1,the undifferentiated component of the tumorwere negative for Dog-1.

Figure 6

Microscopic view of the undifferentiated component in the gastric tumor ,Immunohistochemical staining for Ki-67,the high proliferative activity of the components of an undifferentiated pleomorphic sarcoma is shown here.

Figure 7

Microscopic view of gastric tumor hyaline degeneration.

Figure 8

Result of sequencing analysis at exon 11 of the c-kit gene.

Figure 9

Result of sequencing analysis at exon 12 of PDGFRα

Supplementary Files

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