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A case report of SMARCA4-deficient gastric cancer and review of the literature

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Abstract

We report the case of a 50-year-old female with gastric carcinoma. The tumor was positive for epithelial and other immunological markers; however, SMARCA4 was completely inactivated. The histological and immunophenotypic findings were consistent with a diagnosis of SMARCA4-DTS. Next-generation sequencing identified a frameshift mutation in *SMARCA4*. The pathological diagnosis was SMARCA4-deficient gastric carcinoma. The tumor exhibits a poor response to conventional chemotherapy and has a poor prognosis; therefore, correct diagnosis is necessary. Moreover, new therapies such as EZH2 inhibitors and etoposide should be considered in cases where conventional chemotherapy is ineffective.

Keywords

Gastric carcinoma, SMARCA4-deficiency, Immunohistochemistry

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Introduction

SMARCA4-deficient carcinoma of the stomach is a rare malignant tumor of the digestive tract. The fifth edition of the World Health Organization's Classification of Digestive System Tumors classifies digestive system tumors as undifferentiated carcinoma.[1] Histopathological observations revealed undifferentiated cells ranging from round to epithelioid, unevenly distributed, with the tumor cells in the central region resembling striated muscles.

The expression of SMARCA4/BRG1 is lost at the molecular level. *SMARCA4* is involved in the regulation of various biological functions. It is characterized by helicase and ATPase activities, which regulate gene transcription and function as a tumor suppressor gene during tumor initiation and progression.[2–4] Recent studies have identified SMARCA4 deficiency in various cancers and sarcomas, including undifferentiated or dedifferentiated cancers in the chest sarcoma, nonsmall cell lung cancer, esophageal adenocarcinoma, and cancers of the stomach, uterus, ovary, and kidney.[5–14]

These tumors are characterized by high malignancy, low differentiation rates, intense invasiveness, and brief survival periods.

SMARCA4-DTS are not responsive to conventional radiotherapy or chemotherapy, and there is currently no effective treatment. Gastric cancer with SMARCA4 deficiency is particularly prone to misdiagnosis as various types of poorly differentiated or undifferentiated tumors due to a lack of clear differentiation pathways and the limitations of molecular testing. Consequently, reports of gastric cancer with SMARCA4 deficiency are limited to a few instances,[14] with no support from prospective clinical trials, which still require more investigation with larger sample sizes.

To address this gap in the literature, this article presents a case of gastric SMARCA4-deficient carcinoma, focusing on its histological characteristics, immune marker expression, and second-generation sequencing outcomes. The aim is to provide a reliable source for accurate diagnosis and targeted treatment for such cases.

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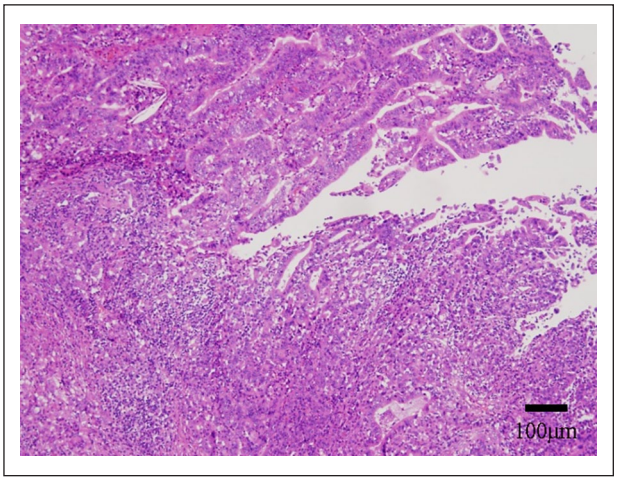

Figure 1. Widespread growth of dense layers of weakly bound tumor cells observed through a low-power microscope (H&E stain, 100×; right-bottom bar, 100 μm).
H&E: hematoxylin and eosin.

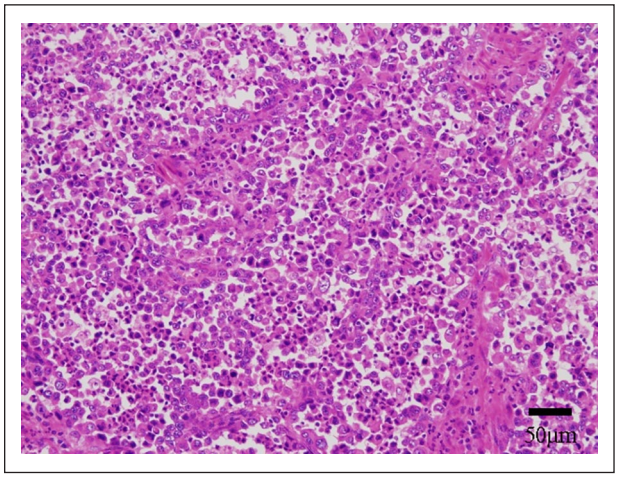

Figure 2. Under low magnification, a diffuse infiltration of heterotypic cells is observed, with the tumor cells exhibiting a lack of adhesion (H&E stain, 200×; right-bottom bar, 50 μm).
H&E: hematoxylin and eosin.

Case presentation

A 50-year-old female presented with a 3-month history of upper abdominal fullness and discomfort. She reported no epigastric pain, acid reflux, diarrhea, nausea, or vomiting. Upper gastrointestinal endoscopy revealed a large, curved, and rough anterior wall of the upper stomach, with a malformed stomach cavity and a fragile biopsy. Advanced gastric cancer was suspected. Pathological examination of the endoscopic biopsy showed a diffuse or adenoid-like arrangement of heterotypic cells with infiltrative growth patterns. The diagnosis was poorly differentiated adenocarcinoma of the gastric body. Chest and abdomen enhanced computed tomography (CT) showed thickening and enhancement of cardia, gastric fundus, and gastric body. Multiple enlarged lymph nodes were suggestive of advanced gastric cancer. Radical resection of cardiac cancer was performed, followed by pathological examination of the total gastrectomy specimen. The stomach measured 18 cm by 9 cm by 5 cm, with a lesser curvature of 13 cm and a greater curvature of 28 cm. A prominent ulcer tumor was visible on the gastric body's mucosal surface, positioned 0.8 cm away from the upper and 7 cm from the lower edges, covering an area of 12 cm by 11 cm.

The tumor infiltrated the entire layer of the stomach wall. Microscopic examination revealed diffuse infiltration of heterotypic cells at low power in the gastric wall. The cells were arranged in a glandular tabloid with a cordate and flaky pattern, with some areas lacking adhesion. At high power, cells were medium to large, with vesicular nuclei, evident nucleoli, and a clearly visible mitotic image. Additionally, rhabdoid cells and tumor cells with abundant cytoplasm were observed, with some cells exhibiting eosinophilic cytoplasm characterized by rhabdomyoid traits (Figures 1–3).

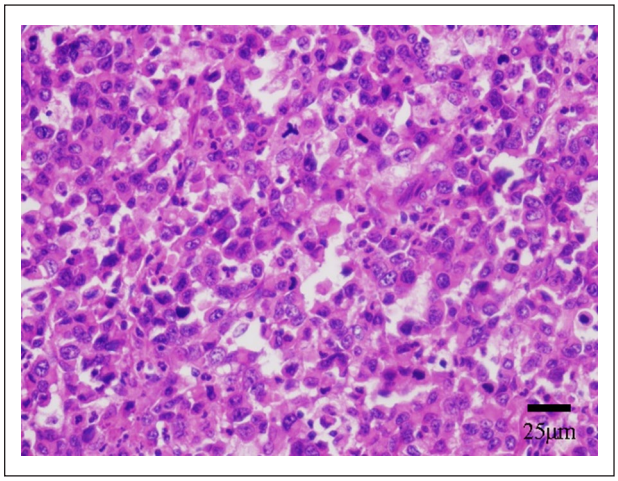

Figure 3. Under high magnification, the tumor cells appear medium to large, with clearly visible vesicular nuclei, distinct nucleoli, mitotic imagery, and abundant cytoplasm. The tumorSeveral cells exhibit eosinophilic cytoplasm and rhabdomyoid-like features (H&E stain, 400×; right-bottom bar, 25 μm).
H&E: hematoxylin and eosin.

Immunohistochemical analysis

The tumor cells tested positive for AE1/AE3, CK8/18, MSH2, MSH6, MLH1, PMS2, p53, and INI-1. They were focal positive for hepatocyte, MUC-2, MUC-5AC, and MUC6, and negative for Glypican-3, CD10, CDX-2, CD34, SOX2, SALL4, p40, and SMARCA4. HER-2 was negative, and the Ki67 proliferation index was approximately 60% (Figures 4–7).

Hybridization in situ results for EBER were negative.

Sequencing results for SMARCA4 showed the absence of mutations at site 2475 (indicated by the blue marker). However,

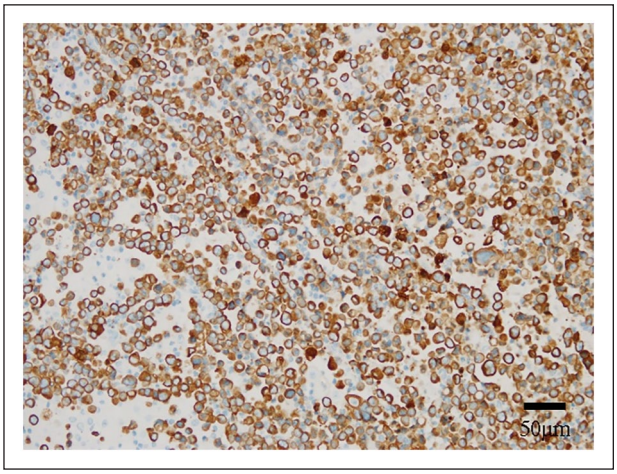

Figure 4. Immunostaining for CK18 revealed a positive result (IHC stain, 200×; right-bottom bar, 50 μm).
CK: cytokeratins; IHC: immunohistochemistry.

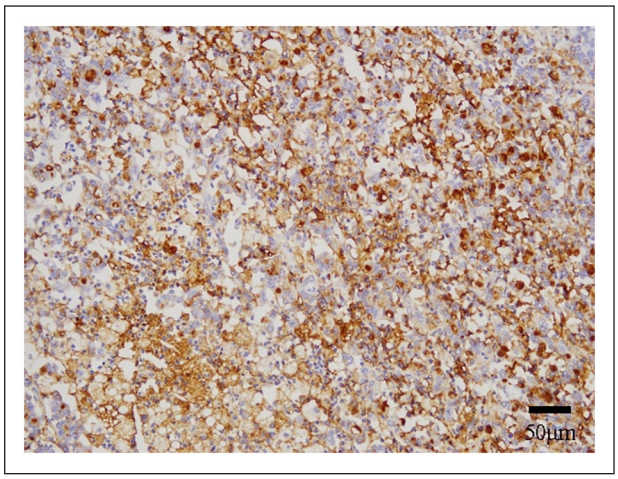

Figure 6. Immunostaining test for MUC-5AC revealed a scattered positive result (IHC stain, 200×; right bottom bar, 50 μm).
IHC: immunohistochemistry.

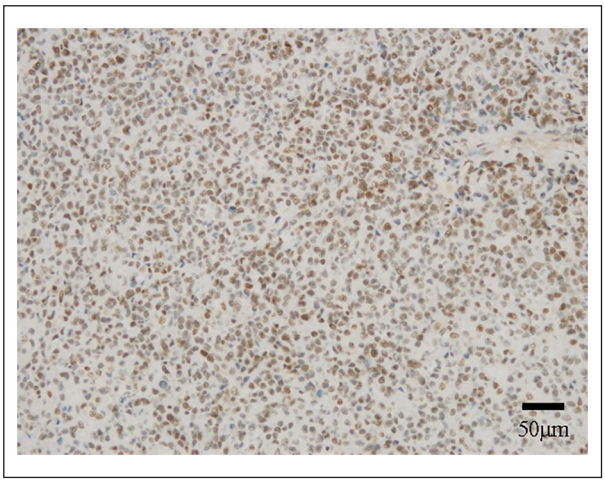

Figure 5. Immunostaining test for INI-1 revealed a positive result (IHC stain, 200×; right-bottom bar, 50 μm).
IHC: immunohistochemistry.

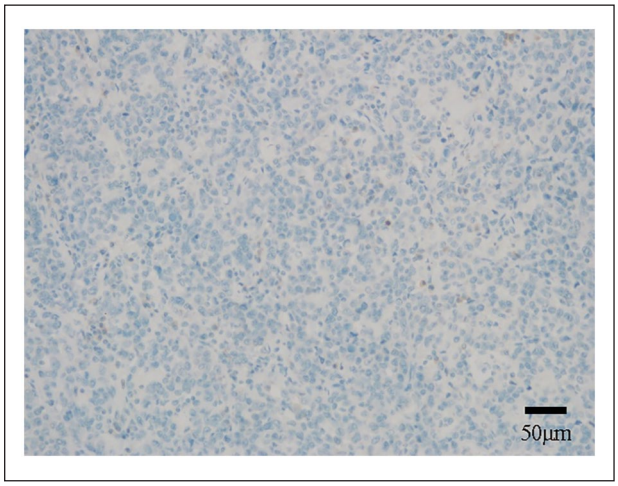

Figure 7. Immunostaining results for SMARCA4 revealed a negative result (IHC stain, 200×; right-bottom bar, 50 μm).
IHC: immunohistochemistry.

at the two sites marked in dark green, the sequencing results showed the presence of additional C bases, suggesting base insertion (Figure 8).

Discussion

SMARCA4 encodes the BRG1 protein on chromosome 19q13. SMARCA4/BRG1 is an ATPase subunit of the highly conserved SWI/SNF chromatin remodeling complex.[2] The SWI/SNF complex family also includes SMARCA2/BRM, SMARCB1/INI1, ARID1A, and ARID1B. The SWI/SNF complex regulates gene activity through chromatin remodeling, participates in DNA repair and replication, controls cell growth, division, differentiation, and other processes, regulates the transcription of many genes, and acts as a tumor suppressor during tumorigenesis and progression.[3,4]

Recent research links high-frequency mutations in the SWI/SNF chromatin remodeling complex subunits to tumor initiation and progression. Notably, common inactivating mutations in MARCA2 and SMARCA4 result in the loss of their protein expression in the nucleus. Specifically, studies indicate that biallelic inactivation due to sporadic or genetic mutations in *SMARCA4* primarily drives tumorigenesis in ovarian hypercalcemia small cell carcinoma. Moreover, SMARCA4 deficiency is also implicated in several other cancers, including thoracosarcoma, nonsmall cell lung cancer, esophageal cancer, stomach cancer, uterine cancer, ovarian cancer, and kidney cancer.[5–14]

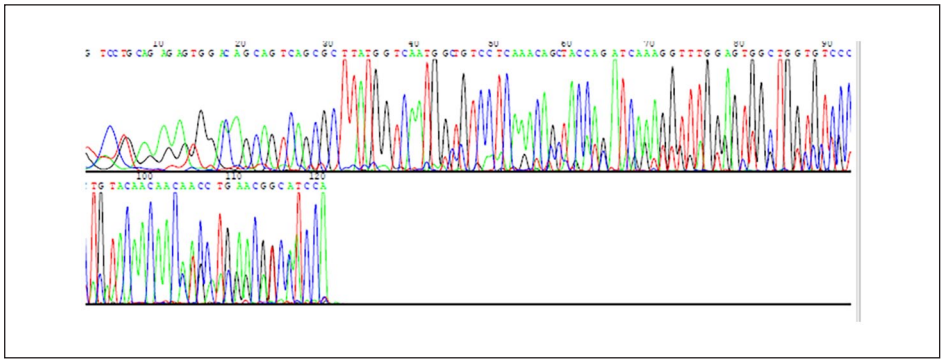

Figure 8. Results of SMARCA4 sequencing.

The occurrence of SMARCA4-deficient stomach cancer is sporadic. Only a few cases have been reported, and such tumors have not been described in the World Health Organization's new classification.[14] Histologically, these tumor cells exhibit similar solid structures. The mildly adhesive epithelioid cells are usually arranged in flakes or nests. Tumor cells have eosinophilic cytoplasm, and their nuclear deviations are often characterized by rhabdoid morphology: the nucleus is rounded, slightly polymorphic, and has apparent nucleoli. Tumor tissues frequently show a high number of mitotic figures and significant necrosis and apoptosis. Spindle cell components may also occur, accompanied by fibroconnective group or myxoid stroma proliferation.

Immunohistochemistry revealed that SMARCA4/BRG1 expression was deficient, and Ki67 showed a high proliferation index. In this case, tumor cells displayed glandular, cord, and sheet patterns, with adhesion-deficient cells noted. The cells, medium to large, had abundant, sometimes eosinophilic, cytoplasm with rhabdomyoid features. The chromatin appeared vacuolar, and nucleoli were prominent. Immunophenotypically, the cells expressed epithelial markers like cytokeratin (CK) and showed SMARCA4/BRG1 deficiency, but retained INI-1 expression. Although some research links SWI/SNF complex alterations to rhabdomyoid differentiation in dedifferentiated cancers across organs, not all rhabdomyoid tumors exhibit *SWI/SNF* gene anomalies.

SMARCA4-deficient carcinoma of the stomach should be distinguished from the following tumors. (1) Melanoma: the tumor cells usually show a diffuse and patchy arrangement, with diverse cell morphology, such as epithelioid, spindle, and plasma cells, with or without pigment, and significant eosinophilic nucleoli can be seen. The tumor cells express melanin markers, such as S100 protein, SOX10, HMB45, and Melan-A, which helps differentiate SMARCA4-deficient carcinoma. (2) Lymphoma: heterotypic lymphoid cells exhibit diffuse infiltration with an irregular nucleus, dense chromatin, and patchy, nest-like structures without fibrous septa. The tumor cells often express lymphocyte markers such as leucocyte common antigens. (3) Neuroendocrine carcinoma: the tumor cells are arranged in nests with abundant interstitial blood sinuses forming organoid structures. Poorly differentiated neuroendocrine carcinoma, such as giant cell neuroendocrine carcinoma, has rich cytoplasm and needs to be differentiated from SMARCA4-deficient carcinoma. The tumor cells express neuroendocrine markers such as Syn, CgA, CD56, and NSE. CK is usually positive in paranuclear foci, and SMARCA4 is positive. (4) Malignant extrarenal rhabdoid tumor: this primarily occurs in infants and children, mostly in the central nervous system (atypical teratoma/rhabdoid tumor) or soft tissue, and occasionally in the gastrointestinal tract. It comprises nested or solid sheet rhabdoid cells with poor adhesion. Immunohistochemistry revealed tumor cells expressing vimentin, CKpan, and EMA. Microscopic examination shows some overlap with the immunophenotypes.

Additionally, the immunohistochemical result reveals a lack of SMARCB1/INI1 expression.[5]

Metastatic ovarian small cell carcinoma with hypercalcemia is common among young women. The typical clinical manifestation is an ovarian mass, which may be accompanied by hypercalcemia. Tumor cells are widely distributed and sometimes form a follicular pattern containing eosinophilic fluid. Immunohistochemistry reveals SMARCA4/BRG1 deficiency, similar to this case, but no significant tumor is found in the ovaries. Positron emission tomography/CT identifies the gastric body as the primary site.[6] Ewing's sarcoma/primitive neuroectodermal tumor presents as diffuse, sheet-like, and lobular arrangements of tumor cells with rounded or elliptic nuclei, fine chromatin, clear nuclear membrane, small or indistinct nucleoli, and lightly stained or translucent cytoplasm with unclear cell boundaries. Moreover, Homer–Wright Daisy clusters are common. Tumor cells showed diffuse and strong staining for CD99, with *EWSR1* translocation that distinguished it from SMARCA4-deficient carcinoma.[7] Notably, epithelioid gastrointestinal stromal tumor primarily occurs in the stomach and omentum. Tumor cells are arranged in organ-like, sheet-like, or nest-shaped patterns and are primarily round, oval, or short spindle-shaped epithelioid cells. The tumor cells are medium-sized with slightly eosinophilic cytoplasm and round or elliptical nuclei. In some cases, there are vacuole-like cells or cells resembling signet rings. Furthermore,

CD34, CD117, and DOG1 were expressed in typical cases, with KIT or *PDGFRA* mutations present.

Studies show that patients with SMARCA4-deficient expression have shorter survival, indicating a poor prognosis. Thus, it is crucial to expand sample sizes to further assess their prognostic relevance in gastric cancer. Tumors with SMARCA4/BRG1 deficiency correlate with a notably poor prognosis, with no effective treatments currently available. Distinguishing this tumor from other undifferentiated or poorly differentiated tumors is clinically significant, and targeted therapy could be a viable therapeutic option. Precision therapy is expected to enhance patient outcomes in the future.

Conclusion

SMARCA4-deficient tumors, characterized by absent SMARCA4/BRG1 expression, possibly stem from pluripotent cells. These tumors generally present as undifferentiated or dedifferentiated with diffuse, patchy cells varying from round, epithelial-like to rhabdomyoblast-like, often showing single cells with moderate dysplasia. Immunohistochemical tests confirm the lack of SMARCA4/BRG1, critical for diagnosing these aggressive tumors with poor prognosis. Such testing is essential in poorly differentiated tumors to guide treatment and prognosis. SMARCA4-deficient undifferentiated carcinomas, typically resistant to standard FLOT chemotherapy, have bleak outcomes. Therapeutic alternatives such as EZH2 inhibitors, histone deacetylase inhibitors, and cyclin inhibitors are being explored. New treatments, including EZH2 inhibitors and etoposide, should be considered when conventional therapies fail.

Author contributions

L.C. material preparation, data curation, literature search, writing original draft. Z.C. data curation, formal analysis, writing original draft. Y.X. data curation, formal analysis, providing pathological diagnoses. H.F. conceptualization, funding acquisition, writing original draft, editing.

Declaration of conflicting interests

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Ethics approval

Our institution does not require ethical approval for reporting individual cases or case reports.

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article

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