

A Case of Pftin Negative Gastrointestinal Stromal Tumor (GIST), Metastasized to the Liver Five Years after Surgery: A Surgical Challenge

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Abstract

Background: Despite complete resection, GIST sometimes recurs and/or metastasizes. Accurate prognosis is needed and various risk stratification methods have been discussed. We have reported Pftin as a risk factor for recurrence of GIST.

In this study, we report a case of Pftin-negative GIST of the stomach which was classified as low risk according to Fletcher-classification, but metastasized to the liver five years after surgery and was completely removed.

Case presentation: A 60-year-old-man with abdominal pain and hematemesis was diagnosed with GIST of the stomach. Though the risk of recurrence was low according to Fletcher-classification, Pftin expression was negative. We performed long term frequent medical follow-up, and five years after partial resection of the stomach, the GIST metastasized to the liver and we resected it completely.

Conclusions: We experienced a case of GIST of the stomach which was assessed as low risk, but was Pftin-negative. Pftin-negative status alone indicated poor prognosis for this GIST. Pftin-negative status may be an independent biomarker indicating poor prognosis for GIST. In Pftin-negative cases, it is desirable that long term frequent medical checkup be performed even if other factors suggest that the GIST is low risk. Early detection of recurrence can lead to effective treatment.

Keywords: GIST; Gastrointestinal stromal tumor; Pftin; Liver metastasis

Introduction

Although they comprise fewer than 1% of all gastrointestinal tumors, GIST are the most common mesenchymal tumors of the gastrointestinal (GI) tract. Almost 90% of these tumors are associated with mutations of the characteristic KIT or platelet-derived growth factor receptor alpha (PDGFRA). Surgical removal is the standard treatment whenever possible and for years, it was the only effective treatment. Despite complete resection, recurrent and/or metastatic disease sometimes occurs. Now, Imatinib mesylate (IM, Gleevec) plays an important role in adjuvant therapy after surgery and metastatic or recurrent GIST too. IM prolongs recurrence-free survival in patients with high risk of recurrence. Risk classification is composed of three main factors: tumor size, the mitotic index, and tumor location. These risk assessment are very useful but we have sometimes experienced the recurrence of low risk GIST. Accurate prognostic prediction is needed and various risk stratification methods have been discussed.

We have proposed Pftin as a new, strong prognostic biomarker [1]. Pftin is a potassium channel protein, but its function in cancer development is unclear. Some reports have shown that Pftin expression and tumor metastasis are inversely related and Pftin-negative GIST has a poorer prognosis than Pftin-positive cases [1-3].

In this study, we report a case of Pftin-negative GIST of the stomach which was assessed as low risk according to Fletcher-classification. Because of Pftin-negative status, long term frequent medical follow-up was performed after partial resection of the stomach. Five years after surgery, the GIST metastasized to the liver and early detection lead to complete surgical removal.

Case Presentation

The patient was a 60-year-old man who presented to the ER with

abdominal pain and hematemesis. GI fiber examination revealed a submucosal tumor in the stomach with ulceration on its top (Figure 1). Histopathological examination of biopsy was performed and the specimen contained spindle cells. CT scan indicated a tumor measuring 40 × 35 mm in the stomach and the tumor had not spread to other parts of the body (Figure 2). We diagnosed him as CIST, localized in the stomach. The patient underwent partial resection of the stomach. The resected tumor specimen measured 4 cm × 4 cm × 3.5 cm in size: C-kit+, CD34+, S-100+, αSMA-, caldesmon-, Ki67 1~10%, mitosis <5 (/50 HPF), indicating GIST of the stomach. Following the Fletcher-classification, the risk of recurrence was assessed as low in this case.

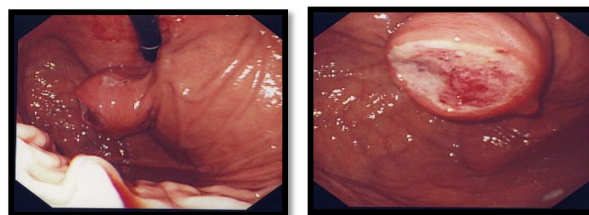


Figure 1: GI fiber examination revealed a submucosal tumor with ulceration on its top in the fundus of the stomach.

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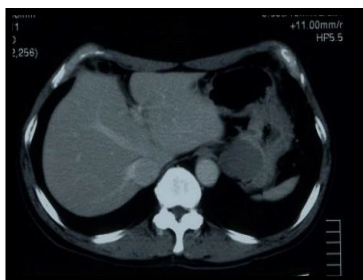


Figure 2: CT scan indicated a tumor measuring 40×35mm in the stomach and the tumor had not spread distant parts of the body.

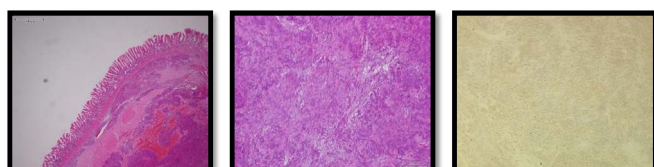


Figure 3: The tumor consisted of spindle cells and immunohistochemical studies showed that the tumor cells were positive for C-kit, CD34, S-100, and negative for αSMA, caldesmon. Less than 20% of tumor cells were stained with the anti-Pftin antibody, so we considered Pftin expression to be negative.



Figure 4: Ultra sonography showed SOL: S3, 38 mm, in the liver.



Figure 5: CT scan indicated low density area in the liver (S3).

We tested for Pftin expression and this specimen was found to be Pftin-negative (Figure 3). Though a low risk GIST, the Pftin-negative status was cause for concern. We obtained his consent and performed frequent examination (every 3 months) without adjuvant medication. We checked CT scans every 6 months, ultrasonography every 3 months, and GI fiber examination every year. Five years after surgery, Ultra sonography showed a space occupying lesion in the liver: S3, 38 mm (Figure 4). CT scan indicated low density area in the liver (S3) (Figure 5). The tumor had spread to only liver metastasis. Left hepatectomy was performed. The resected tumor specimen measured 4.5 cm × 4.5 cm × 30 cm in size :C-kit+, CD34+, S-100-,αSMA-, caldesmon-, Ki67 20-

30%, mitosis >5 (/50 HPF) (Figure 6). The specimen was compatible with metastatic GIST. He has been treated with Imatinib mesylate and is free of recurrence and metastasis two years after the operation.

Pathology

The resected tumor specimen measured 4 cm × cm × 3.5 cm in size: Ki67 1~10%, mitosis <5 (/50 HPF). The tumor morphology was classified as predominantly epithelioid or spindle-shaped. Mitotic rate was determined by counting the number of mitotic figures per 50 high power fields (HPF). Immunohistochemical studies showed that the tumor cells were positive for C-kit, CD34, S-100, and negative for αSMA, caldesmon. This specimen was found to be Pftin-negative (Figure 3).

Discussion

GISTs are the most common mesenchymal tumors of the GI tract, and management of patients with GIST has progressed rapidly in the last few decades [4]. Surgery is typically the initial therapy when tumors are resectable. But despite complete resection, recurrent and/or metastatic disease sometimes occurs, depending on the grade of malignancy [5-8]. Various risk stratification methods have been proposed and may be categorized according to three main factors: tumor size, the mitotic index, and tumor location [5-8]. Treatment after surgery is determined by the risk of recurrence. Imatinib mesylate (IM, Gleevec) plays an important role in adjuvant therapy after surgery, and prolongs recurrence-free survival. Modified-Fletcher classification is exceedingly useful and we have reported on its utility. But GIST classified as low risk sometimes recur. If a more sensitive prognostic biomarker was available, patients with low risk of recurrence could receive more accurate adjuvant medication using IM to prevent it. And though IM is standard treatment for high-risk GIST, it has side effects, it is very expensive, and tumors often develop resistance to it, so we also need more accurate prognostic prediction for high risk cases. To evaluate the risk of recurrence, we have proposed Pftin as a new, strong prognostic biomarker [1].

Pftin is a potassium channel protein. It is highly expressed in fetal cochlea and in the brain, consistent with the fact that the origin of GIST is Cajal cells, and neuronal cells in the gut [2]. Pftin was discovered by using a proteomics approach [2] and its usefulness as a prognostic biomarker has been reported. Suehara et al. proposed that Pftin expression and tumor metastasis were inversely related [2] and that GIST with Pftin-negative status has a poorer prognosis than Pftin-positive GIST [1-3]. We also have reported the fact that Pftin is an independent predictor of recurrence/metastasis for completely resected primary, localized GIST. In our study, thirteen cases were Pftin negative and 5/13 of these cases recurred. Conversely, thirty-two cases were Pftin positive and 2/32 of these cases recurred ($p=0.002$) [1]. We

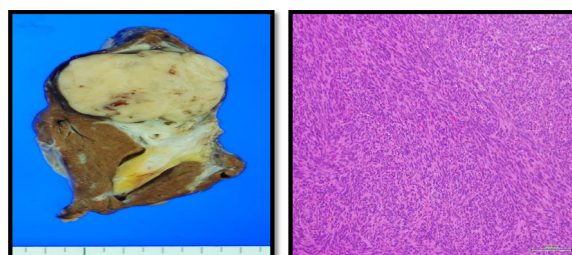


Figure 6: The resected tumor specimen measured 4.5cm×4.5cm×30cm in size: C-kit+, CD34+, S-100-,αSMA-, caldesmon-, Ki67 20-30%, mitosis >5 (/50 HPF).

examine Pftin expression immunohistochemically using paraffin-embedded tissues, and when more than 20% of tumor cells are stained with the anti-Pftin antibody, they are considered to be Pftin positive.

In this case, the resected tumor specimen measured 4 cm × 4 cm × 3.5 cm in size: C-kit+, CD34+, S-100+, αSMA-, caldesmon-, Ki67 1~10%, mitosis <5 (/50 HPF), indicating GIST of the stomach. It was assessed as low risk according to Fletcher-classification, but was Pftin-negative. There are no published data to indicate the optimal routine follow-up policy for surgically treated patients with localized disease. Under 2% of patients with low risk developed recurrent tumors and the mean time to recurrence of the tumor was about 23.1 ± 17.5 months (range: 2-54) [9-13]. Generally speaking, the possibility of recurrence five years after surgery is very low, but we decided to perform frequent (every 3 months) long term (over five years) examinations because of the Pftin-negative condition. The patient did not receive IM. Five years after surgery, metastatic disease in the liver was revealed. Because the recurrence was detected early by frequent long term check-ups, we were able to remove it surgically. We again realized the utility of Pftin as a prognostic biomarker in GIST. Although the ideal period to continue follow-up examinations and frequency of medical follow-up after surgery is still unclear, long term frequent medical follow-up should be performed in Pftin-negative cases. Early detection of recurrence/metastasis leads to surgical removal or secondary treatment.

This case also shows that Pftin-negative status may be an independent biomarker for recurrence of GIST. In this case, we determined that the three main risk factors: tumor size, the mitotic index, and tumor location, indicated low risk for recurrence. Only Pftin-negative status implied recurrence. Pftin is a possible prognostic biomarker which is independent of other factors.

Another notable feature of this case is that the mitotic index (MI) changed. The specimen from the first operation was MI <5 (/50 HPF), and the specimen from the second operation was MI >5 (/50 HPF). This is another indication that Pftin-negative status has the potential to change malignancy status. Mechanisms of acquired MI change are unclear, but there are some articles which report secondary mutations in the kinase domain of the *KIT* gene in imatinib-resistant GIST [11,12]. We estimate that MI change GIST have similar secondary mutations at the genetic level. Further study of Pftin is planned and may reveal facts which are useful in determining optimal adjuvant therapy [13-16].

Conclusions

We experienced a case of GIST of the stomach which was assessed as low risk, but was Pftin-negative. Pftin-negative status alone indicated poor prognosis for this GIST. Pftin-negative status may be an independent biomarker indicating poor prognosis for GIST [17-20]. In Pftin-negative cases, it is desirable that long term frequent medical checkup be performed even if other factors suggest that the GIST is low risk. Early detection of recurrence can lead to effective treatment.

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