

CASE REPORT

Vasculogenic mimicry in gastrointestinal stromal tumor of the stomach: A case report

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ABSTRACT

Here we report a case of gastrointestinal stromal tumor of the stomach showing vasculogenic mimicry phenotype. A well-demarcated nodule, measuring 5 cm in diameter, was found incidentally in the stomach of a 66-year-old Japanese man. The tumor consisted of a dense proliferation of fairly uniform spindle cells with a prominent nuclear palisading pattern. Immunohistochemically, tumor cells showed strong positivity for KIT (CD117) and CD34. In an extensive area of the tumor, we found periodic acid-Schiff-positive patterned pseudo-vascular channels filled with a large amount of red blood cells. The interior surface of these structures was directly lined by tumor cells but not CD31-positive vascular endothelial cells. In addition, tumor cells showed a vascular phenotype, expressing vascular endothelial growth factor and vascular endothelial-cadherin. We also observed elevated expression of retinoic acid-metabolizing enzyme CYP26A1, which has been shown to have an oncogenic function in carcinogenesis. Since vasculogenic mimicry results from the ability of tumor cell plasticity, our observations suggest an unidentified insight into neoplasia of a gastrointestinal stromal tumor.

Key Words: Vasculogenic mimicry, Vascular endothelial cell, Gastrointestinal stromal tumor, Stomach, Retinoic acid-metabolizing enzyme CYP26A1

1. INTRODUCTION

Much attention has been paid to the role of angiogenesis during cancer progression. In this context, neoplastic cells are able to show vasculogenic mimicry.^[1,2] This is defined as a condition in which aggressive tumor cells can *de novo* generate their own network of fluid-conducting pseudo-vascular spaces. The vasculogenic mimicry phenotype facilitates tumor perfusion without the participation of angiogenesis, due to the ability of cancer cell plasticity. Immunohistochemical and electron microscopic examinations have provided evidence of the absence of vascular endothelial cells in the

interface between tumor cells and blood perfusion.^[3] In addition, vasculogenic mimicry has been observed in various malignancies, including carcinomas arising in the gastrointestinal tract, breast, prostate, and ovary, as well as melanoma and soft tissue sarcomas.^[1-5]

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract, and it spans a clinical spectrum from benign to malignant.^[6] Only one report has shown that vasculogenic mimicry was observed in 21 (25%) of 84 GIST cases, but morphological features were not described.^[7] In this article, we present

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the histology of GIST showing the vasculogenic mimicry phenotype.

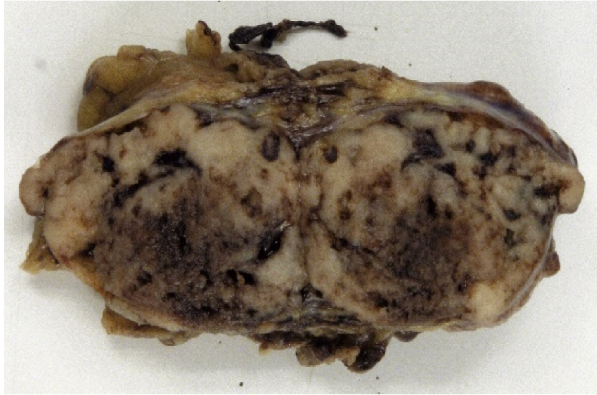


Figure 1. Gross appearance of the gastric nodule. The cut-surface was solid but was heterogeneous in color. Bar, 1 cm.

2. CASE PRESENTATION

The patient was an asymptomatic 66-year-old Japanese man. During a routine thorough medical examination, a well-demarcated nodule was identified in his stomach by ultrasonographic and computed tomographic examinations. He underwent laparoscopy-assisted partial gastrectomy.

The tumor was an encapsulated and well-circumscribed, solid and round nodular lesion, measuring 5 cm in diameter. On sectioning, the cut-surface was heterogeneous, showing colors from yellowish to black (see Figure 1).

Light microscopic examination showed that the tumor consisted of a dense proliferation of monotonous spindle cells with a prominent nuclear palisading pattern (see Figure 2A-B). There was no evident atypia or pleomorphism of tumor cells, and there was no distinct evidence of hemorrhage, necrosis, or high mitotic activity (< 2 mitoses per 50× arbitrary high-power fields and Ki-67 labelling index < 5% in this case). Immunohistochemically, tumor cells showed diffuse strong positivity for KIT (CD117), CD34, and vimentin in their cytoplasm, but were negative for smooth muscle actin, desmin, and S100 protein (see Figure 3A). Based on the tumor size and mitotic activity, the tumor in this case was clinically graded according to the Modified Fletcher Classification system as “low risk group” GIST.^[8]

In an extensive area of the tumor, we found periodic acid-Schiff (PAS)-positive patterned vascular-like channels filled with a large amount of red blood cells (see Figure 2C-F). The interior surface of the channels was directly lined by tumor cells, but there were not CD31- or Factor VIII (von Willebrand factor)-positive vascular endothelial cells (see Figure 3B-C). We defined vasculogenic mimicry as tumor cell-

surrounded channels in which erythrocytes are abundantly present, and we required criteria of both CD31-negative and PAS-positive vascular-like patterns. Since red blood cells may on occasion be found in lymphatic blood vessels (lymphangiogenesis) that could also be CD31-negative, instead of vasculogenic mimicry. However, we verified the absence of D2-40-positive lymphatic endothelial cells in the interface between tumor cells and blood perfusion (data not shown). Therefore, we confirmed patterned channels of this case as vasculogenic mimicry. Consistently, tumor cells showed a vascular phenotype with expression of vascular endothelial growth factor (VEGF) and vascular endothelial (VE)-cadherin (see Figure 3D-E). We also observed elevated expression of retinoic acid (RA)-metabolizing enzyme CYP26A1, which has been shown to be a possible candidate oncogene in carcinogenesis (see Figure 3F).^[9]

3. DISCUSSION

Accumulated evidence has demonstrated that most GIST samples ($\geq 90\%$) contain *KIT*- or *PDGFRA* (platelet-derived growth factor receptor alpha)-activating mutations.^[10,11] Here we observed elevated CYP26A1 expression in a GIST case showing the vasculogenic mimicry phenotype. It is generally accepted that vasculogenic mimicry is found in high-grade malignancies with aggressive characteristics, and it has a potent prognostic significance.^[1-5] In addition, CYP26A1 has been shown to promote oncogenic behavior of carcinoma cells, implicating *CYP26A1* as a possible candidate oncogene.^[9] Thus, the data suggest that CYP26A1 can promote tumorigenicity of a GIST, potentially increasing the clinical risk category of the tumor. In corollary, CYP26A1-mediated upregulation of *KIT* is likely to be involved in the development of a GIST. This explanation is supported by published data, showing that RA suppresses *KIT* expression and its activity in GIST cells.^[12]

Vasculogenic mimicry is a genetically regulated process that is played by dysregulated neoplastic cells having a pluripotent embryonic stem cell-like feature.^[1] This phenomenon provides a new blood-supplying model in cancer, and it is distinctive characteristic from that controlled by angiogenesis. In contrast, our observations are consistent with data, revealing that a large number of genes differentially expressed in a tumor showing vasculogenic mimicry are implicated in angiogenesis, including *VEGF* and *Cadherin 5*, which encode VEGF and VE-cadherin, respectively.^[13] Given that CYP26A1 modulates the expression of a wide variety of genes, including *VEGF*, it is not surprising that CYP26A1 potentially contributes to acquisition of the vasculogenic mimicry phenotype.

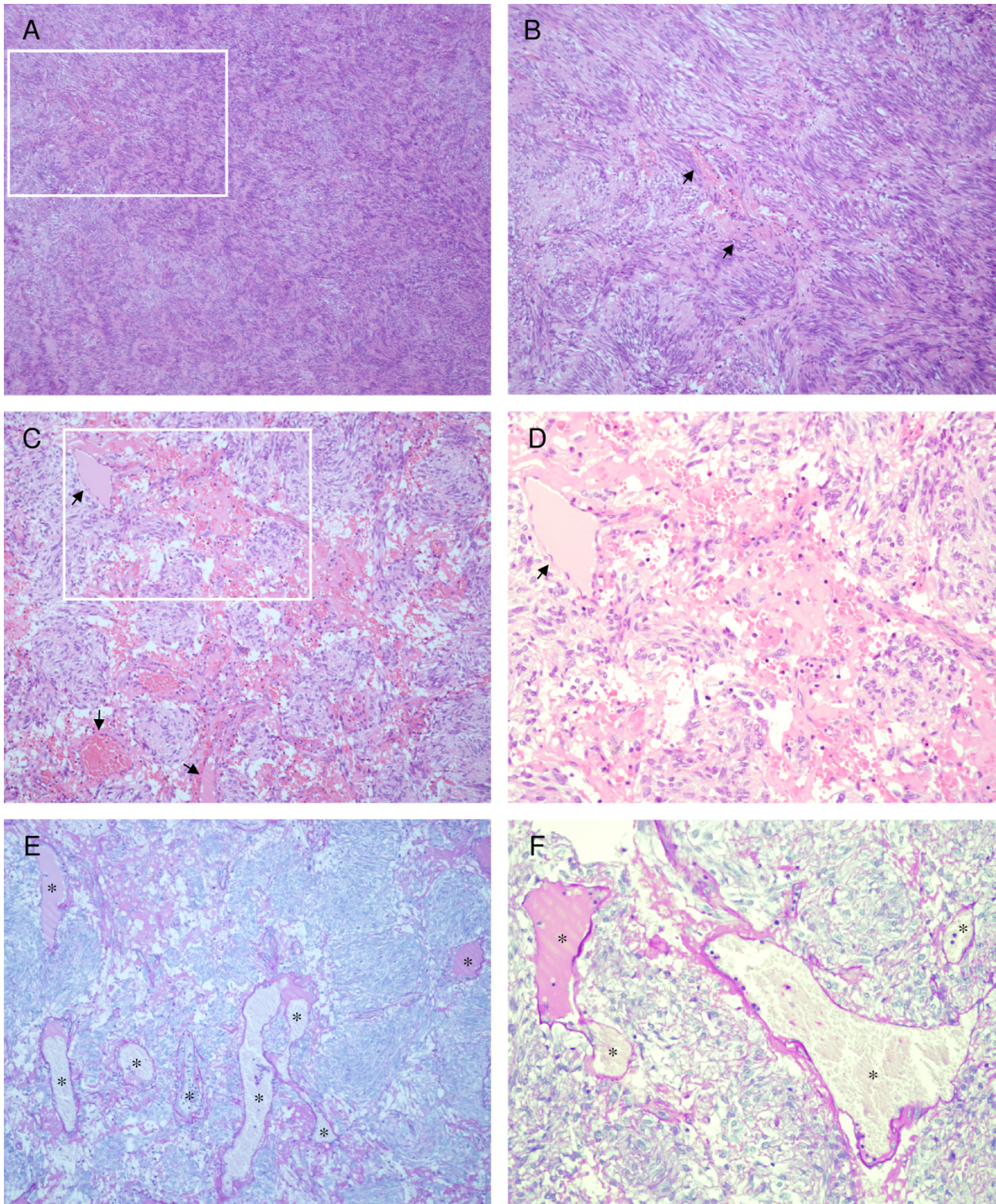


Figure 2. Histology of the gastric tumor.

(A–D) Hematoxylin and eosin staining, showing spindle cell GIST with prominent nuclear palisading (A, B). Note an erythrocyte-containing network of pseudo-vascular structures (C, D), and only a small number of veins in the solid area of the tumor (B–D, arrows). Magnified views (B and D) of rectangular areas (A and C, respectively). (E, F) PAS staining, highlighting the vascular-like channels (*). Magnifications: A, $\times 40$; B, C, E, $\times 100$; D, F, $\times 200$.

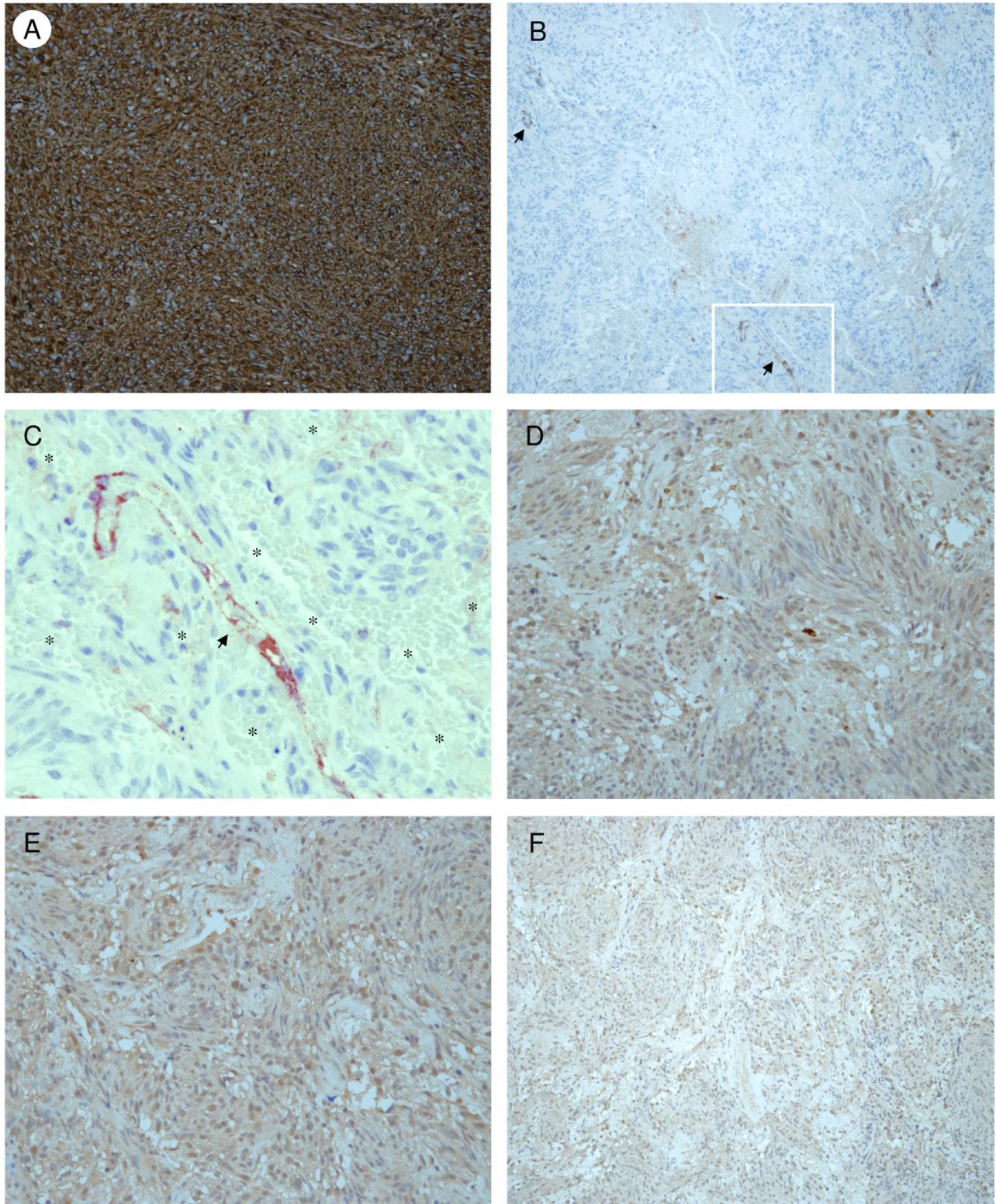


Figure 3. Immunohistochemistry.

Representative results of immunostaining of KIT (A), CD31 (B, C), VEGF (D), VE-cadherin (E), and CYP26A1 (F). Note the fluid-containing pseudo-vasculatures (*) and a small number of scattered CD31-positive vascular endothelial cells (B and C, arrows). Magnifications: A, B, F, $\times 40$; D, E, $\times 100$; C, $\times 200$.

While it is possible that the network of vascular-like channels was formed in areas with necrosis and fibrosis, we found a layer of a PAS-positive basal membrane in the inner surface of blood transport channels. Interestingly, some of the cells near the inner wall in the channels were shown to express CD31.^[14] This expression can be explained by a plausible hypothesis that a limited number of neoplastic cells have potent plasticity and can mimic the activity of endothelial cells to have the capacity to express CD31. There is still the possibility that vascular endothelial cells were lost during preparation of the specimen. However, it is difficult to believe that all of these cells inside the complexly branching

spaces were lost simultaneously on each single sectioning. Importantly, immunohistochemical examination provided the evidence of the absence of endothelial cells in the channels due to several serial sectioning of the tumor.

Our observations suggest an unidentified insight into neoplasia of a GIST. Future studies are warranted to clarify the regulatory mechanism of vasculogenic mimicry and its significance in various pathologies.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

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