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Multiple Succinate Dehydrogenase-Deficient Gastrointestinal Stromal Tumors of the Stomach: A Case Report

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 27-year-old
Final Diagnosis: Succinate dehydrogenase-deficient gastrointestinal stromal tumor (SDH-deficient GIST)
Symptoms: Melena
Clinical Procedure: —
Specialty: Surgery

Objective: Rare coexistence of disease or pathology

Background: Gastrointestinal stromal tumors (GISTs) are a rare subset of gastrointestinal neoplasms, with approximately 85% of cases being characterized by genetic alterations in either the KIT gene or the platelet-derived growth factor receptor alpha (PDGFRA) gene. In contrast, succinate dehydrogenase-deficient gastrointestinal stromal tumors (SDH-deficient GIST) account for only 5-10% of cases. SDH-deficient GISTs is a rare form of gastrointestinal tumor, predominantly affecting young people and women. It typically presents with multifocal lesions, has a tendency to invade lymph nodes, follows an indolent course, and is poorly responsive to imatinib; sunitinib and regorafenib may be effective against it. For patients with resectable lesions, surgical intervention remains the cornerstone of treatment.

Case Report: A 26-year-old male patient was admitted with the presenting symptom of melena. Subsequent diagnostic evaluations revealed the presence of multiple gastric neoplasms. He underwent laparoscopic distal gastrectomy for multiple gastric tumors and postoperative pathology was consistent with GIST, SDH-deficient type. Genetic testing for KIT, PDGFRA, KRAS, NRAS, BRAF, SDHA, SDHB, SDHC, SDHD, and NF1 showed no mutations. The patient is still being followed and no evidence of relapse has been found 6 months postoperatively.

Conclusions: Although SDH-deficient GISTs generally exhibit indolent biological behavior, clinically significant manifestations such as gastrointestinal bleeding, as observed in this case, occasionally occur. The postoperative resolution of hemorrhagic symptoms in this patient demonstrated the therapeutic efficacy of surgical intervention. This case underscores the importance of timely surgical management while highlighting the need for improved diagnostic precision and optimized treatment algorithms. The present report provides valuable clinical insights for prognostic evaluation and clinical decision-making in SDH-deficient GISTs, while also offering a reference for future investigations into novel targeted therapies.

Keywords: Gastrointestinal Neoplasms • Gastrointestinal Stromal Tumors • Lymphatic Metastasis • Hemorrhage • Succinate Dehydrogenase

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Introduction

GISTs are the most prevalent type of mesenchymal tumors within the gastrointestinal tract, originating from the interstitial cells of Cajal. These tumors are usually located in the stomach (60-65%) and small intestine (20-35%), and rarely in the esophagus, colon, and rectum [1-3]. In advanced stages, GISTs can metastasize, with the liver being the most common site of metastasis (50-65%), followed by the peritoneum (20-43%). Metastatic spread to lymph nodes, bones, and lungs is relatively uncommon, while metastases to other anatomical sites are exceedingly rare [4]. Most GISTs are driven by mutations in the KIT or PDGFRA genes, and it has been demonstrated that this group of patients has a greater degree of responsiveness to imatinib treatment. However, approximately 85% of pediatric GISTs and 10-15% of adult GISTs lack mutations in these genes and are classified as wild-type GISTs [4], which can be subdivided into SDH-deficient GISTs and SDH-competent GISTs [2,3,5,6]. Since the loss of expression of any SDH subunit (SDHA/B/C/D) results in absent SDHB expression, immunohistochemistry for SDHB is a valuable diagnostic tool for identifying SDH-deficient GISTs [2,7]. The clinical presentation of GISTs is often non-specific, with gastrointestinal bleeding being the most common symptom, followed by anemia, abdominal pain, weight loss, and abdominal masses [8]. Surgical resection remains the preferred treatment for GISTs, particularly in cases where the tumor is resectable. For larger tumors that cannot be fully excised or in cases of metastatic disease, targeted therapy may be administered prior to surgery. However, wild-type GISTs lack the specific binding sites for tyrosine kinase inhibitors (TKIs), which leads to the poor efficacy of current targeted therapies in this subset of patients [9].

Case Report

A 26-year-old male patient was admitted to the Department of Gastrointestinal Surgery with the presenting symptom of melena. Upon physical examination, his abdomen was flat, non-tender, without rebound or palpable masses, and exhibited mildly active bowel sounds (6 per minute). He had no chronic illnesses, no history of surgery, and no family history of hereditary diseases. However, he did have a history of smoking. Laboratory tests revealed mild anemia (hemoglobin 94 g/L) and a positive fecal occult blood test, while tumor markers (CEA, AFP, TAA-50, CA 125, CA 15-3, CA 19-9) were within normal limits. An abdominal CT scan showed multiple round masses in the gastric body and antrum (**Figure 1**). Gastroscopy suggested multiple intragastric lesions with bleeding (**Figures 2, 3**). Gastrointestinal endoscopy and endoscopic ultrasound provided visual evidence of the cause of the gastrointestinal bleeding. With the patient's consent, surgery was performed. Intraoperatively, multiple nodules were found in the gastric antrum and body. These nodules were firm, non-penetrative of the serosa, and did not invade surrounding tissues or organs. Numerous enlarged lymph nodes were also noted around the stomach. A laparoscopic distal gastrectomy (Billroth II + Braun anastomosis) was carried out. The patient underwent resection of two-thirds of the distal stomach, with ligation of the left gastric artery, right gastric artery, and left and right gastroepiploic arteries and veins. Pathology examination confirmed the presence of GISTs in the gastric antrum and body, of the spindle cell type, SDH-deficient (**Figures 4, 5**). Next-generation sequencing (NGS) genetic testing revealed no mutations in KIT, PDGFRA, KRAS, NRAS, BRAF, SDHA, SDHB, SDHC, SDHD, or NF1. The patient was started on a liquid diet on postoperative day (POD) 1, with gradual advancement to semi-liquid intake. Gastrointestinal contrast study performed on POD 4 demonstrated intact anastomotic integrity without evidence of contrast leakage, and no postoperative complications were documented. He was discharged on POD 6 without adjuvant chemotherapy. Serial follow-up evaluations at 1, 3, and 6 months postoperatively revealed no evidence of tumor recurrence.

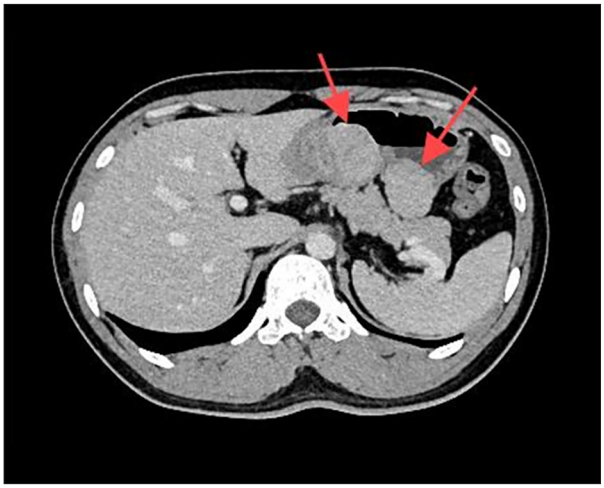

Figure 1. Radiographic images. Abdominal CT scan showed multiple round masses (arrows) in the gastric body and antrum, with the largest measuring 3.7×2.8 cm. These masses protruded beyond the gastric contour, exhibiting moderate and uneven enhancement in some areas. Additionally, the anterior surface of the pancreas was compressed by the masses.

Discussion

SDH, also known as mitochondrial complex II, is an inner mitochondrial membrane enzyme involved in the citric acid cycle and oxidative phosphorylation. It consists of SDHA, SDHB, SDHC, and SDHD. SDHA catalyzes succinate conversion, SDHB transfers electrons, while SDHC/SDHD anchor the complex [7].

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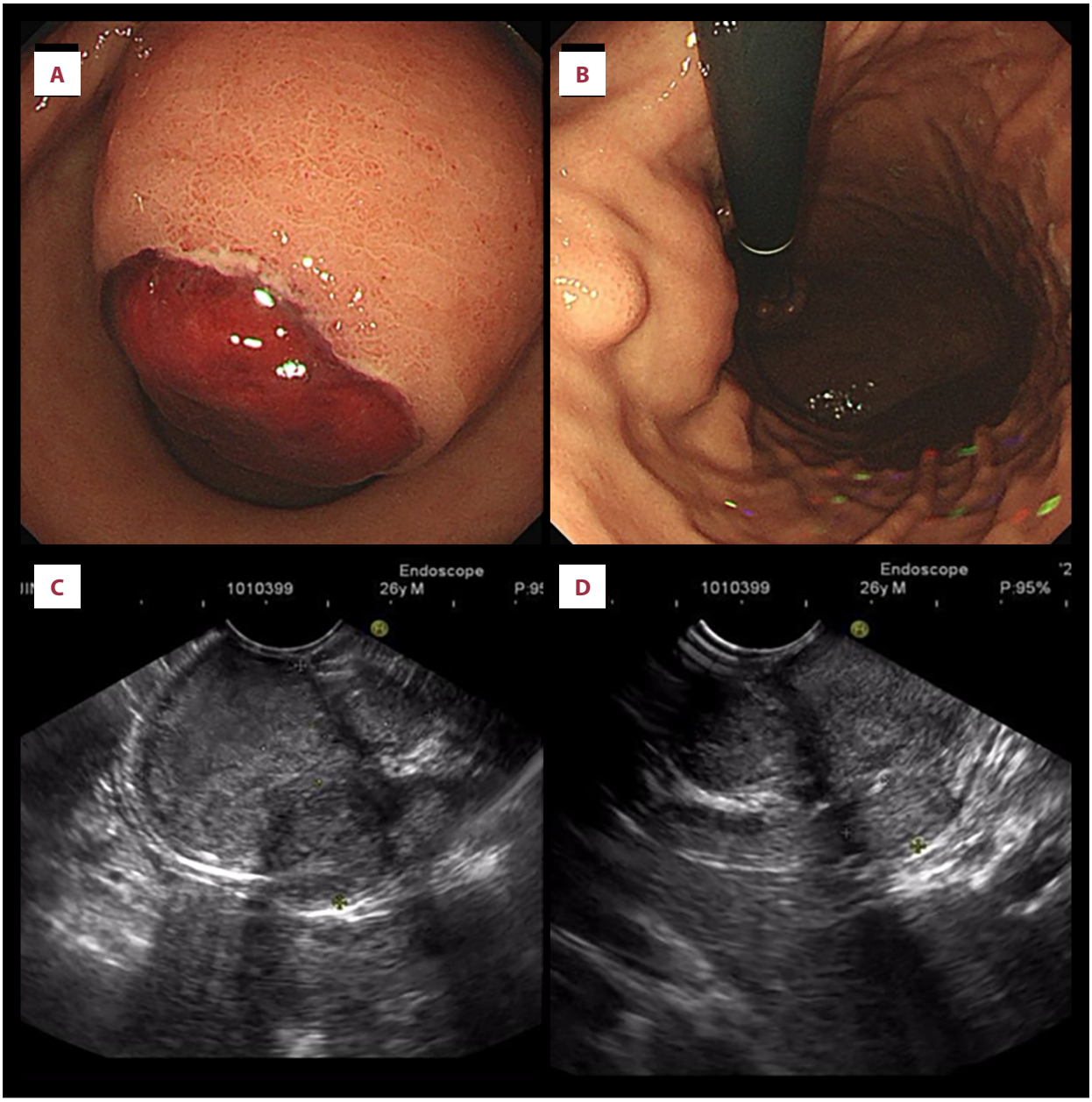

Figure 2. Digestive endoscopy and endoscopic ultrasound (EUS) images. Gastroscopy revealed 2 small polyps (0.5 cm to 0.6 cm) in the lesser curvature of the stomach, an irregular submucosal elevation (2.0×1.8 cm) with smooth mucosa on the posterior wall of the lower stomach, and a spherical submucosal elevation (3.5×3.0 cm) with a dark red blood clot in the lesser curvature. (**A**) Gastric antrum; (**B**) Gastric body (tumors are marked with arrows); (**C**) Gastric antrum (circles indicate tumors) (EUS); (**D**) Perigastric lymph node (circles) (EUS).

SDH deficiency destabilizes the enzyme, reducing activity, detectable by absent SDHB staining, making it a key diagnostic tool for SDH-deficient GISTs [10]. These tumors arise from SDHx mutations (mostly SDHA) or SDHC promoter hypermethylation, although some lack mutations [5]. SDH-deficient GISTs accumulate succinate, inhibiting PHD, stabilizing HIF1, and upregulating VEGF/IGF1, promoting angiogenesis and proliferation [11,12], leading to metastasis, particularly to lymph nodes [9]. Succinate also upregulates ZNF148, enhancing tumor invasion [13,14].

GISTs primarily occur in the stomach (~60%) and small intestine (~30%) but can be found elsewhere [15]. Symptoms are non-specific, including bleeding, anemia, pain, or incidental detection [16]. SDH-deficient GISTs, mainly gastric, affect young patients and often involve lymph nodes [15], following

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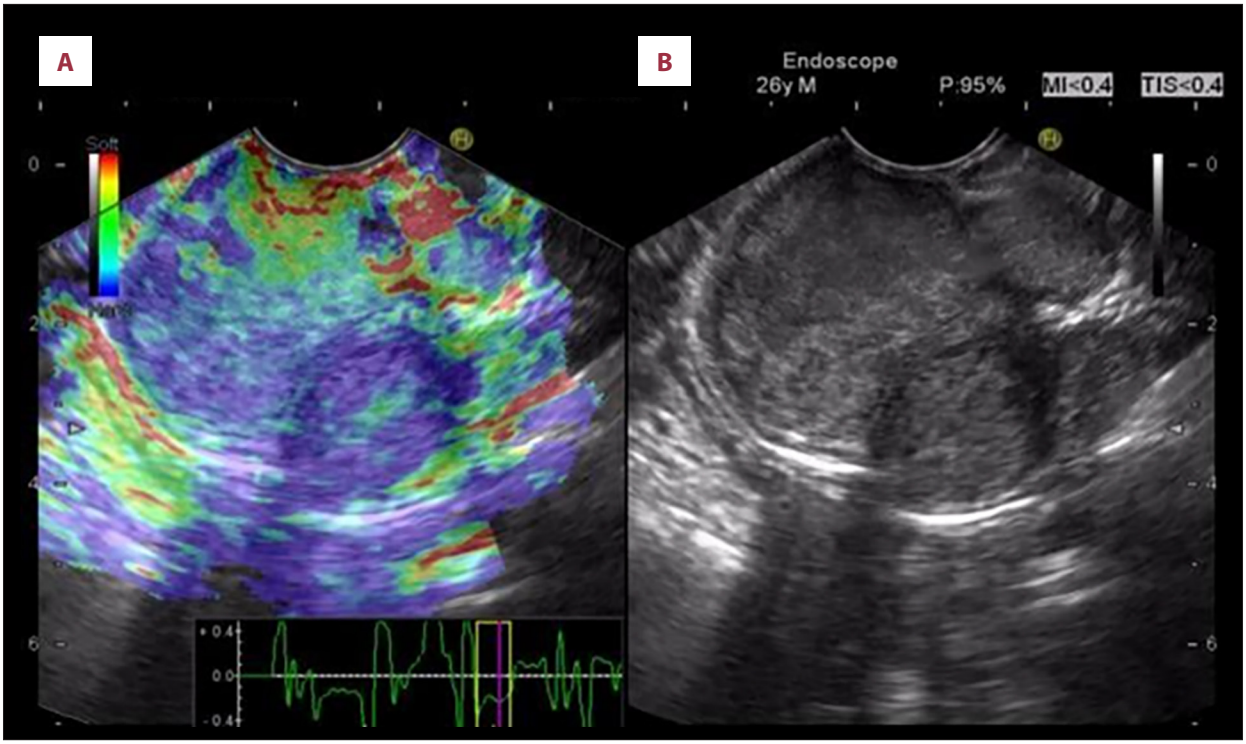

Figure 3. Tumor of the gastric antrum (circles) (endoscopic ultrasound-elastography).

an indolent course. We present the case of a man with lesions in the stomach, multiple foci, and enlarged perigastric lymph nodes. These features strongly suggested SDH-deficient GIST, a diagnosis that was further confirmed by postoperative immunohistochemistry. Notably, NGS failed to detect any mutations in the SDH subunits. SDH-deficient GISTs may be sporadic or syndromic, as in Carney triad or Carney-Stratakis syndrome (CSS)[17]. In 1977, Dr. J. Aidan Carney identified an association between GISTs, paragangliomas (PGLs, tumors originating from sympathetic and parasympathetic paraganglia), and pulmonary chondromas (PCH) [18], later termed the Carney triad. Over time, adrenal cortical adenomas and esophageal leiomyomas were also included in the triad (Carney triad is a multiple endocrine tumor, and although it describes more than 3 lesions, the nomenclature has been used because of the customary name in the past and the fact that it was called Carney triad in McKusick's Mendelian Inheritance in Man) [19]. CSS, an autosomal dominant syndrome, involves GISTs and pheochromocytomas [20], associated with SDHB, SDHC, SDHD, and SDHA mutations [21,22]. Therefore, a comprehensive diagnostic evaluation is essential to ensure accurate diagnosis and guide clinical management.

For the treatment of SDH-deficient GISTs, complete surgical resection of the primary tumor remains the main treatment. While R1 resection (microscopic residual tumor) does not significantly impact recurrence risk or overall survival in GISTs, the primary goal is to achieve R0 resection (no residual tumor) [9]. Avoiding tumor rupture during surgery is critical, as this is a significant risk factor for recurrence and reduced disease-free survival [23]. Although routine lymph node dissection is not mandatory, lymph node metastasis is common in SDH-deficient GISTs. In this case, we performed dissection of the enlarged perigastric lymph nodes, with postoperative pathology revealing a 50% lymph node positivity rate (4 of 8 nodes positive). This finding supports the necessity of lymph node removal in such cases. Boikos et al reported [6] that nodular lesions occur in up to 65% of SDH-mutant GISTs, further justifying the removal of enlarged lymph nodes in these patients [6,24]. However, surgical treatment alone may not suffice due to the frequent recurrence and progression following surgery, making adjunctive drug therapy necessary to improve patient outcomes. Studies have shown that neoadjuvant therapy with imatinib or other TKIs can slow tumor progression, reduce tumor size, and enhance progression-free survival (PFS) and overall survival (OS) in patients with unresectable or metastatic GISTs, increasing the chances of complete resection [24]. The advent of TKIs has significantly improved therapeutic outcomes for GISTs. Imatinib, in particular, has become the first-line treatment, especially for GISTs driven by KIT and PDGFRA mutations. Second- and third-line treatments, such as sunitinib and regorafenib, have also shown strong efficacy [25]. However, the effectiveness of TKIs in treating SDH-deficient GISTs remains limited and controversial, primarily due to poor response and resistance to imatinib. In a retrospective observational study conducted in China involving 12 patients with

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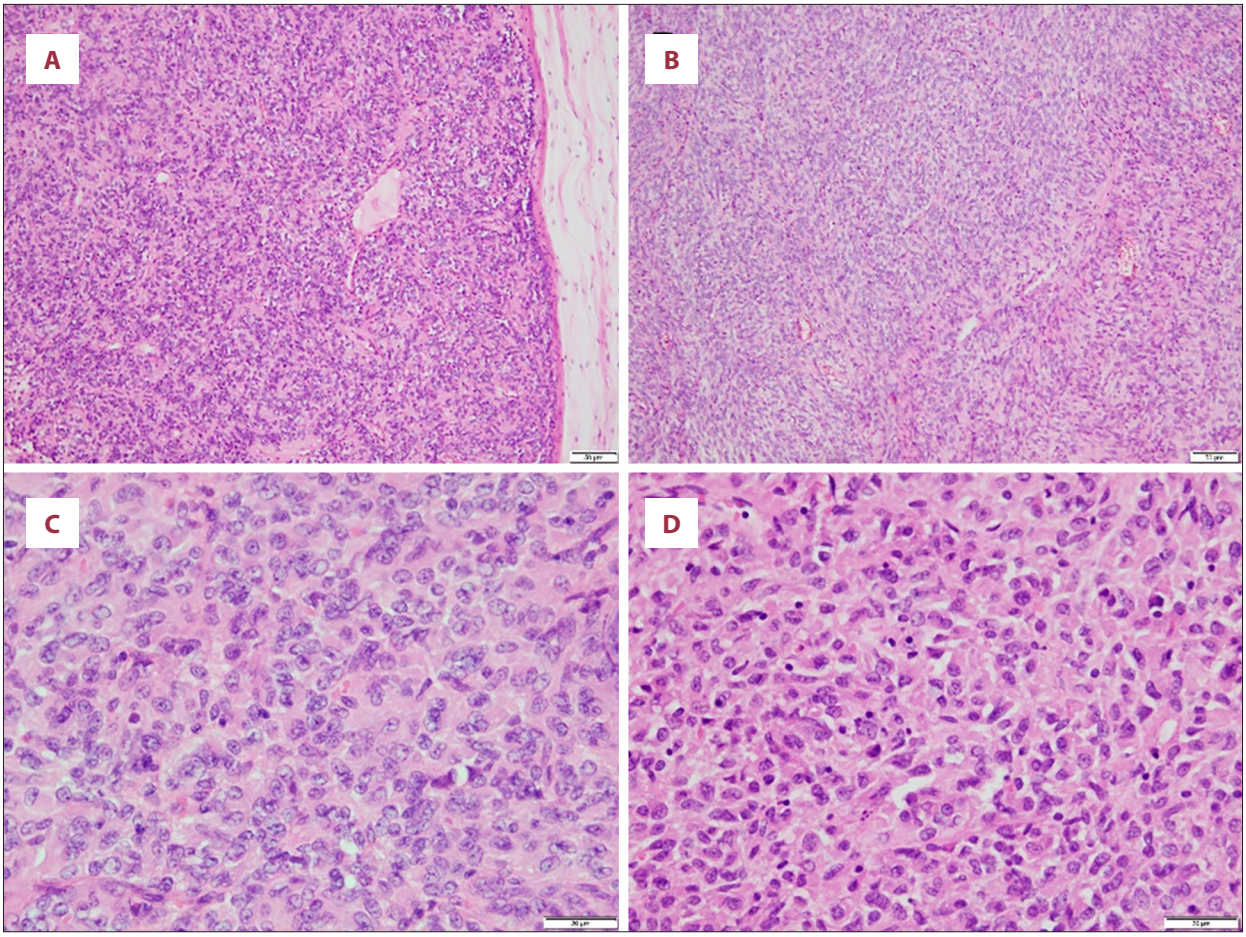

Figure 4. Pathological images. (**A, B**) H&E stain ×100 magnification. The tumor tissue exhibits a diffuse distribution with tightly packed cells, occasionally arranged in sheet-like or fascicular patterns. The tumor margins are relatively well-defined, with some areas showing fibrous stromal separation and sparse vascular distribution. (**C, D**) H&E stain ×400 magnification. The tumor cells are round-to-oval, with mildly eosinophilic cytoplasm. The nuclei are large, with distinct nuclear membranes and visible nucleoli. Nuclear atypia is evident, with irregular chromatin distribution and occasional hyperchromatic nuclei.

SDH-deficient GISTs [26], 4 patients who had progressed on imatinib achieved disease control after switching to sunitinib. Sunitinib not only inhibits the ATP-binding sites of KIT and PDGFRA, but also blocks VEGFR and PDGFRA receptors, making it a multi-receptor tyrosine kinase inhibitor. This mechanism may explain its efficacy in treating SDH-deficient GISTs [25]. Regorafenib, a third-line treatment for progressive GIST patients, is a multi-kinase inhibitor that targets angiogenesis (VEGFR1-3, TIE2), stromal generation (PDGFR-β, FGFR), and oncogenic activation (KIT, RET, RAF-1, BRAF, and BRAFV600E). A phase II clinical trial (NCT02638766) in Europe reported an 86.7% disease control rate (DCR) after 12 weeks in 15 SDH-deficient GIST patients treated with regorafenib, suggesting that anti-angiogenic agents may be more effective than imatinib for SDH-deficient GISTs[27]. Another multicenter phase II trial (NCT01068769) involving 6 patients with wild-type GISTs found that effective VEGFR inhibition is critical for controlling SDH-deficient GISTs [28].

As previously mentioned, SDH-deficient GISTs often exhibit promoter hypermethylation, leading to the transcriptional silencing of 6-O-methylguanine DNA methyltransferase (MGMT). This suggests that alkylating agents, such as temozolomide, may be effective for treating SDH-deficient GISTs. A phase II study (NCT03556384) evaluating temozolomide in advanced SDH-deficient GIST patients yielded promising preliminary results, with 2 out of 5 patients showing partial responses and the remaining 3 achieving disease control [2]. Additionally, a phase II clinical trial (NCT04595747) is currently investigating the efficacy of the novel small molecule fibroblast growth factor receptor (FGFR) inhibitor rogaratinib in SDH-deficient GISTs. Given the rarity of this condition and the limited number of cases, ongoing clinical trials for various targeted therapies are essential. Further research into the underlying mechanisms of the disease will help identify more effective therapeutic targets. In the present case, the patient is not being treated with targeted drugs such as imatinib due to the absence of mutations detected by

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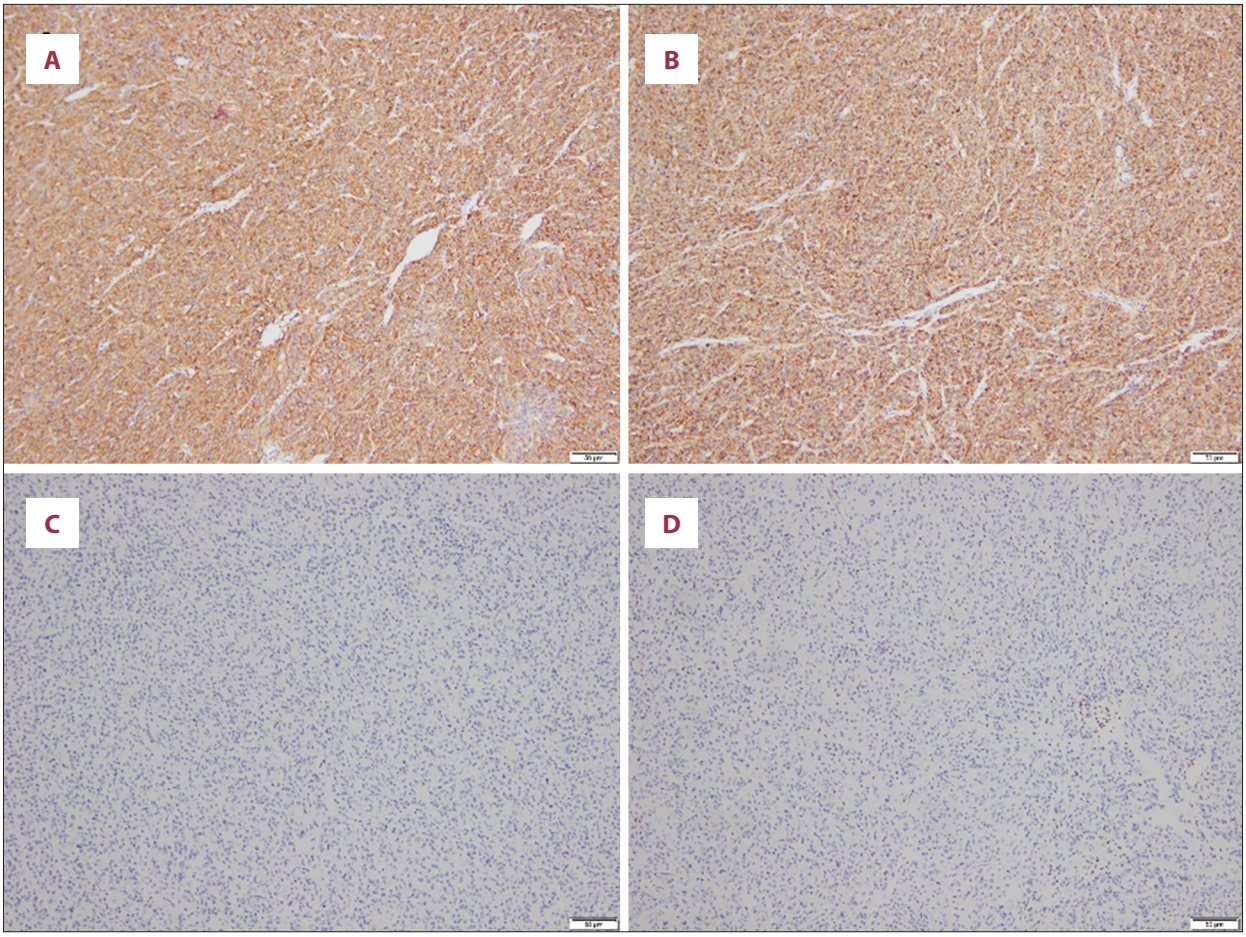

Figure 5. Pathological images. Immunohistochemistry showed positivity for CD117 and Dog-1, with negative results for PDGFRA and SDHB. The Ki-67 index was approximately 4%. (**A**) CD117(+); (**B**) Dog-1(+); (**C**) PDGFRA(-); (**D**) SDHB(-).

NGS. Nevertheless, the absence of a comprehensive genetic mutation analysis may have resulted in certain deletions being undetected. The patient is currently 6 months after surgery with no signs of recurrence and is being closely monitored.

Conclusions

This surgical case of SDH-deficient GIST presenting with hemorrhage reveals 2 pathognomonic features: multifocal tumorigenesis and nodal metastasis, which are key differentials from KIT/PDGFRA-mutant GISTs. Despite typical indolence, radical resection remains imperative when anatomically viable. Current therapeutic limitations necessitate multidisciplinary management with neoadjuvant targeted therapy, surgical excision, and adjuvant protocols. Trial enrollment for novel therapies should be considered in eligible patients after comprehensive assessment. Our findings elucidate diagnostic challenges and therapeutic optimization in SDH-deficient GISTs, while providing clinical insights for exploring novel therapeutic targets through molecular pathogenesis investigation.

Department and Institution Where Work Was Done

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Declaration About Informed Consent

Patient consent was obtained.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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