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Gastric SMARCA4-deficient undifferentiated tumors: clinicopathological analysis of two cases in a single center

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Abstract

Objectives Gastric SMARCA4-deficient undifferentiated tumors are rare and have a poor prognosis. We analyzed two cases of gastric SMARCA4-deficient undifferentiated tumors with clinicopathologic characteristics, treatment and flow-up.

Methods Immunohistochemistry was used to evaluate the expression of BRG1 (SAMRCA4), SMARCB1 (INI-1), CKpan, Ki-67, CD3, CD20, CD163, PD-1, and PD-L1 in gastric SMARCA4-deficient undifferentiated tumors. Additionally, the clinical characteristics, imaging features, diagnosis, and treatment were analyzed.

Results Two elderly male patients (69 and 61 years old) with a large ulcerated mass located in the gastric fundus and cardia. Histologically, the tumor is of low adhesion, diffusely infiltrating lamellar growth, without any percentage of epithelial differentiation zones, and with little stromal component. Tumor cells round, oval, a small amount of irregular shape, easy to see mitotic figures. Some of them had obvious nucleoli, and a few had multiple nucleoli. The cytoplasm varies, and some cells are more abundant. Significant vascular and neural invasion. BRG1(SMARCA4) was absent, INI-1 was present, and Ki-67 proliferation index was highly expressed (≥ 80%). The remaining sarcoma-specific markers were negative. In case 1, the epithelial markers were negative and the PD-L1 combined positive score was 5. In case 2, CKpan was weakly expressed in only a dozen cells, and the PDL1 CPS was 10. The two patients received chemotherapy and anti-PD1 immunotherapy after radical gastrectomy for gastric cancer. The postoperative follow-up time of the two patients was 16 (case 1) and 3 months (case 2), respectively. The general condition was good, no recurrence or metastasis was observed, and the plasma tumor markers were in the normal range.

Conclusions Large SMARCA4-deficient tumors are more likely to have massive necrosis on the surface, leading to negative biopsy results. This tumor has a diffuse lamellar growth and needs to be differentiated from a variety of tumors with similar morphology, such as lymphoma, malignant melanoma, neuroendocrine carcinoma and undifferentiated sarcoma. The tumor cells were negative or only slightly positive for CKpan increases the difficulty of pathological diagnosis of this disease. However, loss of BRG1 (SMARCA4) expression can confirm the diagnosis. Chemotherapy combined with anti-PD1 treatment may have potential benefits in the management of gastric

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SMARCA4-deficient undifferentiated tumors. However, given the rarity of these tumors and the limited number of cases in our study, further research with larger cohorts is needed to validate these preliminary results.

Keywords Gastric cancer, SMARCA4-deficient, Pathological diagnosis, Immunotherapy, Prognosis

Introduction

According to the World Health Organization (WHO) fifth edition classification of tumors of the digestive system, undifferentiated gastric cancer is a rare highly aggressive tumor without specific cytological or structural type differentiation [1]. Multiple genetic changes drive the development of gastric cancer. Agaimy et al. reported that some undifferentiated GI cancers may be driven by mutations in genes encoding different components of the yeast mating-type switching/sucrose nonfermentation (SWI/SNF) complex [2]. These genetic alterations involve SMARCA4, SMARCA2, and SMARCB1, among which SMARCA4 and SMARCA2 are mutually exclusive. Gastric SMARCA4-deficient tumors are relatively rare, with only a dozen reports in the literature involving the two diagnostic terms of undifferentiated carcinoma and undifferentiated tumor. Some scholars tend to diagnose SMARCA4-deficient undifferentiated tumors when there is no glandular structure, poor adhesion and no diffuse strong keratin expression [3]. Regardless of nomenclature, the rhabdoid morphology of tumor cells is considered an important indication of SMARCA4-deficient tumors but is not observed in all cases. Owing to the insufficient understanding of this tumor in daily work, it is challenging for pathologists to make a correct diagnosis from biopsy samples. Even a diagnosis of general poorly differentiated or undifferentiated carcinoma in a radical specimen is possible. This paper reports two cases of gastric SMARCA4-deficient undifferentiated tumors and discusses their clinicopathological features, diagnosis and differential diagnosis on the basis of the diagnosis and treatment process, follow-up data and literature review.

Materials and methods

Study cases

Two patients with gastric SMARCA4-deficient undifferentiated carcinoma diagnosed at the Shexian Branch, Second Affiliated Hospital of Zhejiang University School of Medicine (Shexian People's Hospital), from May 2023 to November 2024 were included. The clinical and pathological data of the patients were collected and followed up by telephone. The last follow-up time was December 2024. This study was approved by the Shexian People's Hospital Ethics Committee (2024–009).

Hematoxylin and Eosin (HE) staining biopsy and surgical samples were fixed in 10% neutral formalin, routinely dehydrated, embedded in paraffin, sectioned at a thickness of 4 μm and stained with HE.

Immunohistochemical (IHC) staining: the primary antibodies used included BRG1 (SAMRCA4), SMARCB1 (INI-1), CKpan, Ki-67, CD3, CD20, CD163, PD-1, and PD-L1. Leica automatic immunohistochemical staining instrument was used, and the specific steps were performed according to the kit instructions.

IHC scoring of PD-L1 combined positive score (CPS) in gastric gancer. The CPS was calculated as the ratio of PD-L1 positive cells (tumor cells, lymphocytes, and macrophages) to the total number of viable tumor cells, multiplied by 100. Specifically, PD-L1 positivity was defined as any intensity of membranous staining in tumor cells or cytoplasmic/membranous staining in immune cells. BRG1 (SAMRCA4) was evaluated based on nuclear staining. Tumors were classified as SMARCA4-deficient if there was complete loss of nuclear staining in tumor cells, while non-neoplastic cells (e.g., endothelial cells and lymphocytes) served as internal positive controls., SMARCB1 (INI-1) expression was similarly assessed based on nuclear staining. Tumors were considered INI-1-deficient if there was complete absence of nuclear staining in tumor cells, with retained expression in non-neoplastic cells serving as internal controls.

Results

Clinical history of the patients

In Patient 1, a 69-year-old male presented with abdominal distention and discomfort for 2 months and pain for 1 week. Contrast-enhanced computed tomography (CT) of the upper abdomen revealed irregular thickening of the wall of the gastric fundus and cardia, uneven moderate enhancement on contrast-enhanced scan, and enlarged lymph nodes with a diameter of approximately 1.7 cm in front of the retroperitoneal aorta, which were uniformly enhanced after contrast enhancement, indicating a space-occupying lesion in the gastric fundus and cardia. Gastroscopy revealed a large ulcerated mass in the fundus of the stomach (Fig. 1A), measuring 9.0 cm by 7.5 cm. The biopsy pathology was negative. A second biopsy was performed, and the pathology was still negative. Radical gastrectomy was performed with the consent of the patient and his family, and the tumor stage was pT4N1Mx.

In Patient 2, a 61-year-old male presented with subxiphoid discomfort for 1 year and recurrent upper abdominal pain for more than 1 month. Gastroscopy revealed a large ulcerated mass in the fundus and cardia (Fig. 2A), measuring 7.0 cm by 5.0 cm. Contrast-enhanced CT of

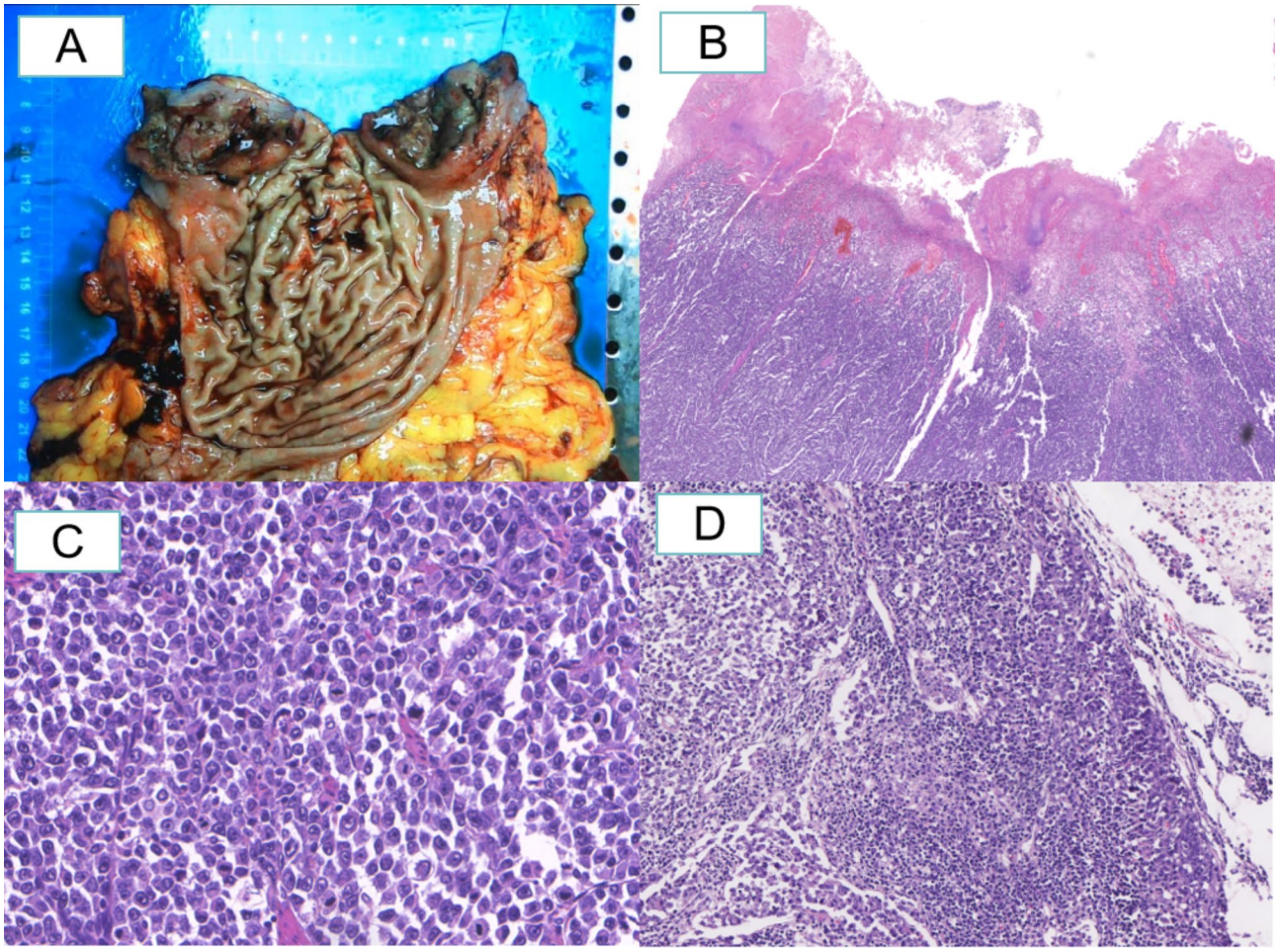

Fig. 1 Gross and histomorphological findings of Patient 1. Gross examination revealed a large ulcerated mass in the cardia and fundus (**Fig. 1A**), a large necrotic area on the tumor surface (**Fig. 1B**, 40x), poor adhesion of tumor cells, abundant cytoplasm and nuclear deviation similar to those of the plasma cell tumor, an obvious nucleolus (**Fig. 1C**, 400x), and tumor tissue in the lymph node (**Fig. 1D**, 100x)

the upper abdomen revealed a dense mass of soft tissue in the fundus and cardia, with obvious enhancement, and multiple small lymph nodes between the liver and stomach. The results suggested the presence of malignant tumors in the fundus and cardia. Gastroscopic biopsy pathology revealed malignancy, and undifferentiated or poorly differentiated carcinoma was considered. The patient underwent radical gastrectomy for gastric cancer, and the tumor stage was pT3N0MX. Laboratory tests of tumor markers and liver and kidney function revealed no obvious abnormalities in the two patients.

Histological features

Microscopic examination in Patient 1 revealed necrosis on the surface of the tumor, and the cells showed diffuse growth (Fig. 1B). In some areas, solid nested structures were not obvious, and there were few interstitial fibers. The tumor cells were round and oval, with a few irregular shapes, and mitotic figures were easy to visualize. Some of the nuclear chromatin was dark and coarse-grained, some had obvious nucleoli, and a few had multiple nucleoli. Some nuclei were eccentric, resembling plasmablastic morphology (or atypical rhabdomyoblastic differentiation), with a few odd nuclei and multinuclear tumor giant cells (Fig. 1C). Vascular and neural invasion and lymph node metastasis were observed (Fig. 1D). Peripheral tumor tissue and tumor-surrounding stroma were accompanied by varying amounts of lymphocyte infiltration. In Patient 2, necrosis and diffuse lamellar growth of tumor cells were observed in the mass (Fig. 2B), with minimal stromal fiber components, multiple foci with a small amount of lymphocyte accumulation in the central area of the tumor (Fig. 2C), and scattered eosinophil infiltration. The tumor cells were deeply stained, mainly round cells, with little cytoplasm, and most of the cells had fine granular nuclear chromatin. Most tumor cells had obvious nucleoli, mainly single nucleoli, which resembled an immunoblastic morphology. Some cells presented obvious red nucleoli (Fig. 2D), and even 2–3 nucleoli were observed close to the nuclear membrane,

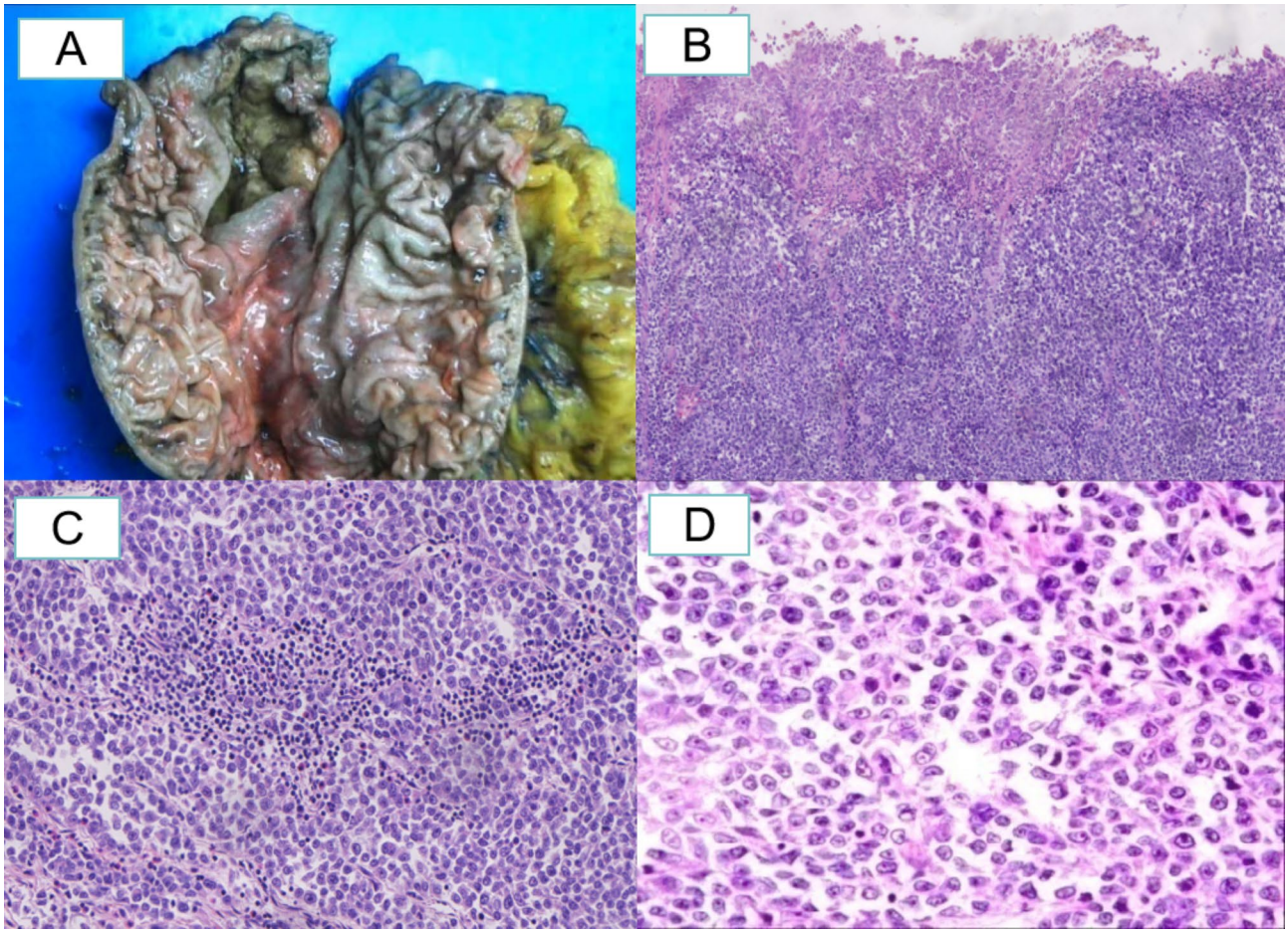

Fig. 2 Gross and histomorphological findings of Patient 2. Gross examination revealed a large ulcerated mass in the cardia and fundus (**Fig. 2A**), with necrotic and diffuse hyperplasia of tumor cells at low magnification (**Fig. 2B**, 100x). The tumor cells had poor adhesion, and lymphocyte aggregation was observed in the stroma, which mimicked the structure of lymphoma (**Fig. 2C**, 200x). Red nucleoli were observed in some tumor cells (**Fig. 2D**, 400x), and 2 to 3 adherent nucleoli were similar to centroblast in some cells

similar to the morphology of centroblast. Mitotic figures were easy to visualize, the boundary between the tumor and surrounding normal tissues was clear, the infiltration pattern was similar to that of sarcoma or lymphoma, and vascular and nerve invasion was observed.

Immunophenotypic features

In Patient 1, the tumor cells were negative for CKpan (Fig. 3A) and negative for BRG1 (SMARCA4) (Fig. 3B). INI-1 was present, the Ki-67 proliferation index reached 80% (Fig. 3C), and the combined.

positive score (CPS) of PD-L1 was 5 (Fig. 3D). PD-1 was weakly expressed at approximately 1%. CD3 was positive in tumor stroma and peritumoral, tumor-associated macrophages were positive for CD163. CD20, CD34, S-100, CD38, CD138 and CD56 were negative for the tumor cells (Supplementary Fig. 1). In Patient 2, the tumor cells were very weakly positive for CKpan (Fig. 4A) and absent for BRG1 (SAMRCA4) (Fig. 4B). INI-1 was present, the Ki-67 proliferation index reached 90% (Fig. 4C), and the PD-L1 CPS was 10 (Fig. 4D). PD-1 was weakly expressed in approximately 2% of the samples. CD3 and CD20 showed a small number of lymphocytes positive. CD163 highlight tumor-associated macrophages. CD34, S-100, CD38, CD138, CD56, CD99, ALK, TDT and MPO were all negative for the tumor cells (Supplementary Fig. 2).

Postoperative treatment and follow-up

After total gastrectomy, Patient 1 received paclitaxel, oxaliplatin, sintilimab chemotherapy and anti-PD1 immunotherapy for 6 courses, followed by maintenance treatment with sintilimab until now. The patient was followed up for 18 months, and no recurrence or metastasis was found via color Doppler ultrasound, whole-abdominal enhanced CT or laboratory examination. After total gastrectomy, Patient 2 was given etoposide, cisplatin, and sindilizumab chemotherapy and anti-PD1 immunotherapy for 2 courses, followed for 3 months, and was still under treatment. Imaging studies revealed no recurrence or metastasis. The plasma tumor markers CEA, CA199

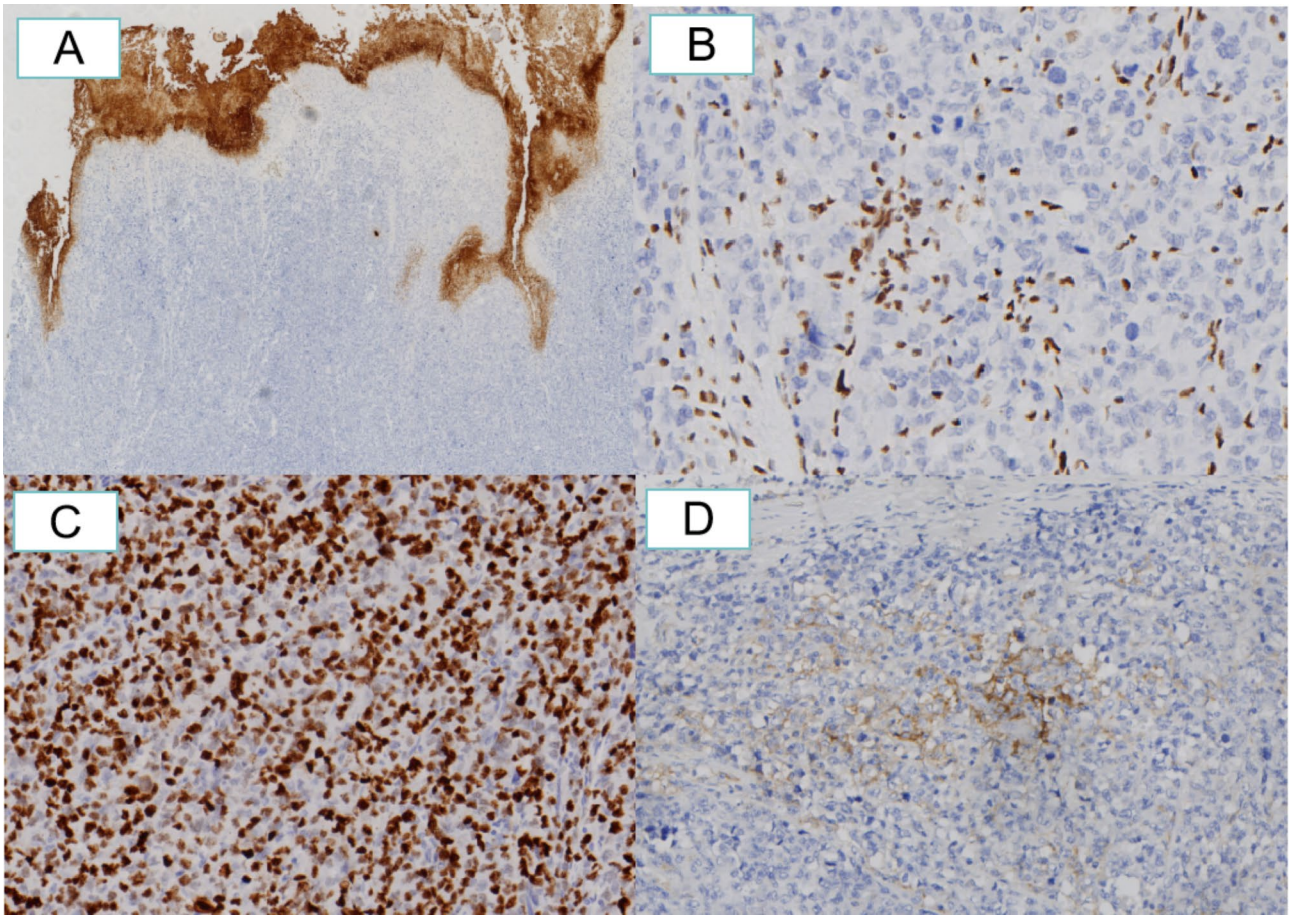

Fig. 3 Immunohistochemical staining findings of Patient 1. Immunohistochemical staining revealed that tumor cells were negative for CKpan (**Fig. 3A**, 400x), SMARCA4 expression was absent (**Fig. 3B**, 400x), Ki-67 proliferation was approximately 80% (**Fig. 3C**, 200x), and the PD-L1 combined positive score (CPS) was 5 (**Fig. 3D**, 200x). En Vision method

and AFP were all in the normal range during diagnosis and follow-up.

Discussion

SMARCA4 is located on chromosome 19p13.2, also known as BRG1, and belongs to the ATP hydrolase subunit of the SWI/SNF complex. Compared with SMARCB1, the core subunit of this complex, SMARCA4 mutations are relatively rare and are abnormal in approximately 5–7% of human malignancies [4]. Studies on SMARCA4-deficient tumors have focused mainly on the chest, and a relatively large number of SMARCA4-deficient lung cancer cases have been reported recently [5]. Gastric SMARCA4-deficient tumors are rare, and the maximum number of cases reported in a single study is 8 [6]. Neil et al. reported that 3.6% (42/1174) of patients with esophageal, esophagogastric junction and gastric cancer had SMARCA4 pathogenic mutations, 28.6 (12/44) of which were located entirely in the stomach [7]. A study in Asia revealed that approximately 2% of gastric cancers, 0.5% (6/1199) of which were completely absent, had altered SMARCA4 expression [8]. Lin et al. [9] summarized the previous 31 cases: 77.4% (24/31) were male patients, and the incidence of gastric disease was the highest (45.5%, 10/24), followed by that of gastric disease (33%, 8/24). Since then, a total of 16 cases have been described in detail in 5 studies [3, 10–13]. Only 1 patient was female, and gastric body lesions were still the most common (43.8%, 7/16), followed by cardia and fundus lesions (37.5%, 6/16); the incidence of proximal gastric lesions increased significantly. Among the 47 reported cases [3, 9–13], the ages of the patients ranged from 21 to 82 years, with an average age of 62.0 ± 13.1 years and a median age of 64 years, among which 7 patients were younger than 50 years and 2 patients were younger than 30 years. The sizes of 29 tumors ranged from 2 to 14 cm, with an average of 7.2 ± 3.0 cm and a median of 7 cm, with 20.6% (6/29) ≥ 10 cm. 72% (34/47) of the tumors were TNM stage III or IV at the time of diagnosis. Lymph node metastasis occurred in 85.7% (36/42) of patients, and other site metastasis occurred in 42.1% (16/38) of patients.

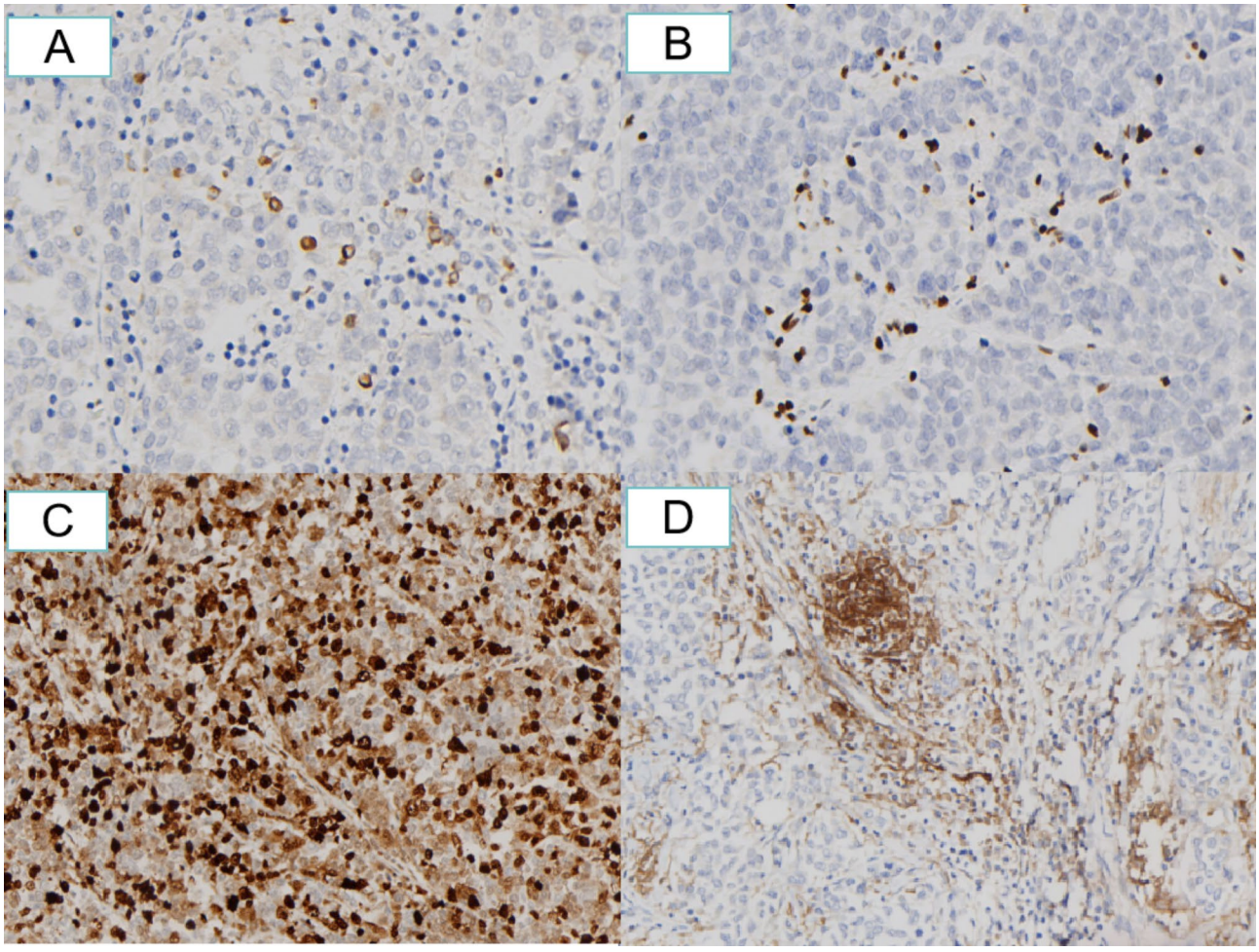

Fig. 4 Immunohistochemical staining findings of Patient 2. Immunohistochemical results revealed that CKpan was weakly positive in a dozen scattered cells (**Fig. 4A**, 400x), which was the only positive area in the whole section. The tumor cells lost SMARCA4 expression (**Fig. 4B**, 400x), Ki-67 proliferation was approximately 80% (**Fig. 4C**, 200x), and PD-L1 CPS was 10% (**Fig. 4D**, 200x). En Vision method

An ulcerated mass is the most common gross manifestation of gastric SMARCA4-deficient undifferentiated tumors [9–13]. Our two patients had large ulcerated masses located in both the gastric fundus and the cardia. In Patient 1, two biopsies failed to confirm the tumor diagnosis. Zhong et al. [12] reported a case of a large mass located in the cardia and fundus that underwent two failed biopsies. Compared with normal gastric cancer, large SMARCA4-deficient tumors are more likely to show massive necrosis on the surface, leading to negative biopsy results. It is very helpful for gastroscopists to recognize this characteristic of the tumor and biopsy it again in time.

Gastric SMARCA4-deficient undifferentiated tumors are mainly diffuse or solid structures with dedifferentiated or poorly differentiated cell morphology, poor cell adhesion, and with or without rhabdoid cell differentiation [3, 6]. The cytoplasm of the tumor cells was different, with light pink staining. The nuclei were mainly round or oval and vacuolated. Blue or blue-purple nucleoli were easily observed, and large red nucleoli were rarely observed [12]. Tumor giant cells were observed in some cases. Mitotic figures are easy to see. The gastric SMARCA4-deficient tumors reported in the literature can be divided into two patterns: one pattern is a pure undifferentiated morphological pattern, which can be diagnosed as tumor or carcinoma on the basis of the expression of epithelial markers [3]. The other type is undifferentiated carcinoma accompanied by a somewhat different pattern of epithelial differentiation components. The latter is dominated by glandular structures [6, 9] and rarely involves squamous differentiation [11], which are basically diagnosed as undifferentiated carcinomas. Our patient had the first type and was diagnosed with an undifferentiated SMARCA4-deficient tumor.

Rhabdoid differentiation of tumor cells is suggestive for diagnosis, but it is difficult to interpret when the morphology is not typical. It is more misleading

when epithelial markers are not expressed, when tumor cells are relatively uniform, when plasmablastic and/or centroblast-like.

morphology is present, and when red nucleoli are even present. The differential diagnosis includes lymphohaematopoietic tumors, malignant melanoma, neuroendocrine carcinoma, and undifferentiated sarcoma. (1) Lymphoma hematopoietic tumors mainly include diffuse large B and anaplastic large-cell lymphomas, with the former expressing B-cell markers and the latter expressing CD30 and EMA. Some patients can also express ALK; if necessary, B- and T-receptor gene rearrangement can be performed to confirm the diagnosis. SMARCA4-deficient undifferentiated tumors with abundant cytoplasm need to be differentiated from histiocytic sarcomas, which diffusely express CD18 and CD138. (2) Malignant melanoma: This is essentially a metastatic lesion, and the patient should be carefully asked about his or her history. Immunohistochemical S-100 protein, SOX10, and HMB45 were helpful. (3) Neuroendocrine carcinoma: the solid nested growth pattern of cells was more obvious, and neuroendocrine markers (CD56, Syn, INSM1 and CgA) were diffusely positive in most cases. However, some SMARCA4-deficient undifferentiated tumors express CD56 and Syn [3, 6, 12], but no positive results for CgA have been reported. (4) Undifferentiated sarcoma: the cell atypia is large, and the pleomorphism is more obvious. Loss of SMARCA4 expression in tumor nuclei is an important indicator of diagnosis and can also be distinguished from undifferentiated sarcoma. Lesions with glandular structures in which more cells express epithelial markers may be diagnosed as common poorly/undifferentiated carcinomas. It is advisable to pay attention to the above details of tumor cells or to supplement SMARCA4 IHC staining in all cases of poorly/poorly differentiated carcinoma.

SMARCA4 deletion is thought to promote tumor dedifferentiation [14], with high invasiveness [15] and a poor clinical prognosis. Therefore, timely diagnosis and treatment options are very important. Conventional chemotherapy is considered to be of limited benefit to patients and is prone to progression [5]. Some studies have also revealed that SMARCA4-deficient lung cancer may have a better response to immunotherapy [5, 16]. The median survival of patients with SMARCA4-deficient gastric cancer is only 7 months [9]. To date, nine patients with gastric SMARCA4-deficient undifferentiated tumors have been reported to have received chemotherapy combined with anti-PD1 immunotherapy [3, 6, 10–12, 17]. Eight patients survived during the follow-up period (2–17 months), and two patients died at 5 months (patients with squamous differentiation) and 7 months [10, 11]. All were young patients with multiple distant metastases and/or liver metastases. In our study, two patients received postoperative chemotherapy combined with anti-PD1 immunotherapy, and the tumors did not progress during the follow-up period.

Sundaram Vickrama et al. underscored the significance of immune biomarkers in the immunotherapy of gastric cancer, highlighting that biomarkers such as PD-L1, MSI, TMB, EBV status, tumor microenvironment and immune cell infiltration play crucial roles in patient selection and predicting treatment response [18]. The high PD-L1 CPS in both cases indicates that PD-L1 expression on tumor cells themselves may be a critical target for anti-PD-1 therapy. This is consistent with findings in other studies demonstrating that PD-L1 expression on tumor cells can drive immune checkpoint inhibitor efficacy [19]. In our study, the presence of CD163-positive macrophages suggests that they may play a significant role in mediating the antitumor effects of immunotherapy. However, further validation of their efficacy and reliability requires additional cases and studies [20].

The study is limited by its small sample size ($n = 2$), which precludes definitive conclusions regarding treatment efficacy. The short follow-up period for one patient (3 months) also restricts our ability to draw long-term conclusions. Additionally, the variable expression of epithelial markers and the reliance on immunohistochemistry for diagnosis highlight the need for more advanced molecular techniques to improve diagnostic accuracy and therapeutic targeting in future studies.

Conclusion

Gastric SMARCA4-deficient undifferentiated tumor cells exhibit diffuse lamellar growth and should be differentiated from a variety of tumors with similar morphologies. Loss of immune BRG1 (SMARCA4) expression can be a definite diagnosis. The tumor progresses rapidly, and the prognosis is poor. Our findings suggest that chemotherapy combined with anti-PD1 treatment may have potential benefits in the management of gastric SMARCA4-deficient undifferentiated tumors. However, given the rarity of these tumors and the limited number of cases in our study, further research with larger cohorts is needed to validate these preliminary results.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13000-025-01651-0.

Supplementary figure 1: IHC staining findings of Patient 1. IHC staining results showed that tumor cells were negative for CKpan (**A**), Ki-67 proliferation was about 80% (**B**), PD-L1 CPS was 5 (**C**), INI-1 expression was intact (**D**), CD3 was positive in tumor stroma and peritumoral (**E**), Tumor-associated macrophages (TAM) were positive for CD163 (**F**). Low magnification, En Vision method

Supplementary figure 2: IHC staining findings of Patient 2. IHC staining results showed that tumor cells were negative for SMARCA4 (**A**), CD3 and CD20 showed a small number of lymphocytes positive (**B**, **C**). PD-L1 CPS

was 10 (**D**), Tumor-associated macrophages were positive for CD163 (**E**), Tumor cells were negative for CD138 (**F**). Low magnification, En Vision method

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None.

Author contributions
Xiaolin Cheng drafted the manuscript. Shuyue Chen provided the patient's history and documents. Xushui Jiang performed the immunohistochemical testing and image collection. Tao Li performed the electronic gastroscopy, and the results were analyzed. Hong Zhang summarized the patient's treatment process. Fengbo Huang and Tianhui Bao designed the study, made the pathological diagnoses, and revised the paper. All the authors contributed to the management of the patient, reviewed the images, histopathological and IHC slides, and edited the manuscript. All the authors read and approved the final manuscript and its submission for publication.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Shexian People's Hospital. Written informed consent was obtained from the patients and their families for the publication of this clinical case report.

Human ethics declaration
This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication
Written informed consent was obtained from the patients and their families for the publication of this study and any accompanying images.

Conflict of interest
Xiaolin Cheng, Shuyue Chen, Xushui Jiang, Tao Li, Hong Zhang, Fengbo Huang, and Tianhui Bao declare that they have no conflicts of interest.

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