RESPONSE TO REVIEWERS' COMMENTS

August 12, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format.

Title: DOG1 is useful for diagnosis of KIT-negative gastrointestinal stromal tumor of stomach

Author: Takuya Wada, Satoshi Tanabe, Kenji Ishido, Katsuhiko Higuchi, Tohru Sasaki, Chikatoshi Katada, Mizutomo Azuma, Akira Naruke, Myunguchul Kim, Wasaburo Koizumi, Tetsuo Mikami

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4010

The manuscript has been revised in accordance with the suggestions of the reviewers:

1. The format has been updated

2. Revisions have been made as suggested by the reviewer.

(1) For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies .
If you believe that the language of your manuscript has reached or exceeded Grade A and would like to sign a guarantee. However, if we later find that the language of your manuscript has not reached GradeA, your paper will be rejected
Please highlight the changes made to the manuscript according to the peer-reviewers' comments
Response: We have had our manuscript edited by American Journal Experts (AJE).

(2) Please be accurate and consistent with gene and protein nomenclature. In some fields, for example, gene names are italicized and lowercase but protein names are non-italicized and capitalized. Please make any corrections needed to suit the convention used in your field of study and maintain consistency throughout the manuscript.
Response: We have made the following revisions: protein names are non-italicized and capitalized, gene names are italicized and lower case, except to *PDGFRA* gene.
(Page 4, line 13; Page 6, line 12; Page 7, line 22; Page 8, line 8)
Before: PDGFRA gene
Revised version: *PDGFRA* gene

(3) Please mark the citation in accordance with the format. E.g. intervention[1]. So are the followings

Response: We have made all revisions suggested.

4) Would you please provide the decomposable figure of Fiugres, whose parts are movable andwords can be edited .So please put the original picture as word or ppt format so that I can edit them easily

Reponse: We have revised Figure 3 and Figure 4 as suggested.

Minor point 1

(5) Peer reviewer; 02151749

This case report described that DOG1-staining could be a pathological diagnostic aid for c-Kit-negative GIST. The text was generally well-written. One minor concern is that little was described about the character of D842V PDGFA mutation found in the patient. Because the mutant form is resistant to imatinib similar to D816V c-Kit, this reviewer requests the authors to discuss a therapeutic option for this patient when recurrence is found. Minor point; 1. Page 6. Line 17. "A useful antibody" should be a useful molecule. 2. Figures 3 and 4 require high resolution images.

Response: We have added ""Because the exon18 (D842V) mutation of *PDGFRA* gene is resistant to imatinib, sunitinib is prescribed when recurrence is found [13,14]." as follows (Page 8, lines 4-10)

Before:

In our patient, pathological examination of the surgically resected specimen showed a mixed-type GIST including epithelioid cells. Immunostaining was negative for both KIT and CD34, but was positive for DOG1. Consistent with these findings, a mutation was found in exon 18 (D842V) of the *PDGFRA* gene, with no mutation in the c-kit gene.

Revised version:

In our patient, pathological examination of the surgically resected specimen showed a mixed-type GIST including epithelioid cells. Immunostaining was negative for both KIT and CD34, but was positive for DOG1. Consistent with these findings, a mutation was found in exon 18 (D842V) of the *PDGFRA* gene, with no mutation in the c-kit gene. Because the exon18 (D842V) mutation of the *PDGFRA* gene is resistant to imatinib, sunitinib is prescribed when recurrence is found [13,14].

Minor point 2

"A useful antibody" should be a useful molecule (Page 6, Line 17.)

Response: We have revised the sentence as follows (Page 7, line 16):

Before: Recently, DOG1 has received considerable attention as a useful antibody for the diagnosis of GIST [2].

Revised version: Recently, DOG1 has received considerable attention as a useful molecule for the diagnosis of GIST [2].

Minor point 3

Figures 3 and 4 require high resolution images.

Response: We have changed Figure 3 and Figure 4 images to high-resolution images.

(6)Peer reviewer 02537158
The manuscript "KIT-negative GIST of stomach in which DOG1 staining was useful for diagnosis" by Wada et al. describes a characterization of a c-kit negative GIST of stomach presenting a positive staining for DOG1, which was useful for the final diagnosis. The manuscript is interesting for those of the field and has good results for the clinical area. However, some minor points should be revised before the manuscript is considered accept for publication, such as a more "scientific" style.
The title should be more concise for the readers.

In several parts of the text, few modifications in the written style should be performed, especially on the abstract (the first phrase should be re-written). A good english review should also be performed.
In conclusion, I believe that the manuscript has a great potential for publication after the written style improvement.

Minor point 1
The title should be more concise for the readers.
Response: We have revised the title as follows (Page 1, line 4):
Before:
KIT-negative GIST of stomach in which DOG1 staining was useful for diagnosis

Wada T, *et al.* KIT-negative GIST diagnosed on DOG1.

Takuya Wada, Satoshi Tanabe, Kenji Ishido, Katsuhiko Higuchi, Tohru Sasaki, Chikatoshi Katada, Mizutomo Azuma, Akira Naruke, Myunguchul Kim, Wasaburo Koizumi, Tetsuo Mikami

Revised version:
DOG1 is useful for diagnosis of KIT-negative gastrointestinal stromal tumor of the stomach

Wada T, *et al.* DOG1 is useful for KIT-negative GIST.

Takuya Wada, Satoshi Tanabe, Kenji Ishido, Katsuhiko Higuchi, Tohru Sasaki, Chikatoshi Katada, Mizutomo Azuma, Akira Naruke, Myunguchul Kim, Wasaburo Koizumi, Tetsuo Mikami

Minor point 2:
In several parts of the text, few modifications in the written style should be performed, especially on the abstract (the first phrase should be re-written).

Response: We have revised the Abstract as follows (Page 3, Abstract):

Before:
Abstract
A 60-year-old man presented to our hospital because of severe anemia, the hemoglobin level 3.6 g/dL. Upper gastrointestinal endoscopy revealed a submucosal tumor accompanied by an ulcer, arising in the anterior wall of the gastric antrum. Endoscopic

ultrasonography showed a homogeneous, hypoechoic mass, about 4 cm in diameter, which arose from the fourth layer of the gastric wall. A distal gastrectomy was performed. On pathological examination, the tumor measured 45 mm in diameter and was characterized by 1 mitosis per 50 high-power fields, diffuse proliferations of spindle cells, and epithelioid cells. Immunohistochemical staining was negative for KIT, CD34, and smooth muscle actin, but was positive for discovered on GIST-1 (DOG1), a membrane channel protein. Genetic analysis showed mutation in exon 18 (D842V) of the platelet-derived growth factor receptor alpha (*PDGFRA*) gene. As of 3 years after surgery, the patient is being followed up and remains free of metastasis and recurrence.

Revised version:

Abstract

About 80% to 95% of gastrointestinal stromal tumors (GISTs) show positive staining for KIT, while the other 5% to 20% show negative staining. If the tumor is negative for KIT, but is positive for CD34, a histological diagnosis is possible. However, if the tumor is negative for KIT, CD34, S-100, and SMA, a definitive diagnosis is often challenging. Recently, DOG1 has received considerable attention as a useful molecule for the diagnosis of GIST. DOG1, a membrane channel protein, is known to be overexpressed in GIST. Because the sensitivity and specificity of DOG1 are higher than those of KIT, positive staining for DOG1 has been reported even in KIT-negative GIST. KIT-negative GISTs most commonly arise in the stomach and are mainly characterized by epithelioid features histologically. We described our experience with a rare case of KIT-negative GIST of the stomach that was diagnosed on positive immunohistochemical staining for DOG1 in a patient who presented with severe anemia. Our findings suggest that immunohistochemical staining for DOG1 in addition to gene analysis is useful for the diagnosis of KIT-negative tumors suspected to be GIST.

(7) We have revised the figure legend (Page 17, line 9) as follows:

Before:
Figure Legends
Figure 3 D: Vimentin staining (×100)
Vimentin staining was negative

Revised version:
Figure 3 D: Vimentin staining (×100)
Vimentin staining was positive.

(8) We have revised the Introduction as follows (Introduction, lines 1-5):

Before:

Gastrointestinal stromal tumor (GIST) is a mesenchymal tumor derived from the mesoderm that arises in the gastrointestinal tract. The estimated incidence is 2 cases per 100,000 persons per year. The most common age at diagnosis is 50 to 60 years. GIST is thought to arise from interstitial cells of Cajal surrounding the autonomic nerves of Auerbach's plexus, which has a role in gastrointestinal peristalsis. KIT protein is characteristically expressed on immunohistochemical staining.

Revised version:

Gastrointestinal stromal tumor (GIST) is a mesenchymal tumor derived from the mesoderm that arises in the gastrointestinal tract. The estimated incidence is 2 cases per 100,000 persons per year. The most common age at diagnosis is 50 to 60 years. KIT protein is characteristically expressed on immunohistochemical staining.

(9) We have revised the word as follows: (Core tip, Page 4 line 2, line 4)

Before: immunochemical staining

Revised version: immunohistochemical staining

3 References and typesetting were corrected

Thank you again for considering our manuscript for publication in the *World Journal of*

Gastroenterology.

Sincerely yours,

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Name of journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4010

Columns: Case Report

DOG1 is useful for diagnosis of KIT-negative gastrointestinal stromal tumor of stomach

Takuya Wada, Satoshi Tanabe, Kenji Ishido, Katsuhiko Higuchi, Tohru Sasaki, Chikatoshi Katada, Mizutomo Azuma, Akira Naruke, Myunguchul Kim, Wasaburo Koizumi, Tetsuo Mikami

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Author contributions: Wada T, Tanabe S, and Ishido K designed and wrote the paper; Higuchi K, Sasaki T, Katada C, Azuma M, Naruke A, Kim M, and Koizumi W performed image diagnosis; and Mikami T performed pathological examinations.

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Abstract

About 80% to 95% of gastrointestinal stromal tumors (GISTs) show positive staining for KIT, while the other 5% to 20% show negative staining. If the tumor is negative for KIT, but is positive for CD34, a histological diagnosis is possible. However, if the tumor is negative for KIT, CD34, S-100, and SMA, a definitive diagnosis is often challenging. Recently, DOG1 has received considerable attention as a useful molecule for the diagnosis of GIST. DOG1, a membrane channel protein, is known to be overexpressed in GIST. Because the sensitivity and specificity of DOG1 are higher than those of KIT, positive staining for DOG1 has been reported even in KIT-negative GIST. KIT-negative GISTs most commonly arise in the stomach and are mainly characterized by epithelioid features histologically. We described our experience with a rare case of KIT-negative GIST of the stomach that was diagnosed on positive immunohistochemical staining for DOG1 in a patient who presented with severe anemia. Our findings suggest that immunohistochemical staining for DOG1 in addition to gene analysis is useful for the diagnosis of KIT-negative tumors suspected to be GIST.

Keywords: KIT negative, gastrointestinal stromal tumors, DOG1, and PDGFRA

Core tip:

We described our experience with a rare case of KIT-negative GIST of the stomach that was diagnosed on positive immunohistochemical staining for DOG1 in a patient who presented with severe anemia. Our findings suggest that immunohistochemical staining for DOG1 in addition to gene analysis is useful for the diagnosis of KIT-negative tumors suspected to be GIST.

Wada T, Tanabe S, Ishido K, Higuchi K, Sasaki T, Katada C, Azuma M, Naruke A, Kim M, Koizumi W, Mikami T. DOG1 is useful for diagnosis of KIT-negative gastrointestinal stromal tumor of the stomach.

World Journal of Gastroenterology 2013

Introduction

Gastrointestinal stromal tumor (GIST) is a mesenchymal tumor derived from the mesoderm that arises in the gastrointestinal tract. The estimated incidence is 2 cases per 100,000 persons per year. The most common age at diagnosis is 50 to 60 years. KIT protein is characteristically expressed on immunohistochemical staining. Gain-of-function mutations of the *c-kit* gene (about 90%) or the platelet-derived growth factor receptor alpha (*PDGFRA*) gene (about 5%) are the major cause of GISTs [1]. Immunohistochemical staining and gene analysis are considered useful for diagnosis, but if the tumor is negative for KIT, CD34, S-100, and SMA, a definitive diagnosis is often challenging. We describe our experience with a patient in whom immunohistochemical staining for discovered on GIST-1 (DOG1) enabled the diagnosis of a KIT-negative GIST [2].

Case patient

A 60-year-old man was referred to the Department of Gastroenterology of our hospital because of wooziness, shortness of breath on effort, and tarry stools. A blood test showed that the hemoglobin level was 3.6 g/dL, indicating severe anemia. Upper gastrointestinal endoscopy disclosed a submucosal tumor accompanied by an ulcer with an adherent clot, arising in the superior portion of the anterior wall of the gastric antrum (Fig. 1). Endoscopic ultrasonography (EUS) revealed a well-demarcated, homogeneous hypoechoic mass with a flat border. The mass was about 4 cm in diameter and arose from the fourth layer of the gastric wall (Fig. 2). Endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNAB) [3,4] was performed to obtain a definitive diagnosis and showed aggregations of cells with spindle-like or polygonal nuclei. However, immunohistochemical staining was negative for KIT, CD34, S-100, and smooth muscle

actin (SMA). A gastrointestinal stromal tumor (GIST) was strongly suspected, but a definite diagnosis was not reached. Gene analysis could not be performed because the tissue sample was too small. However, the patient had a symptomatic, submucosal tumor, with no distinct evidence of distant metastasis or direct invasion on enhanced computed tomography of the chest and abdomen. Surgery was therefore indicated according to the clinical practice guidelines for GIST in Japan [5], and a distal gastrectomy was performed. On macroscopic examination, the surgically resected specimen showed no evidence of bleeding or necrosis. The tumor measured 45 mm in diameter, and the resection margins were tumor negative. Histopathological examination showed that the tumor consisted of mixed components, including diffuse proliferations of spindle cells with eosinophilic cytoplasm as well as epithelioid cells in some regions. One mitosis was found per 50 high-power fields, and the MIB-1 index was 3%. Immunohistochemical staining was negative for KIT, CD34, S-100, and SMA, but was positive for vimentin and DOG1, a membrane channel protein (Fig. 3). The tissue specimen obtained by EUS-FNA also stained positively for DOG1 (Fig. 4). Genetic analysis showed a mutation in exon 18 (D842V) of the platelet-derived growth factor receptor alpha (*PDGFRA*) gene, with no mutation in the c-kit gene. On the basis of these results, a KIT-negative GIST with low risk according to Fletcher's classification [6] and very low risk according to Miettinen's classification was diagnosed [7]. The patient recovered uneventfully after surgery. As of 3 years after surgery, the patient is being followed-up on an outpatient basis and remains free of metastasis and recurrence.

Discussion

GIST is a mesenchymal tumor of the mesoderm arising from the interstitial cells of

Cajal in the gastrointestinal tract. The most common site is the stomach (60%), followed by the small intestine (30%), duodenum (5%), and large intestine (4%) [8]. GIST can be associated with diverse clinical symptoms, such as gastrointestinal bleeding, abdominal pain, and tumor obstruction. Histopathologically, GIST can be classified into 3 categories: spindle-cell type, epithelioid-cell type, and mixed type. Epithelioid-cell type accounts for about 70% of all GISTs, epithelioid-cell type for about 20%, and mixed type, as was found in our patient, for about 10% [8].

At present, specific tumor markers for the diagnosis of GIST are unavailable. A definite diagnosis is established by immunostaining tissue specimens obtained by EUS-FNAB or at surgery for KIT, CD34, SMA, desmin, S-100, and Ki-67 [4,6]. About 80% to 95% of GISTs show positive staining for KIT, while the other 5% to 20% show negative staining. If the tumor is negative for KIT, but is positive for CD34, a histological diagnosis is possible, but if the tumor is negative for KIT, CD34, S-100, and SMA, similar to our patient, a definitive diagnosis is often challenging.

Recently, DOG1 has received considerable attention as a useful molecule for the diagnosis of GIST [2]. DOG1, a membrane channel protein, is known to be overexpressed in GIST. Because the sensitivity and specificity of DOG1 are higher than those of KIT, positive staining for DOG1 has been reported even in KIT-negative GIST [9-11]. KIT-negative GISTs most commonly arise in the stomach and are mainly characterized by epithelioid features histologically. KIT-negative GISTs are often associated with *PDGFRA* gene mutations [8]. Rizzardi et al. genetically analyzed a DOG1-positive, KIT-negative GIST of the stomach and reported the presence of a deletion in exon 14 of the *PDGFRA* gene, with no mutation in the c-kit gene [12].

In our patient, pathological examination of the surgically resected specimen

showed a mixed-type GIST including epithelioid cells. Immunostaining was negative for both KIT and CD34, but was positive for DOG1. Consistent with these findings, a mutation was found in exon 18 (D842V) of the *PDGFRA* gene, with no mutation in the c-kit gene. Because the exon18 (D842V) mutation of the *PDGFRA* gene is resistant to imatinib, sunitinib is prescribed when recurrence is found [13,14].

In histological specimens obtained by EUS-FNAB before surgery, immunostaining was negative for KIT. A definite diagnosis could not be made. Immunohistochemical staining for DOG1 was additionally performed and showed that the cytoplasm of the tumor cells was positively stained. Hwang et al. reported that DOG1 was a useful marker for the cytologic diagnosis of GIST in tissue specimens obtained by EUS-FNAB [15]. However, one study reported that about 30% of KIT-negative GISTs are negative for DOG1, suggesting that tumors suspected to be GIST should be comprehensively evaluated, including analysis of other genes [10].

We described our experience with a rare case of KIT-negative GIST of the stomach that was diagnosed on positive immunostaining for DOG1 in a patient who presented with severe anemia. Our findings suggest that immunostaining for DOG1 in addition to gene analysis is useful for the diagnosis of KIT-negative tumors suspected to be GIST.

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Figure Legends

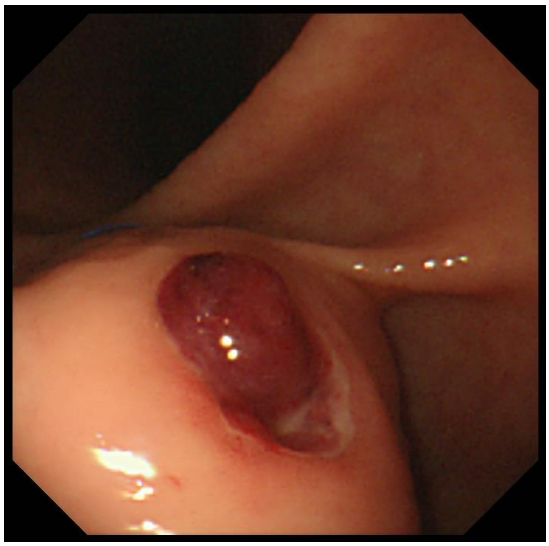

Figure 1 Findings on upper gastrointestinal endoscopy.

A submucosal tumor accompanied by an ulcer with an adherent clot was found in the superior portion of the anterior wall of the gastric antrum.

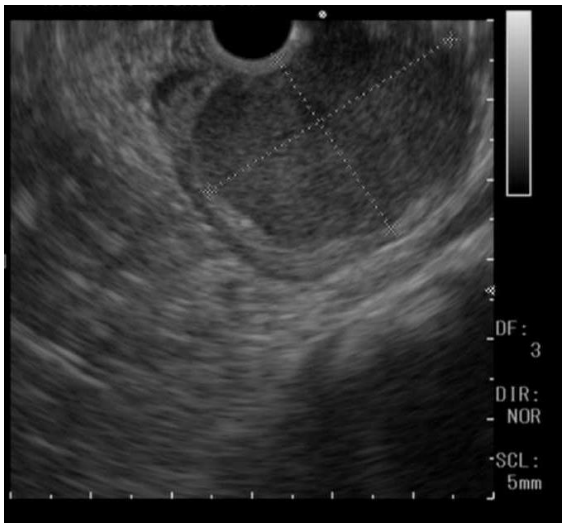

Figure 2 Findings on upper endoscopic ultrasonography.

A homogeneous, hypoechoic, well-demarcated mass, about 4 cm in diameter with a flat border, arose from the fourth layer of the gastric wall.

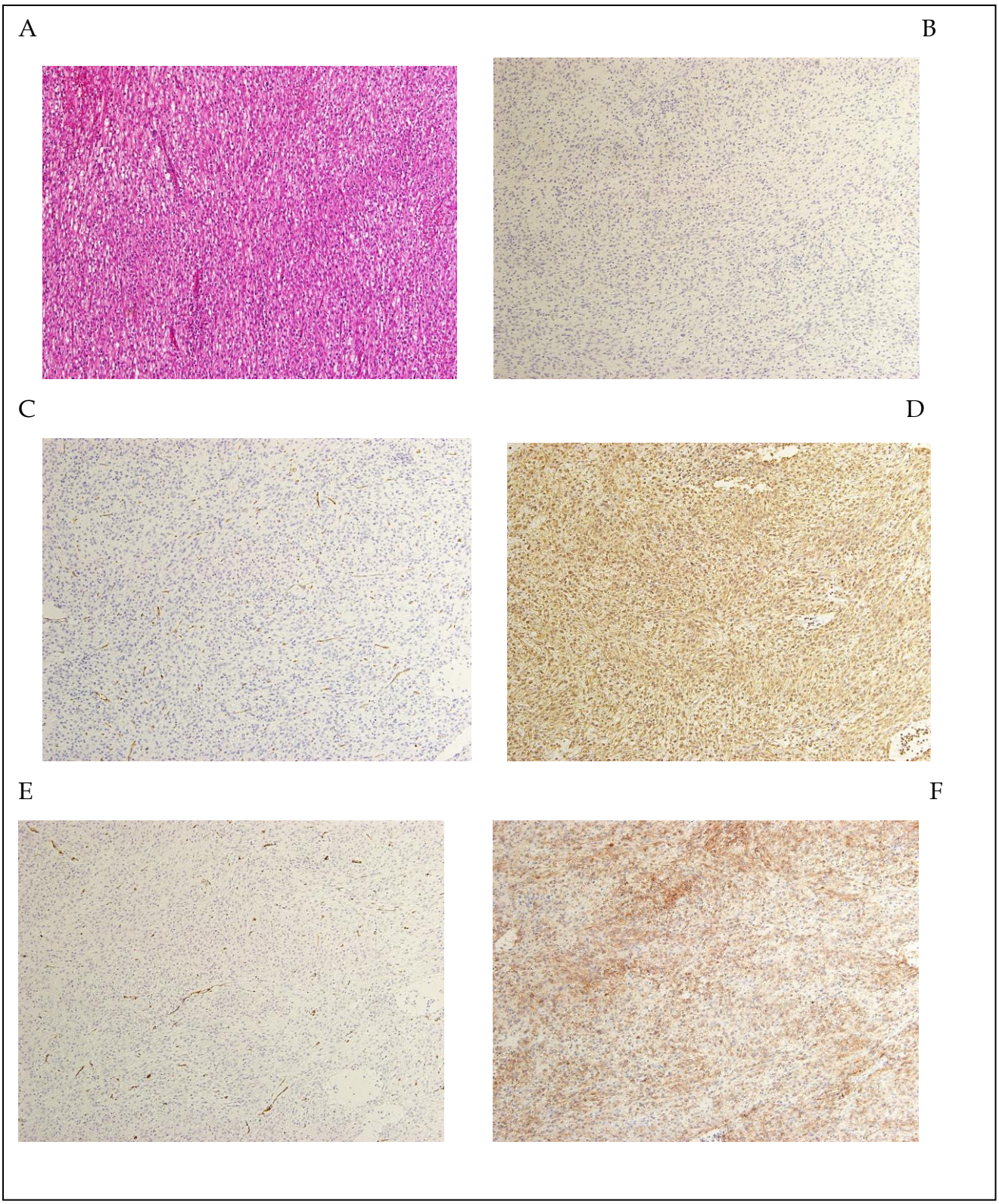

Figure 3 Histopathological findings of the surgically resected specimen.

A: Hematoxylin and eosin staining (×100)

The tumor consisted of mixed components, including spindle cells with eosinophilic cytoplasm as well as epithelioid cells in some regions.

B: KIT staining (×100)

KIT staining was negative.

C: CD34 staining (×100)

CD34 staining was negative.

D: Vimentin staining (×100)

Vimentin staining was positive.

E: Smooth muscle actin (SMA) staining (×100)

SMA staining was negative.

F: DOG1 staining (×100)

Immunostaining for DOG1 was positive mainly in the cell membrane and cytoplasm.

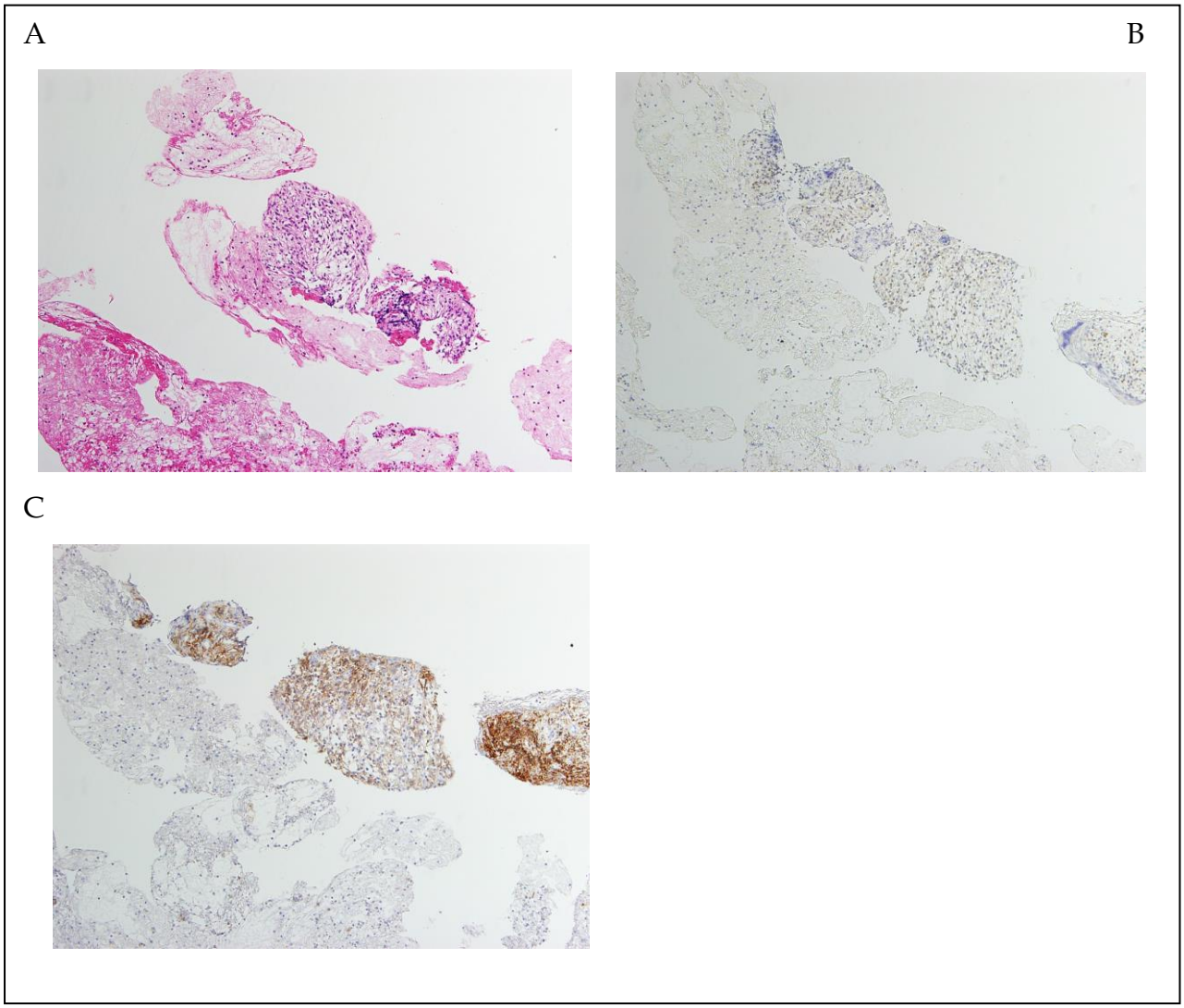

Figure 4 Histopathological findings (specimen obtained by EUS-FNAB)

A: Hematoxylin and eosin staining (×100)

The tumor consisted of mixed components, consisting of spindle cells with eosinophilic cytoplasm as well as cells with epithelioid features in some regions.

B: KIT staining (×100)

KIT staining was negative.

C: DOG1 staining (×100)

Immunostaining for DOG1 was positive mainly in the cell membrane and cytoplasm.