

Case Report

Rare Epithelioid Tumor with ACTB-GLI1 Fusion in the Stomach - Differential Diagnosis and Literature Review of Proposed New Entity: A Case Report

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Abstract

GLI1-altered tumors were initially reported as pericytomas with t (7; 12) and ACTB-GLI1 fusion. These rare tumors stem from alterations in perivascular myoid cell differentiation and were first reported as a group of rare soft-tissue neoplasms of pericytic origin. Several series of GLI1-altered tumors have since been described. In 2024, the World Health Organization recognized these neoplasms as rare soft-tissue tumors of the head and neck in the tumor classification. They have been recently reported in multiple organs but rarely in the gastrointestinal tract. Most of these tumors are classified into low-grade malignancies; however, several malignant cases have been described. The present case report presents a gastric tumor with ACTB-GLI1 fusion in a 40-year-old male who completed a long-term follow-up. The tumor histology exhibited uniform polygonal cells with clear to slightly eosinophilic cytoplasm arranged in an organoid pattern. Immunohistochemical studies of the tumor cells revealed nonspecific finding and a definite diagnosis of ACTB-GLI1 fusion tumor was confirmed through fluorescence *in situ* hybridization. This report conducted a literature review and discussed the differential diagnosis, malignant potential, and clinical expression and treatment of these tumors.

Keywords: ACTB, case report, epithelioid tumor, gastric, GLI1, pericytoma

INTRODUCTION

Pericytes, first described by Zimmermann in 1923, are the mural cells of blood microvessels.^[1] Dahlén *et al.* identified the entity “pericytoma with t (7:12) and ACTB-GLI1 fusion” as a perivascular myoid tumor in 2004.^[2] These tumors usually exhibit a multinodular pattern of uniform ovoid or spindle cells with clearly visible eosinophilic cytoplasm. No major nuclear atypia is present, and mitotic figures (MFs) are rare.

Submitted: 11-Jun-2025 Revised: 01-Jul-2025

Accepted: 14-Jul-2025 Published: 24-Sep-2025

Numerous mesenchymal tumors resulting from GLI1 rearrangement or amplification have been reported in recent years.^[2-18] Among the 99 cases of such tumors that have been reported, only eight gastric tumors with GLI1 gene alternation have been described to date,^[2,4,14,18] and in one case, liver

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Website:
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DOI:
10.4103/ejcrp.eJCRP-D-25-00021

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How to cite this article: Huang SH, Chou YY. Rare epithelioid tumor with ACTB-GLI1 fusion in stomach - Differential diagnosis and literature review of proposed new entity: A case report. J Cancer Res Pract 2025;12:85-9.

metastasis developed. Because of their rarity, the understanding of these tumors is not well-established, and they are easily misdiagnosed in initial specimen analyses.

We present a case of gastric ACTB-GLI1 fusion tumor and also reviewed previously reported cases of gastrointestinal GLI1-altered tumors.

CASE REPORT

This was the known case of a 40-year-old male patient who had a history of arrhythmia. According to the patient's statements and medical record, an antral submucosal tumor was discovered during a health checkup. The patient experienced poor appetite and body weight loss of 3 kg/month; consequently, he visited our gastrointestinal department for further evaluation. Abdominal computed tomography revealed a 2.0-cm submucosal lesion at the greater curvature side of the antrum. No definite lymphadenopathy was noted. The lesion was suspected to be a gastrointestinal stromal tumor (GIST), and the patient received wedge resection.

The gross examination revealed that the tumor measured 2.2 cm × 2.0 cm × 1.5 cm and was covered by intact mucosa. The cut surface was solid, tan, and elastic, without necrosis. Microscopic examination revealed a multinodular tumor composed of ovoid cells arranged in a haphazard pattern within smooth muscle bundles. The tumor cells exhibited mild nuclear atypia and 3 MFs in 10 high-power fields (HPFs) [Figure 1a-c]. Areas of hemorrhage, cystic degeneration, and inflammatory cell infiltration were observed.

The initial differential diagnoses included a low-grade neuroendocrine tumor (NET) and an epithelioid type GIST. Immunoperoxidase studies were conducted on paraffin

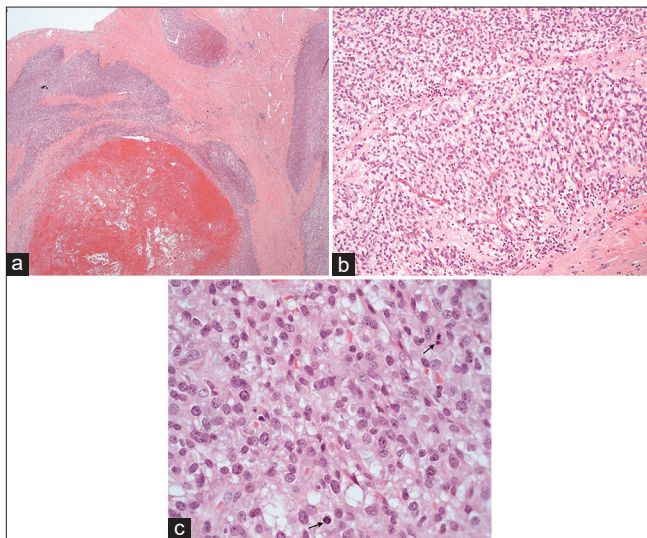


Figure 1: Photomicrographs of gastric tumor. (a) Multiple tumor nodules are separated by fibrous stroma (H and E, ×25). (b) Most tumor cells displaying uniform nuclei are arranged as sheets or organoid structures (H and E, ×200). (c) Tumor cells exhibit ovoid nuclei, distinct nucleoli, and eosinophilic or clear cytoplasm. Some mitotic figures are found (arrow heads) (H and E, ×600)

sections through the avidin-biotin-peroxidase method. Immunohistochemical staining was performed according to the standard techniques on an Autostainer (Ventana BenchMark ULTRA) with standard reagents and the following antibodies: cytokeratin, synaptophysin, chromogranin A, CD56, smooth muscle actin (SMA), desmin, S100, CD34, CD117, and DOG1. Weak staining for CD56 and SMA was noted in scattered tumor cells [Figure 2a and b]; the other markers were negative. Further differentiation of rare tumors, such as perivascular epithelioid cell tumor (PEComa) and metastatic clear cell renal cell carcinoma (RCC), was suggested. Accordingly, the primary antibodies of vimentin, HMB45, CD10, and RCC marker were applied. The tumor cells exhibited diffuse positive reactivity for vimentin and focally weak staining for CD10 [Figure 2c], but they exhibited negative reactivity for the RCC antibody and HMB45. Under the suspicion of a rare perivascular tumor, cyclin D1 was finally used, and 70% tumor cells reveal positive nuclear staining [Figure 2d].

For the definite diagnosis, fluorescence *in situ* hybridization (FISH) was performed on 4-μm tumor sections with custom bacterial artificial chromosome probes for GLI1 and ACTB, with this conducted in accordance with a previously described protocol.^[5] The FISH study confirmed rearrangement in the ACTB and GLI1 genes [Figure 3].

After the initial operation, the patient underwent endoscopic examination. No residual tumor was observed. The patient completed the regular follow-up at the gastrointestinal and surgical outpatient departments. No evidence of recurrent disease or metastatic lesions was observed for 82 months postoperatively.

DISCUSSION

In this case study, we present a gastric epithelioid tumor cell exhibiting unusual histological and nonspecific

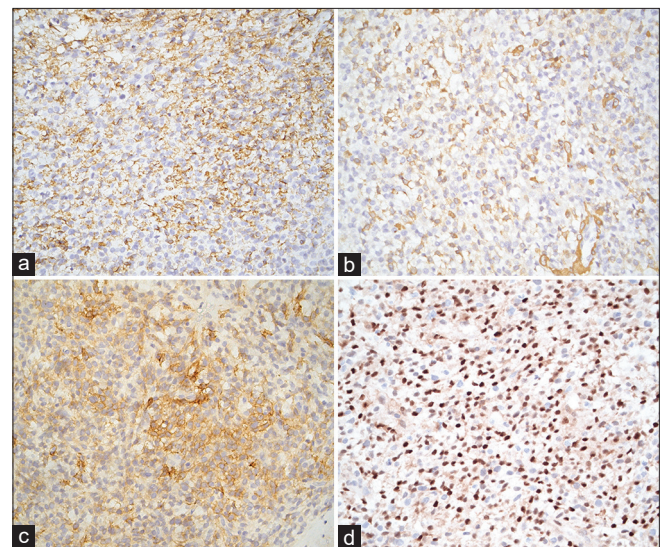


Figure 2: Immunohistochemical staining (×400). Scattered tumor cells express weak staining for (a) CD56, (b) smooth muscular actin and (c) CD10. Most tumor cells show positive staining for (d) cyclin D1

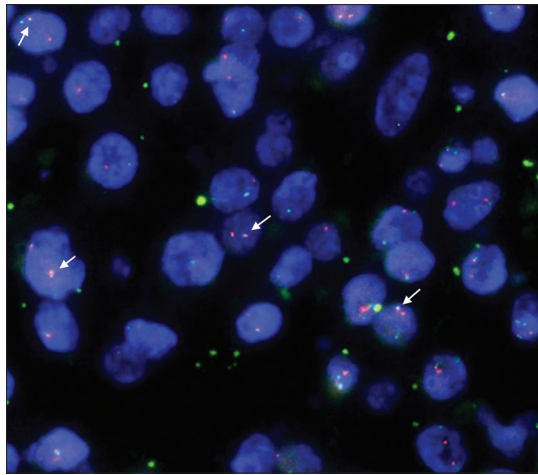


Figure 3: Confirmation of ACTB: GLI1 fusion through fluorescence *in situ* hybridization. The overlapping fusions of red and green signals produce yellow signals (arrow heads)

immunohistochemical expression distinct from that in the typical World Health Organization tumor classifications. The tumor in our case had a nested glomoid appearance and ACTB-GLI1 fusion, consistent with the description of GLI1-altered mesenchymal tumors first identified by Dahlén *et al.* in 2004.^[2]

The typical morphology of GLI1-altered mesenchymal tumors comprises ovoid cells with small nucleoli and abundantly clear to slightly eosinophilic granular cytoplasm. These cells are usually arranged as multiple lobules or nests with perivascular proliferation. Most reported cases of these tumors have exhibited mild nuclear atypia and rare MFs. However, several composed of spindle cells with nuclear pleomorphism and high MFs have been noted. According to large series reports, GLI1-altered mesenchymal tumors commonly expressed CD56 and CD10 and occasionally stained by S100 (23%) and SMA (33%), with negative or only focally weak staining for cytokeratin.^[16,18] While our case only revealed scattered reactivity for CD56, SMA, and CD10. Positive reactivity for cyclin-D1 in our case was consistent with recent reported cases,^[16] and it may be another important marker in suspicion GLI1-altered tumors. Immunohistochemical studies are nonspecific for GLI1-altered tumors but useful for excluding other neoplasms with similar morphological features. Obtaining a definite diagnosis requires FISH or gene sequencing. GLI1 is a transcription factor expressed in certain mesenchymal tumors, including gastroblastoma, plexiform fibromyxoma, pericytoma with t (7;12), and the emerging class of GLI1-altered mesenchymal tumors. A developed monoclonal antibody for GLI1 immunohistochemistry (clone C-1, Santa Cruz Biotechnology) was reported to achieve 98.0% specificity and 91.3% sensitivity for initial differentiation of GLI1 altered mesenchymal tumors from their morphologic mimics.^[19]

In the current study, the initial differential diagnoses for our patient were low-grade NET and epithelioid type GIST,

which are the most common epithelioid tumors observed in the stomach. Several unusual epithelioid tumors were then identified, including glomus tumor, PEComa, and metastatic RCC. NET is the most commonly observed low-grade epithelioid tumor in the gastrointestinal tract, and it is typically considered a diagnosis when tumor cells exhibit abundant granular cytoplasm and an organoid pattern. However, NET diagnosis can easily be eliminated on the basis of positive reactivity for cytokeratin and neuroendocrine markers, such as synaptophysin, chromogranin A, and CD56. Epithelioid GIST is less common than spindle cell GISTs; however, they are also reactive for c-KIT (CD117) or DOG1, which exhibited negative reactivity in our patient. In addition, in our study, metastatic RCC was ruled out on the basis of clinical history, image studies, and negative reactivity for renal cell markers (diffuse positive staining for RCC and CD10). The most likely differentiations were therefore PEComa and glomus tumor, both of which exhibit proliferation of epithelioid cells with perivascular cells differentiation. PEComas have larger cells containing more abundant granular cytoplasm and typically express a melanocytic marker (HMB45 or melan A). Glomus tumors have uniform ovoid cells arranged in a nesting pattern, similar to that observed in our patient. However, glomus tumors usually exhibit distinct cell borders and diffuse SMA staining, which contrasts with the indistinct cell borders and negative reactivity for SMA in our patient. The most likely differential diagnoses of gastrointestinal epithelioid tumors are listed in Table 1. The tumor in our patient was difficult to diagnose as any of those listed. The FISH study revealed ACTB-GLI1 fusion, suggesting the presence of a GLI1-altered epithelioid tumor,^[10,17,18] an emerging tumor classification.

GLI1-altered mesenchymal tumors are typically underdiagnosed because of their rarity, particularly in lower-budget immunohistochemical studies. A literature review revealed that 99 cases of GLI1-altered mesenchymal tumors have been reported with 41%, 43%, and 16% displayed ACTB-GLI1 fusion, GLI1 amplification, other GLI1 rearrangement, respectively. The tumors were observed in bone and soft tissue (54%), the head and neck (25%), the gastrointestinal tract (18%), and rare organs (two cases noted in the ovaries and one in the lungs). The age range of the 99 patients with these tumors was 2–82 years, and the tumor size ranged from 1.2 to 21.0 cm. Fourteen patients (14.1%) had malignant behaviors with seven experiencing local recurrence and nine experiencing metastasis (two patients developed local recurrence of distal metastasis). The most common metastatic sites were regional lymph nodes, followed by the liver, lungs, and brain. No patient with distal metastases died of this cause within 3–168 postoperative months.^[10,16-18] Excision was initiated for 18 GLI1-altered tumors, 2 of which developed metastases. Both metastatic cases exhibited high MFs or a high ki67 index. The clinicopathological features and follow-up data of the eight gastric GLI1-altered tumors reported in the literature and that in our case are provided in Table 2.

The malignant histological observations of GLI1-altered mesenchymal tumors that have been previously reported

Table 1: Differential diagnoses of nesting epithelioid tumors in gastrointestinal tract

Antibodies	Tumors					
	Our case	Epithelioid GIST	Low-grade NET	Glomus tumor	PEComa	Metastatic CCRCC
Cytokeratin	–	–	+	–	–	+
Synaptophysin	–	–	+	–	–	–
Chromogranin A–	–	–	+	–	–	–
CD56	+ (scattered)	–	+	–	–	–
CD34	–	+	–	–	–	–
CD117	–	+	–	–	–	–
SMA	+ (scattered)	V	–	+	V	–
S100	–	V	–	–	–	–
HMB45	–	–	–	–	+	–
CD10	+ (scattered)	–	–	–	–	–
RCC	–	–	–	–	–	–
Cyclin D1	+ (diffuse)	–	–	–	–	–

GIST: Gastrointestinal stromal tumor, NET: Neuroendocrine tumor, PEComa: Perivascular epithelioid cell tumor, CCRCC: Clear cell renal cell carcinoma, V: Variable staining, +: Positive reactivity, -: Negative reactivity

Table 2: Clinicopathological features of gastric GLI1-rearranged tumors

Case number	Age/sex	Size (cm)	Genetics	Mitoses or ki67	LR/DM	Follow-up (months)	Reference
1	65/female	5.5	ACTB:GLI1	NA	No	NED/24	2
2	9/female	6.9	ACTB:GLI1	Ki67 <2%	No	NED/6	14
3	48/female	12	ACTB:GLI1	NA	No	NED/18	14
4	36/female	8	PTCH1:GLI1	Ki67 10%–15%	DM	NED/83	16
5	42/male	5.2	NA	1 MF/10 HPF	No	NA	18
6	52/male	2	NA	1 MF/10 HPF	NA	NA	18
7	82/female	6.5	NA	>20 MFs/10 HPF	NA	NA	18
8	18/male	5.0	NA	>20 MFs/10 HPF	DM	Recent case	18
Present case	40/male	2.2	ACTB:GLI1	3 MFs/10 HPF	No		-

LR/DM: Local recurrence/distant metastasis, NA: Not available, NED: No evidence of disease, MF/HPF: Mitotic figures/10 high-power fields

include tumor size (≥ 5 cm), mitotic count (≥ 4 MFs/10 HPF), and necrosis.^[18] The largest serial study that we identified revealed significantly worse overall survival among patients with GLI1-amplified tumors compared with among those with GLI1-rearranged tumors. The follow-up period for gastrointestinal GLI1-altered tumors was typically short, with limited therapeutic and outcome data provided. Therapy for these tumors has not been standardized; however, complete excision with a safe margin is considered the mainstay treatment. In our patient, the tumor exhibited low MFs and only mild nuclear pleomorphism. No unfavorable histological characteristics were observed. The patient underwent wedge resection of the tumor with a 1.0-cm free margin and was disease-free for 82 months postoperatively.

GLI1-altered mesenchymal tumors usually exhibit epithelioid and glomoid histological features but have been under-recognized, particularly those observed in the GI tract, until recently. Practitioners should remain aware of the characteristic morphological features and application of CD10, CD56, SMA, S100, and cyclin D1 in any suspected tumors with unusual appearance. GLI1-altered tumors, a recently investigated and newly proposed classification of

mesenchymal tumors, may be correctly diagnosed through FISH studies. Most GLI1-altered tumors are indolent, morphologically distinctive, nested glomoid neoplasms that should not be classified as sarcoma, and a long-term patient follow-up is recommended.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Acknowledgements

We would like to thank Dr. JC Lee (Department of Pathology, National Taiwan University Hospital) for performing the FISH study and confirming the diagnosis. This manuscript was edited by Wallace Academic Editing.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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