Small intestinal SMARCA4-deficient undifferentiated carcinoma with intussusception: A case report

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Abstract. Switch/sucrose non-fermentable (SWI/SNF) related matrix associated actin-dependent regulator of chromatin sub-family A member 4-deficient undifferentiated carcinoma (SMARCA4-DUC) of the small intestine is a rare and highly aggressive subtype of gastrointestinal malignancy. The present study reported the case of SMARCA4-DUC in a patient who presented with intestinal intussusception and multi-organ metastasis to the lungs, liver, spleen and skin, which led to rapid progression and death in 43 days. The present case highlighted the unique histological and molecular features of SMARCA4-DUC, characterized by the absence of SMARCA4 expression and undifferentiated cellular morphology. The present case report aimed to describe the clinical presentation, imaging findings, pathological features and treatment course, to further the current understanding of SMARCA4-associated malignancies and improve the recognition of SMARCA4-DUC among clinicians and pathologists. Next-generation sequencing of the primary small intestinal tumor identified pathogenic mutations in PTEN, TP53, ataxia telangiectasia mutated, ephrin type-A receptor 5 and EGFR p.F997L, suggesting a DNA-repair-deficient genomic background and providing potential targets for future precision therapy. Further research is warranted to determine the molecular mechanisms underlying SMARCA4-DUC, for the development of targeted therapeutic strategies and to improve the understanding of the aggressiveness of SMARCA4-DUC.

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Introduction

Gastrointestinal malignancies account for >25% of the global incidence of all tumors and 35% of tumor-related mortality, which poses a notable threat to the health of individuals worldwide (1,2). Based on histological features, gastrointestinal malignancies can be classified into adenocarcinoma, squamous cell carcinoma, sarcomatoid carcinoma and undifferentiated carcinoma (3,4). Among them, switch/sucrose non-fermentable (SWI/SNF) related matrix associated actin-dependent regulator of chromatin sub-family A member 4 (SMARCA4)-deficient undifferentiated carcinoma (DUC) of the gastrointestinal tract is a subtype of gastrointestinal undifferentiated carcinoma (4,5).

SMARCA4 deficiency is more commonly observed in non-small cell lung cancer, with an incidence of 5-10%. However, it is relatively rare in gastrointestinal cancer types, with limited reports available (6). The absence of SMARCA4 in primary tumors is associated with higher tumor invasiveness and a poorer prognosis. Compared with common tumors, there may be differences in clinical features, imaging manifestations, pathological characteristics and treatment responses (7,8). A previous study validated that in 436 cancer cell lines, tumors with low SMARCA4 expression demonstrated markedly higher IC_{50} values for multiple chemotherapeutic drugs compared with those with high SMARCA4 expression, which implied that SMARCA4 deficiency may be a key reason for patient drug resistance (9). Another previous study indicated that SMARCA4 deficiency induces chemoresistance in tumor cells and also activates the EMT process, which thereby enhances tumor invasion (10). Therefore, additional studies and reports of cases of SMARCA4-deficient gastrointestinal undifferentiated carcinoma may enhance the current understanding of its biological behavior and potentially provide key insights for clinical diagnosis, the formulation of treatment strategies and prognosis assessment in the future.

The present study aimed to report a rare case of small intestinal SMARCA4-DUC. The patient presented with intestinal intussusception and progression to metastasis in the lungs, liver, spleen and skin. The condition of the patient deteriorated rapidly, with death occurring 42 days following the initial detection of the lesion. The present study aimed to provide a detailed description of the clinical features, imaging manifestations, pathological characteristics and molecular biological features of the present case, to aid in the diagnosis and treatment of SMARCA4-deficient gastrointestinal undifferentiated carcinoma.

Case report

A 69-year-old man with gastrointestinal discomfort was admitted to Weifang No. 2 People's Hospital (Weifang, China) on April, 2024 (day 1). The patient reported that they had suffered from chronic gastritis and gastric ulcers for >10 years. The mental health of the patient was poor at the time of admission, with dyspnea and no other abnormalities.

After the patient was admitted to the hospital, a biochemical examination was conducted (Table I). Results of the examination demonstrated carcinoembryonic antigen levels of 22.81 ng/ml (reference value, 0-4.5 ng/ml), indicative of a malignant neoplastic lesion. The medical team conducted a chest CT (Optima CT660, GE HealthCare; 5-mm-layer-thickness; helical scanning; Table II) with plain scanning and enhancement examination. Results of the CT examination revealed multiple nodules and masses in both lungs, with the largest mass located in the right lower lobe of the lung in the outer basal segment. The mass exhibited a diameter of ~31 mm, with an average CT value of 19 Hounsfiled unit (HU), clear borders and smooth edges (Fig. 1A). There was no notable enhancement in the central area of the lesion on enhanced scanning (double-phase enhancement CT values of 20 HU and 21 HU, respectively), with circumferential enhancement around the edges (Fig. 1B). Furthermore, the lymph node in the right hilar region of the right lung was enlarged (Fig. 1C), with a maximal short diameter of ~15 mm. An abdominal CT scan (Optima CT660, Cytiva; 5-mm layer thickness; spiral scan) and enhanced examination revealed multiple hypodense nodules in the liver, with the largest nodule observed in the hepatic segment VIII (Fig. 2A). This nodule exhibited a diameter of ~12 mm, a CT value of 20 HU on scanning and enhanced scans of 30 HU, 35 HU and 39 HU in hepatic arterial, portal and delayed phases, respectively. A brain CT was also performed and indicated no evidence of metastasis, hemorrhage or infarction.

The clinical history of the patient, imaging and laboratory findings were suggestive of a malignant neoplastic lesion. On day 6, the patient underwent a puncture biopsy of a mass in the extramedullary segment of the lower lobe of the right lung. The puncture specimen was a greyish-white tissue of two strips with a length of 0.8-1.0 cm and a diameter of 0.1 cm. The puncture specimen was further examined using H&E staining. The tissue sections were fixed with 4% paraformaldehyde at room temperature for 30 min. The thickness of each section was 5 μm. Hematoxylin staining was performed at room temperature for 7 min, followed by eosin staining at room temperature for 1 min. The sections were then observed under an light microscope. The fresh specimen was dehydrated using alcohol in a room-temperature gradient, soaked in xylene at room temperature and embedded in paraffin at 65˚C. Subsequently, the pathological tissue was cut into 5-μm slices and soaked in room temperature xylene, anhydrous ethanol, 95% ethanol, 80% ethanol and H_2O. The tissue sample was stained using hematoxylin for 5 min and eosin for 1 min, followed by gradient alcohol dehydration and neutral resin sealing. Tissue samples were observed using a light microscope (scale bar, 200 μm). The tumor cells in the punctured tissue of the patient were diffusely distributed in the form of sheet nests. Furthermore, the tumor cells exhibited unclear borders, the cytoplasm was weakly basophilic or translucent, the nuclei were ovoid or short spindle-shaped, the frequent mitotic figures was irregular and small nucleoli were partially visible. Mitotic figures and a high amount of necrosis were observed (Fig. 3A). Histopathological staining of the patient tissue sample revealed negative expression of tumor markers for colorectal or lung cancer, though there is focal expression of squamous cell carcinoma markers. The tissue samples were fixed with 4% paraformaldehyde at room temperature for 30 min, and serial sections were cut at a thickness of 5 μm. After blocking, the sections were incubated with the primary antibody at 37˚C for 30 min, followed by incubation with the secondary antibody at room temperature for 8 min. To visualize the nuclei, the sections were treated with 3,3'-diaminobenzidine chromogenic solution for 8 min at room temperature and then counterstained with hematoxylin for 7 min at room temperature. Finally, the stained sections were examined under a light microscope. However, the specific origin of the tumor cannot be determined based solely on these findings. Therefore, clinical manifestations must be taken into account. The patient was admitted due to hematochezia and was found to have a positive fecal occult blood test. No pulmonary symptoms were observed. Imaging studies demonstrated tumors in the lungs and liver, which were peripherally located and well-defined, which suggested a higher possibility of metastatic tumors. Additionally, the mass causing intussusception had already invaded the muscular layer of the small intestine. Combining these clinical findings, it was concluded that the systemic tumors in the patient most likely originated from the small intestine.

Immunohistochemical staining was performed using Benchmark GX (Roche Diagnostics GmbH). The tissue samples were fixed with 4% paraformaldehyde at room temperature for 30 min, after which they were embedded in paraffin wax. Permeabilization was performed by treating the sections with 0.1% Triton X-100 at room temperature for 15 min. Each section was cut to a thickness of 5 μm. EDTA (pH, 8) was used for antigen repair and repair parameters were set at 100˚C for 30 min, according to the manufacturer's protocol. Endogenous catalase was blocked using 3% hydrogen peroxide for 5 min at room temperature. Tumor tissues were incubated with monoclonal antibodies against thyroid transcription factor-1 (TTF-1), NapsinA, cytokeratin (CK)5/6, synaptophysin (Syn), CK7, p40 and SMARCA4 at 37˚C for 30 min. Following primary incubation, samples were incubated with the HRP-labeled secondary antibodies (Roche Diagnostics GmbH) for 8 min at room temperature. Subsequently, the nuclei were visualized using 3,3'-diaminobenzidine chromogenic solution for 8 min at room temperature and stained using hematoxylin for 7 min at room temperature (Table III).

Table I. General examination and laboratory test results on admission.

A, General clinical examination

Parameter	Value	Reference range
Body temperature, ˚C	36.6	36.3-37.2
Heart rate, beats per min	82	60-100
Respiratory rate, breaths per min	18	15-20
Blood pressure, mmHg	130/82	90/60-120/80

B, ABG analysis

Parameter	Value	Reference range
pCO_2, mmHg	36.00	35-45
pO_2, mmHg	86.00	80-100
HCO_3, mmol/l	24.50	18-23
TCO_2, mmol/l	25.60	22-28
SO_2C, %	97.00	95-98
A-aDO_2, mmHg	20.00	15
BE, mmol/l	0.30	-2-3

C, Tumor marker assays

Parameter	Value	Reference range
CEA, μg/l	22.81	0-10
CA125, U/ml	28.62	0-35
CA19-9, U/ml	26.88	0-27
CA72-4, U/ml	2.97	0-6.9
AFP, ng/ml	1.85	0-20

D, Pathogen detection

G test, pg/ml	32.53	<60
CP-DNA test	Negative	Negative
MP-DNA test	Negative	Negative
GM ratio	0.21	<0.5
Fungal smear test	Negative	Negative

ABG, arterial blood gas; BE, base excess; CP, chloroplast; MP, *Mycoplasma pneumoniae*; G, 1,3-β-D-Glucan; GM test, Galactomannan test.

Results of the present study demonstrated that the tumor tissues obtained from the patient were negative for TTF-1, NapsinA, CK5/6 and Syn, positive for CK7, partially positive for p40 and negative for SMARCA4 (Fig. 3B-D; Table IV). The specimen was pathologically examined and used the 7th edition American Joint Committee on Cancer staging system for small bowel cancer (11). The tumor of the patient was stage IV, T2NXM1. The NX staging was due to insufficient peritumoral lymph nodes sampled during surgery. However, with distant metastasis (M1), all T and N categories default to stage IV (12). Results of the pathological analysis demonstrated a SMARCA4-DUC with localized squamous carcinoma expression (Table IV). Given the low incidence of small intestine cancer and the lack of specific clinical guidelines, the guidelines for gastrointestinal tumors were referred to, which indicated that programmed cell death protein-1 (PD-1) therapy as the first-line treatment for advanced patients with SMARCA4-DUC (13). Additionally, previous studies have reported that SMARCA4 deficiency can lead to resistance to platinum-based and other traditional chemotherapeutic drugs (9,10,14). Therefore, PD-1 therapy was chosen as the primary treatment without employing a combination therapy regimen. Tislelizumab (200 mg, intravenous; cat. no. BGB-A317; BeOne Medicines) was intravenously administered to the patient in the clinic on day 11. Paclitaxel and nedaplatin were suggested for the patient on day 13 but not administered due to bleeding that occurred in the patient. The patient was passing tarry stools; thus, a follow-up blood test was performed. The results demonstrated hemoglobin levels of 57 g/l (healthy range, 130-175 g/l). Gastrointestinal bleeding was considered, chemotherapy was stopped and fasting, blood transfusion (4 units) and nutritional support were advised. However, the patient did not agree to the test because the results of the immunotherapy did not meet the expectations of the patient and they were not willing to continue with the immunotherapy.

On day 18, the patient had not passed gas for 1 day. A complete abdominal CT examination and enhanced examination (Optima CT660, Cytiva; 5-mm layer thickness; helical scan) revealed increased and enlarged liver metastases, novel metastases in the spleen, intestinal intussusception in the jejunal segment of the small intestine and intestinal obstruction (Fig. 2B-E). On day 20, a laparoscopic partial resection of the small intestine was performed and observed a resected small intestinal specimen of 8 cm in length in the lumen of the lassoed area. A red elevated area was observed in the intestinal lumen of the intestinal trocar, measuring 3.5x2.5x1.5 cm. This area exhibited an ulcerated vesiculated surface and the cut surface was grayish-white and grayish-red with a moderate solid texture. H&E staining was performed using the previously described protocol and light microscopy revealed that the tumor cells were diffusely distributed in nests of sheets. In addition, the tumor cells were large with unclear borders, weakly basophilic or translucent cytoplasm and large, rounded or oval nuclei with pronounced nuclear membranes. Multiple small nucleoli were observed and nuclear schizophrenia was readily visible. There were numerous hemorrhagic necroses within the lesion and small blood vessels in the tumor interstitium were hyperplastic and partially dilated with bruising (Fig. 4A). Immunohistochemistry demonstrated lack of expression for TTF-1, CK5/6, Syn, PSA, villin, CK20, caudal type homeobox 2 (CDX-2), CD34, Syn, CgA, insulinoma-associated protein 1 (INSM1), melanoma antigen (MelanA), S100, myogenin, leukocyte common antigen and CD30, and positive expression for CK7 and CK8. There were small foci of p40 positive expression, partial positive expression of glypican-3 and CD56, and lack of expression of SMARCA4 and nuclear protein in the testis (Fig. 4B-D; Table V). Small intestinal

Table II. Summary of patient radiological examination results.

Day	Radiological examination	Results
Day 1	Chest CT	Multiple nodules and masses found in both lungs, enlargement of right hilar lymph node in right lung
	Abdominal CT	Multiple low-density nodules in the liver, with larger nodules located in segment VIII of the liver
Day 18	Abdominal CT	Enlarged liver metastases, new metastases in the spleen, intussusception in the jejunal segment of the small intestine, intestinal obstruction
Day 31	Chest CT	Enlarged lesions in both lungs with new ground-glass shadows in the dorsal aspect of both lungs

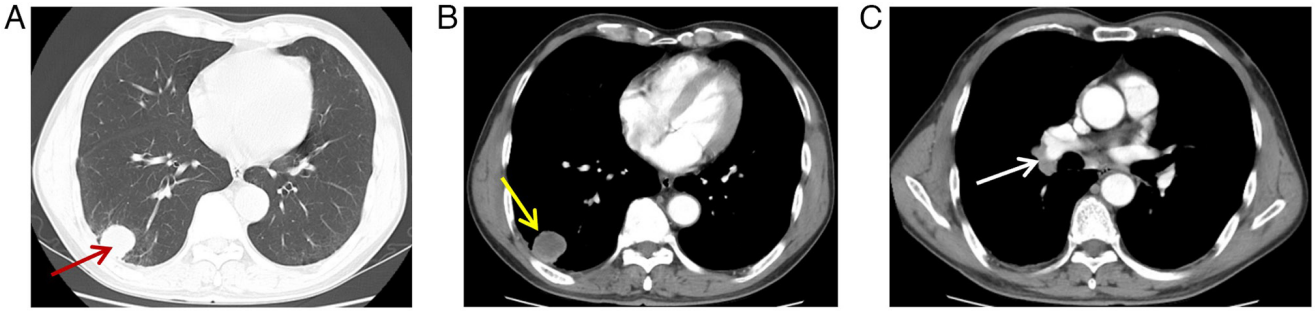

Figure 1. Thoracic CT examination (plain and enhanced) dated on day 1. (A) Lung window. A well-defined, smooth-edged mass measuring 31 mm in diameter was observed in the outer basal segment of the right lower lobe (red arrow). (B) Mediastinal window (enhanced). The central region of the mass in the outer basal segment of the right lower lobe revealed no enhancement, while the peripheral rim exhibited ring-like enhancement (yellow arrow). (C) Enlarged lymph node in the right hilar region (station 11), with a maximum short-axis diameter of ~15 mm (white arrow).

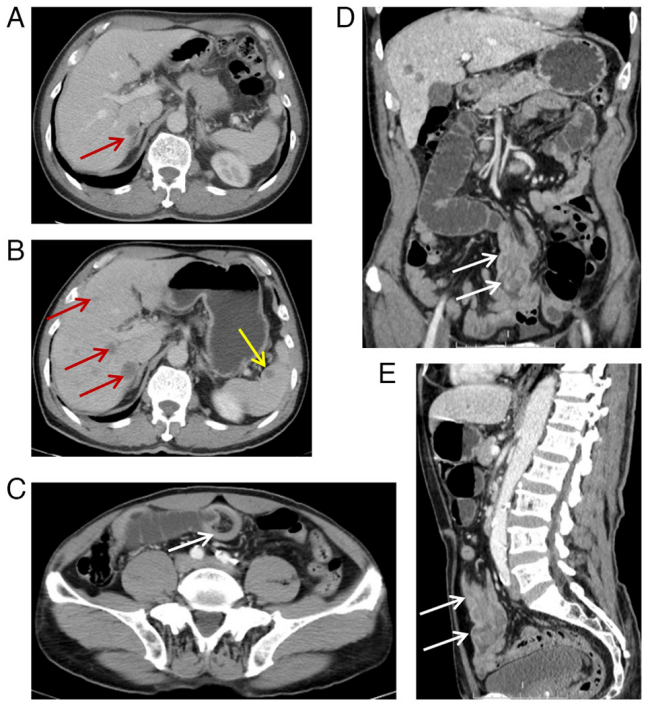

Figure 2. Plain and enhanced abdominal CT examination. (A) Multiple hypodense nodules in the liver, with the largest nodule located in segment VIII, measuring 12 mm in diameter with moderate enhancement (red arrow), on Day 1. (B) Increased and enlarged liver metastases (indicated by the red arrows), novel metastases in the spleen (indicated by the yellow arrows), on Day 18. (C) Transverse plane, (D) coronal plane and (E) sagittal plane views demonstrated localized intussusception in the small intestinal jejunum segment of the patient, with notable thickening and edema of the bowel wall (white arrows), on Day 18.

tumor samples obtained from the patient were investigated for 50 genes associated with lung cancer and 23 genes associated with intestinal cancer using next-generation sequencing (NGS). High-throughput sequencing was conducted on the MGISEQ-2000 platform. DNA libraries were constructed with the EGFR-KRAS-ALK Gene Mutation Combination Test kit (Cat. No. RM0914, Shenzhen Huada Gene Technology Co., Ltd.) to generate 150-bp paired-end reads. Library integrity was validated using the Qsep1™ capillary electrophoresis system (Product No. 100001, BiOptic Inc.) with the Standard Cartridge kit (Cat. No. C105201, BiOptic Inc.). Final library concentrations were quantified with the Equalbit 1x dsDNA HS Assay Kit (Cat. No. EQ121-02, Vazyme) and adjusted to 10 pM for cluster generation. Raw sequencing data were processed and analyzed using HALOS software (v4.1.3, Shenzhen Huada Gene Technology Co., Ltd.), and mutations in PTEN, TP53, ataxia telangiectasia mutated (ATM), ephrin type-A receptor 5 (EPHA5) and EGFR p.F997L were observed (Table SI). The raw sequence data reported in the present case report have been deposited in the Genome Sequence Archive (GSA) in the National Genomics Data Center, China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences (GSA-Human database; accession no. HRA011751) that are publicly accessible at GSA for Human (ngdc.cncb.ac.cn/gsa-human/browse/HRA011751) (15,16). The genes tested include both those recommended for testing by Food and Drug Administration, National Medical Products Administration and National Comprehensive Cancer Network authoritative guidelines and key genes associated with drug targets during clinical

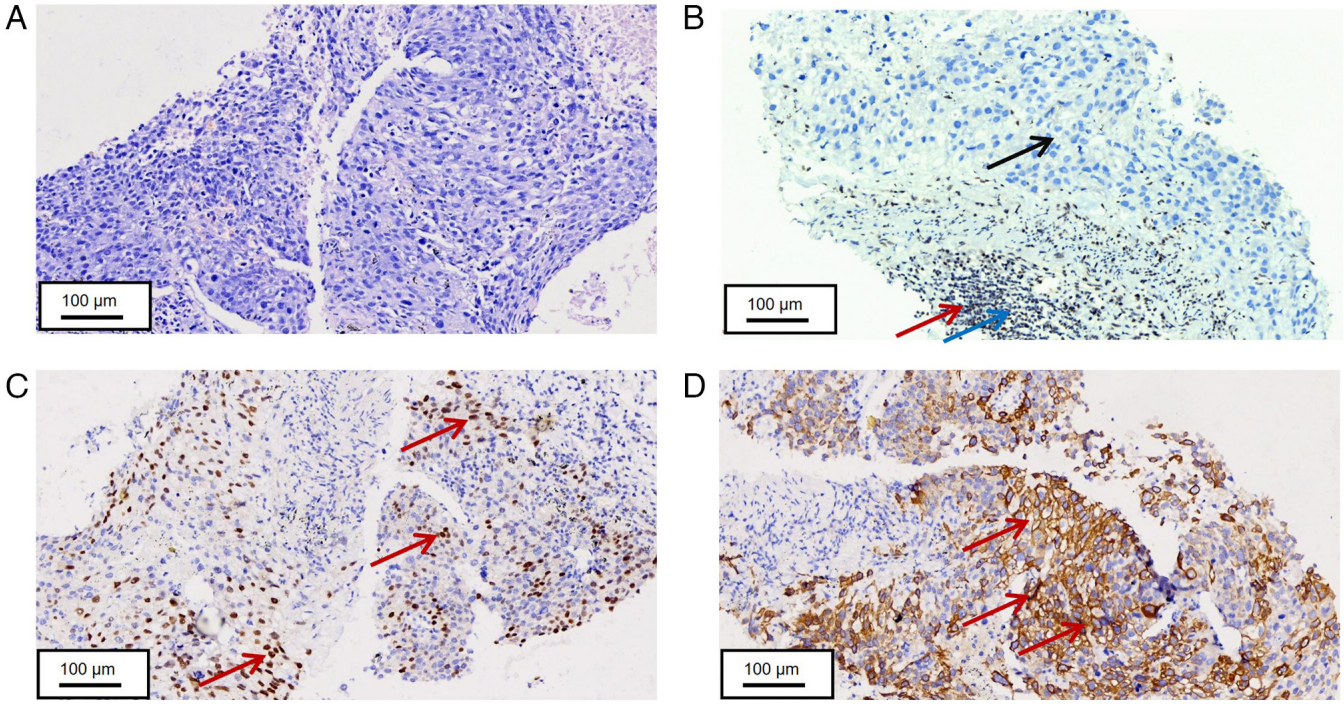

Figure 3. Histopathological staining of lung biopsy tissue. (A) Tumor cells in lung biopsy tissue were arranged in solid sheets, with some cells exhibiting visible nucleoli following H&E staining (scale bar, 100 μm). (B) Tumor cells obtained from the lung biopsy tissue revealed negative expression of SMARCA4 (Red arrows indicate SMARCA4-positive sites, blue arrows indicate lymphoid regions, black arrows indicate tumor regions, scale bar, 100 μm). (C) Partial positive expression of p40 in tumor cells obtained from the lung biopsy tissue (Red arrows indicate p40-positive sites, scale bar, 100 μm). (D) Positive expression of CK7 in tumor cells obtained from the lung biopsy tissue (red arrows indicate CK7-positive sites, scale bar, 100 μm). SMARCA4, switch/sucrose non-fermentable (SWI/SNF) related matrix associated actin-dependent regulator of chromatin sub-family A member 4; CK, cytokeratin.

trials and the development of diseases (17-27). Pan-cancer studies have linked SMARCA4/PTEN loss to DNA repair defects that may underlie the TP53, ATM, EPHA5 and EGFR mutations, as unrepaired DNA damage can trigger oncogenic mutations (28-30). Thus, the clinical features, imaging manifestations and pathological features were indicative of undifferentiated carcinoma with localized squamous carcinoma expression and intussusception in SMARCA4-deficient small intestine, with metastasis to the lung, liver and spleen. Although these mutations were detected, the treatment plan could not be adjusted and optimized based on them due to the rapid progression of the condition of the patient.

On day 31, a CT examination of the chest was performed. The patient exhibited enlarged and increased lesions in both lungs (Fig. 5A-C) and new ground-glass shadows in the dorsal aspect of both lungs, with no evidence of infection, the Response Evaluation Criteria in Solid Tumors (RECIST) score was disease progression (31). Furthermore, immune-associated pneumonia-non-specific interstitial pneumonitis was considered (Fig. 5B) (32). Multiple new lesions were observed on the skin and gingiva, indicative of metastasis (Fig. 6A-C). The patient presented with persistent symptoms of gastrointestinal bleeding and a decrease in hemoglobin levels (69 g/l) and was therefore administered 9 units of erythrocyte transfusions and posterior pituitary hormones (a dilute acetic acid sterilized aqueous solution of posterior pituitary powder containing posterior pituitary hormone) for hemostasis (2 ml intravenously once daily), and was provided with nutritional support. The family of the patient requested that the patient be discharged from the hospital on day 42 and the patient was discharged on the same day. Within 24 h of discharge, the patient succumbed to the disease. The complete timeline is shown in Fig. 7.

Discussion

The SMARCA4 gene subgroup belongs to the SWI/SNF family, which serve a key role in chromatin remodeling and repair. Results from previous studies demonstrated that SMARCA4 serves a key role in developmental processes, transcriptional regulation, DNA repair, cell cycle regulation, tumorigenesis and tumor development. Furthermore, inactivating mutations in SMARCA4 lead to a loss of protein expression in the nucleus, which result in malignancies associated with SMARCA defects (33,34). In non-small cell lung cancer, mutations in the SMARCA4 gene occur in ~10% of cases. Notably, these mutations have been reported in malignant tumors in alternative sites, including the ovaries, esophagus, stomach, uterus and liver; however, the majority of previous studies were case reports (35-39).

SMARCA4-DUC is a rare yet highly malignant tumor that is aggressive and associated with poor prognosis (Table VI). Cases of SMARCA4-DUC in the gastrointestinal tract predominantly affects elderly men and the common sites of development include the stomach, colon, small intestine and lower esophageal cardia, with few cases affecting the ileum, rectum and pancreas (40,41). In a study by Wang *et al* (42), it was noted that lung cancer cells undergo SMARCA4 loss, which results in a reduced response to anti-PD-1 immunotherapy, which may be associated with a notable reduction in the infiltration of dendritic cells and $CD4^+$ T cells into

Table III. Sources of reagents for patient testing.

Reagent or medicine	Manufacturer	Cat. no.	Dilution
EGFR-KRAS-ALK gene mutation combination test kit	Shenzhen Huada Gene Technology Co Ltd	RM0914	Not applicable
Anti-Rabbit IgG H&L (HRP)	Roche Diagnostics GmbH	760-500	1:1
Anti-human NUT	Guangzhou Anbiping Medical Technology	IR429	1:1
Anti-human TTF-1	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-0677	1:1
Anti-human CK5/6	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-0774	1:1
Anti-human Syn	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-0742	1:1
Anti-human Villin	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-0540	1:1
Anti-human CK20	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-0834	1:1
Anti-human CDX2	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-1056	1:1
Anti-human CD34	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-1076	1:1
Anti-human CgA	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-0707	1:1
Anti-human INSMI	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-1017	1:1
Anti-human MelanA	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-1033	1:1
Anti-human S-100	Fuzhou Maixin Biotechnology Development Co., Ltd.	Kit-0007	1:1
Anti-human Myogenin	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-0362	1:1
Anti-human CD30	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-0023	1:1
Anti-human CK7	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-0828	1:1
Anti-human CK8	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-1002	1:1
Anti-human p40	Fuzhou Maixin Biotechnology Development Co., Ltd.	RMA-0815	1:1
Anti-human CD56	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-0743	1:1
Anti-human SMARCA4	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-1016	1:1
Anti-human NapsinA	Fuzhou Maixin Biotechnology Development Co., Ltd.	MAB-0704	1:1

NUT, nuclear protein in testis; TTF-1, thyroid transcription factor-1; Syn, synaptophysin; CK; CDX2, caudal type homeobox 2; INSMI, insulinoma-associated protein 1; MelanA, melanoma antigen; SMARCA4; switch/sucrose non-fermentable-related matrix associated actin-dependent regulator of chromatin sub-family A member 4.

the tumor microenvironment (TME); however, this study focused on cellular and animal experiments. The results of previous studies examining the impact of SMARCA4 loss on the response to PD-1 immunotherapy in lung cancer are conflicting and these discrepancies may be associated with differences in study models. As noted in a study of advanced undifferentiated carcinoma of the duodenum, PD-1 therapy is effective in some patients with SMARCA4 deficiency, which potentially provides an option for the treatment of these highly malignant tumors (43). A clinical study reported that partial SMARCA4 deletion may make patients with lung cancer more sensitive to PD-1 monoclonal antibody drugs (27). However, this study primarily included an animal model for its experiments and the underlying mechanisms may be more complex in humans. Tumors are often located within the muscular wall of the digestive tract and involve the mucosa and may also form masses outside of the wall of the digestive tract (38,44-47). Few characteristic imaging features of SMARCA4-DUC lead to complexities in diagnosis; however, the majority of these tumors exhibit notable signs of malignancy, such as large foci that are lobulated, which encircle blood vessels, invade adjacent tissues and metastasis to mediastinal lymph nodes and distant organs (5). In the present case, a chest CT examination demonstrated multiple nodules and masses with clear borders and smooth edges and enhanced CT examination demonstrated that the majority of areas in the lesions did not exhibit notable enhancement. Furthermore, the edges of the lesions were notably enhanced, which was consistent with the manifestation of bloodstream metastasis in both lungs. Enhanced abdominal CT examination revealed localized condensation of the jejunal segment of the small intestine, with edema and thickening of the tube wall. In addition, multiple nodules in the liver and spleen were observed, with moderate bulls-eye enhancement observed through enhanced examination. These findings were consistent with the manifestation of hematogenous metastasis in the liver and spleen. The imaging manifestations of bilateral lung, liver and spleen metastases were consistent with those reported in previous literature (48-50); however, to the best of our knowledge, the present study is the first to report the case of intestinal intussusception caused by SMARCA4-DUC in the small intestine.

The histology of SMARCA4-DUC is characterized by rounded cells and epithelioid cell structures arranged in sheets, nests or beams within the tumor tissue, which may be accompanied by a loss of adherent growth. Furthermore, rhabdoid morphology, which is defined as the presence of cells with large, eosinophilic cytoplasm, prominent nucleoli and a vesicular chromatin pattern is seen in focal areas in ~2/3 of the cases (34). Results from previous studies revealed that tumor cells are often uniform. However, tumor cells that

Table IV. Summary of patient IHC results.

Name	pH	Incubation time, min	IHC result
NUT	8	32	-
TTF-1	8	32	-
CD5/6	8	32	-
Syn	8	32	-
Villin	8	32	-
CDX2	8	32	-
CD34	8	32	-
CgA	8	32	-
INSM1	8	32	-
Myogenin	8	32	-
CD30	8	32	-
CK7	8	32	+
p40	8	32	+
CD56	8	32	+
SMARCA4	8	32	-
NapsinA	8	32	-
MelanA	8	28	-
S-100	8	24	-
CK8	8	24	+
CD20	8	24	-

IHC, immunohistochemistry; -, negative; +, positive; NUT, nuclear protein in testis; TTF-1, thyroid transcription factor-1; Syn, synaptophysin; CK, cytokeratin; CDX2, caudal type homeobox 2; INSMI, insulinoma-associated protein 1; MelanA, melanoma antigen; SMARCA4; switch/sucrose non-fermentable (SWI/SNF) related matrix associated actin-dependent regulator of chromatin sub-family A member 4.

Table V. Immunohistochemistry of tumor tissues from different sites in patients.

	Lung tumor	Small bowel tumor
CK5/6	-	-
p40	+	+
CK7	+	+
TTF-1	-	-
NapsinA	-	Untested
Syn	-	Untested
CK8	Untested	+
Villin	Untested	-

-, negative; +, positive; TTF-1, thyroid transcription factor-1; Syn, synaptophysin; CK, cytokeratin.

were pleomorphic, contained spindle cell components or exhibited pseudoadenoids or pseudoglandular structures were observed in some cases (5,51). A previous study demonstrated that undifferentiated carcinomas of the gastrointestinal tract often possess multifarious rhabdomyolysis features, accompanied by deletion of SMARCB1, SMARCA2, SMARCA4 and AT-rich interaction domain-containing protein 1A (ARID1A) (41). Notably, a deletion in SMARCA4 is often present in conjunction with a deletion in SMARCA2, which affects ~39.9% of cases. These deletions are often accompanied by negative or reduced expression (<10% positivity) of epithelial markers, including CKpan, CK7, CK20 and CDX2. In addition to epithelial markers, tumor cell markers, such as Sox2, spalt-like protein 4, p53, ARID1A and neuroendocrine markers, such as CgA, Syn, CD56 and INSM1, may also be expressed to varying degrees in SMARCA4-DUC (46,52-54). In a previous study (36), it was noted that SMARCA4 deletion and TP53 have similar mutation rates in gastrointestinal tumors and that this mutation seems to occur more often in the esophagus compared with the stomach or elsewhere, which suggests a possible location of origin for gastrointestinal tumors. The patient from the present case also demonstrated focal expression of p40; however, SMARCA4 deletion was detected in small bowel cancer in a study on SMARCA4 deletion in lung cancer, which indicated that tumors with deletion of SMARCA4 were mostly non-squamous cell carcinomas and the expression of p40 was mostly negative or weakly positive at the focal level (34). This is similar to the expression of p40 detected in the patient in the present case. Considering the DNA repair function of SMARCA4, SMARCA4 deletion may lead to a variety of morphological and immunophenotypic features of tumor cells during differentiation and the focal expression of p40 may reflect the partial squamous differentiation tendency of the associated tumor cells (55). According to previous studies, diffuse strong positivity of p40 expression in tumor tissue can be used to diagnose squamous cell carcinoma. However, the present tumor tissue showed focal p40 expression, which did not meet the diagnostic criteria. Therefore, the patient's treatment plan was based on the criteria for undifferentiated carcinoma (56,57).

During clinical diagnosis, a combination of histological and molecular pathological analyses is required to distinguish SMARCA4-DUC from large-cell neuroendocrine carcinomas with rhabdomyosiform morphology, often accompanied by diffuse or strong positive expression of neuroendocrine markers (58,59). Notably, melanomas with rhabdomyosiform morphology often express melanocyte markers, such as S100, MelanA and human melanoma black-45 (60,61). Rhabdomyosarcoma with distinctive rhabdomyosarcoma-like features often express muscle-specific markers, such as myogenic differentiation antigen 1 and myogenin (62,63). Cases of primary interstitial large-cell lymphoma of the gastrointestinal tract often include large cells with a pronounced nucleolus and these may exhibit high levels of expression of lymphocyte markers, such as CD30 and ALK (64,65). Furthermore, proximal-type epithelioid sarcoma with epithelioid morphology often express epithelioid markers, such as CK and epithelial membrane antigen (66,67), which aid in identification and differentiation.

Genomic analysis of SMARCA4-DUC demonstrated that common co-mutations included TP53, KRAS, serine/threonine kinase 11 (STK11) and Kelch-like ECH-associated protein 1 (KEAP1), with less common co-mutations with common genes, such as EGFR, ROS proto-oncogene 1, receptor tyrosine kinase

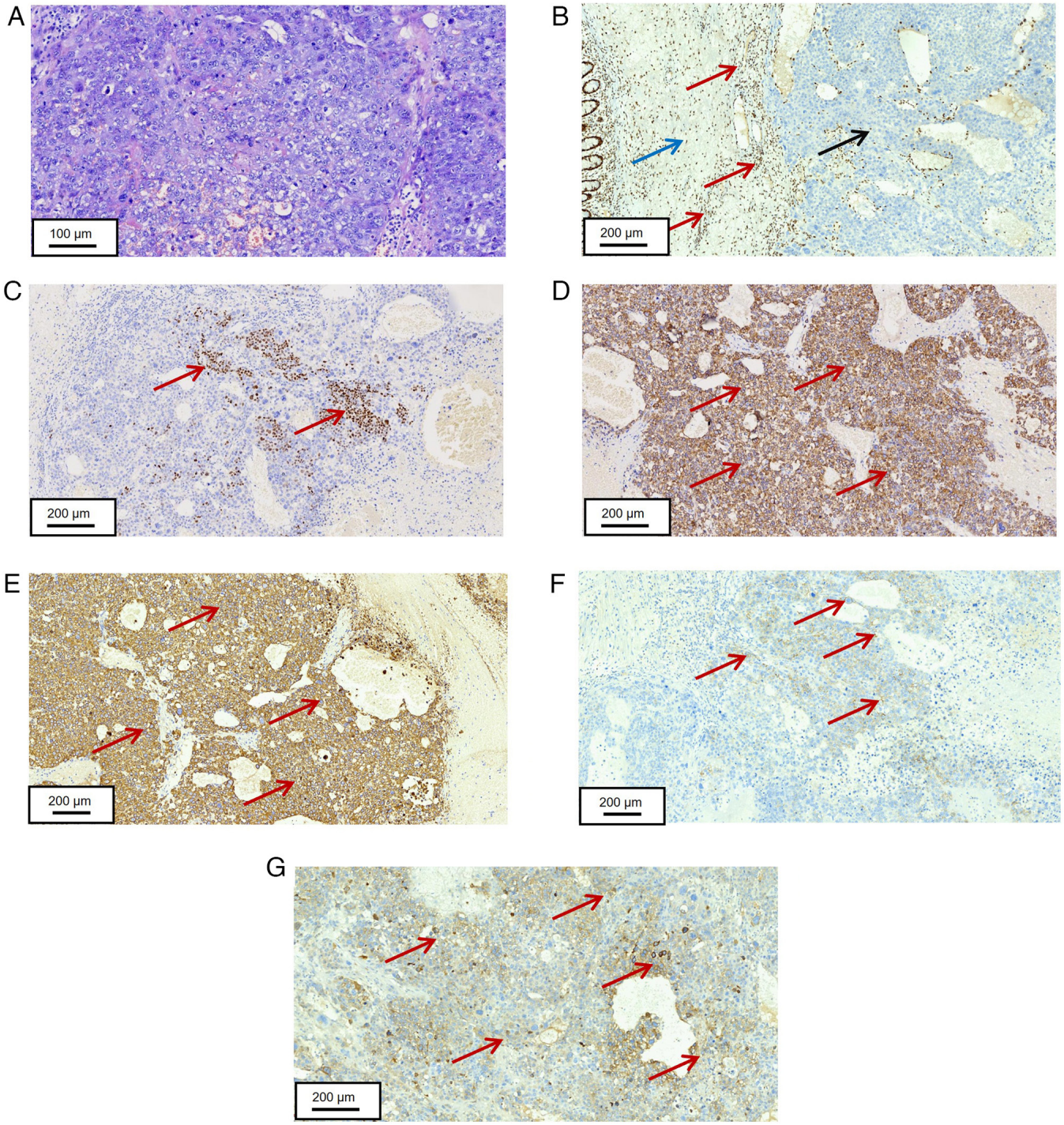

Figure 4. Histopathological staining of tumor tissue in the small intestine. (A) Tumor cells in the small intestine were arranged in solid nests, with large, lightly stained nuclei and one or more visible small nucleoli (scale bar, 100 μm). (B) Negative SMARCA4 expression in tumor cells of the small intestine (red arrows indicate SMARCA4-positive sites, blue arrows indicate lymphoid regions, black arrows indicate tumor regions, scale bar, 200 μm). (C) Partial positive expression of p40 in tumor cells of the small intestine (red arrows indicate p40-positive sites, scale bar, 200 μm). (D) Positive expression of CK7 in tumor cells of the small intestine (Red arrows indicate CK7-positive sites, scale bar, 200 μm). (E) Positive expression of CK8 in tumor cells of lung biopsy tissue (Red arrows indicate CK8-positive sites, scale bar, 200 μm). (F) Positive expression of CD56 in tumor cells of lung biopsy tissue (red arrows indicate CD56-positive sites, scale bar, 200 μm). (G) Positive expression of GPC-3 in tumor cells of lung biopsy tissue (red arrows indicate GPC-3-positive sites, scale bar, 200 μm). SMARCA4, switch/sucrose non-fermentable (SWI/SNF) related matrix associated actin-dependent regulator of chromatin sub-family A member 4; CK, cytokeratin; GPC-3, glypican-3.

and ALK (68,69). The Dana-Farber Cancer Institute (Boston, USA) reported that the KRAS gene is the most commonly co-mutated gene in SMARCA4-DUC, which accounts for 5-11% of gene mutations (70). Patients with SMARCA4-DUC often present with a poor prognosis, with markedly shorter median progression-free survival (4.1 vs. 1.4 months) and median overall survival (15.1 vs. 3.0 months) compared with patients exhibiting the SMARCA4/KRAS wild-type (71,72).

Treatment of SMARCA4-DUC is complex, due to its unique physiological characteristics and low prevalence rates. In

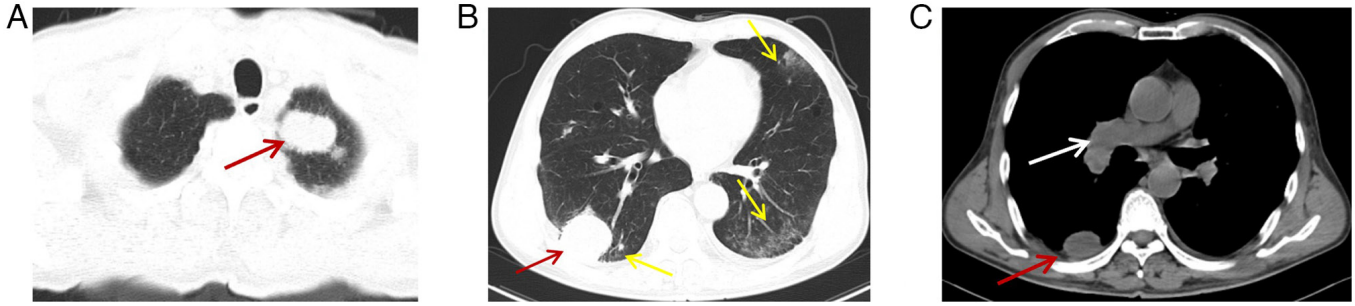

Figure 5. Thoracic CT examination (plain) on Day 31. (A) Lung window. Multiple nodules and masses in the left upper lobe, indicative of novel lesions compared with the thoracic CT examination (indicated by the red arrow), dated on Day 31. (B) Lung window. Mass in the extra-basal segment of the lower lobe of the right lung, enlarged on contrast with chest CT examination, on Day 31 (red arrow). Subpleural ground-glass shadows in both lungs were indicative of a novel lesion consistent with the CT pattern of immune-associated pneumonia-non-specific interstitial pneumonitis (yellow arrow). (C) Mediastinal window (plain). Nodule in the dorsal segment of the lower lobe of the right lung, with a novel lesion compared with that observed on chest CT examination carried out on Day 31 (red arrow). Enlarged lymph nodes in region 11 of the right hilar (white arrow).

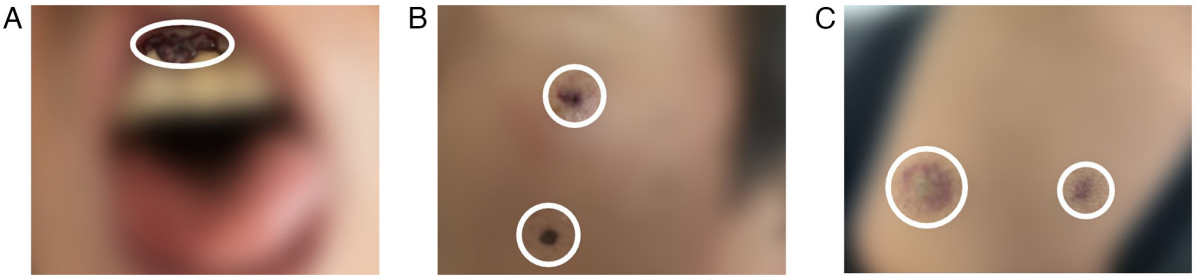

Figure 6. Multiple cutaneous metastases. Images of multiple cutaneous metastases in the (A) gingiva, (B) left face and (C) anterior chest (white circles).

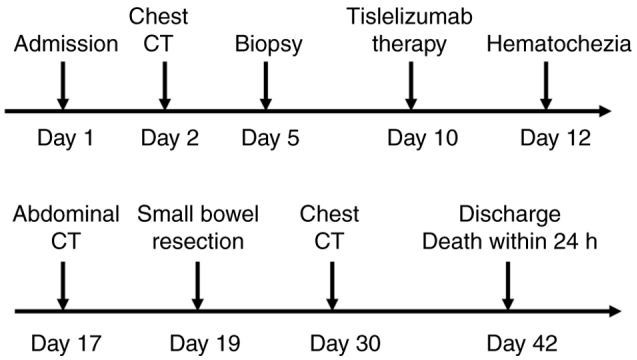

Figure 7. Timeline of major tests and interventions received by the patient from admission to discharge.

addition, there are no unified treatment guidelines to follow, with a lack of effective therapies used in clinical practice (73). Partial SMARCA4 deletion may make patients with lung cancer more sensitive to PD-1 monoclonal antibody drugs, which was noted in a clinical study (44). A previous case report demonstrated that surgical resection may be an effective initial treatment option for patients with SMARCA4-DUC with clinical staging (74). However, the present case report also demonstrated that 4 months following surgery, patients with SMARCA4-DUC developed tumor recurrence with invasion to the adjacent ribs. Results from a previous study revealed that patients with SMARCA4-DUC may benefit from platinum-based chemotherapy and the systemic effects of chemotherapy may control distal tumor metastasis to some extent, due to the high aggressiveness and metastatic nature of the disease (75). Furthermore, targeted drug therapies, including anilotinib, sindilizumab and bevacizumab, may aid in controlling the progression of SMARCA4-DUC (54,76). In a previous case report, a patient with SMARCA4-DUC who developed genetic mutations in STK11/KEAP1, KEAP1, PBRM1, SMARCA4 and STK11 received tirilizumab immunotherapy (77). However, rapid disease progression was observed, with hepatic and pulmonary metastases within 1 month, which ultimately led to the death of the patient. Findings from previous studies revealed that STK11/KEAP1, KEAP1, PBRM1 and STK11 gene mutations may affect the tumor microenvironment of patients, which weakens the tumor-killing effect of immune cells and increases the risk of disease progression following immunotherapy (78-80). Due to the high degree of heterogeneity of tumor cells in patients with SMARCA4-DUC, NGS technology is required for the development of personalized treatment plans (81). The rapid disease progression of the present patient after immunotherapy suggested that there may be hyperprogression, although there is no direct evidence that SMARCA4 may be an independent influence on hyperprogression of immunotherapy in gastrointestinal patients. It was noted in Han *et al* (82) that environmental factors, especially the gut microbiome, can have an impact on immunotherapy and it is possible that the intussusception and gastrointestinal bleeding that the patient suffered at a later stage would have led to an imbalance in the gut microbiome, which could be an important cause of hyperprogression.

In addition, the present patient tumor exhibited partial squamous carcinoma and in a case report by Misra *et al* (83), it was noted that patients with SMARCA4 in the gastrointestinal

Table VI. Summary of key findings on SMARCA4 loss in various malignancies.

First author, year	Type of cancer	Key finding	(Refs.)
Witkowski *et al*, 2023	Ovarian	Associated with tumor aggressiveness and poor prognosis.	(35)
Yu *et al*, 2024	Esophageal	Led to reduced sensitivity to chemotherapeutic drugs.	(55)
Yu *et al*, 2024	Gastric	Associated with tumor aggressiveness and poor prognosis.	(55)
Affandi *et al*, 2018	Endometrial	Associated with tumor aggressiveness and poor prognosis.	(57)
Garcia-Porrero *et al*, 2024	Liver	Associated with tumor aggressiveness and poor prognosis.	(58)
Xue *et al*, 2021;	Non-small cell	Reduced sensitivity to chemotherapeutic drugs; activated	(9)
Kim *et al*, 2021	lung cancer	EMT process and enhanced tumor invasiveness	(10)

EMT, epithelial-mesenchymal transition.

tract exhibiting focal squamous carcinoma differentiation can be resistant to a variety of chemotherapeutic agents (cisplatin and docetaxel) and lead to an increase in their invasiveness, which may also explain the rapid progression of the patient in the present case (84,85). Due to the highly heterogeneous nature of tumor cells in SMARCA4-DUC patients, deep gene sequencing of SMARCA4-DUC patients using NGS technology is of great importance for the development of personalized treatment protocols, taking into account the impact of different gene mutations on patient prognosis and the toxicity and side effects of traditional chemotherapeutic agents (81,86). In addition, some non-pharmacological interventions, such as magnetic fields, exosomes, may also provide options for the treatment of SMARCA4-DUC (87-89). In the present case, the patient was administered tislelizumab once following diagnosis and the disease was reassessed at 22-day intervals. After 1 month of treatment, the symptoms of the patient had worsened, with an increase in the number of metastatic lesions in the lungs and liver, enlargement, novel metastases in the spleen, the development of a CT pattern indicative of immune-associated pneumonia-nonspecific interstitial pneumonitis in both lungs and a Response Evaluation Criteria in Solid Tumors score of progressive disease (31). Following intussusception surgery, gastrointestinal bleeding and treatment for aggressive symptoms, the death of the patient occurred after 12 days. Although the specific cause of death was not determined via autopsy, it was considered that the highly aggressive nature of SMARCA4-DUC, which led to multiple organ metastasis was the main cause of death and the gastrointestinal hemorrhage and immune-associated pneumonia caused by the intussusception may have accelerated the deterioration of the disease.

The present study exhibits numerous limitations. For example, the present study included a retrospective analysis of rare cases, with a lack of guideline support and inexperience. In the present case, diagnosis and treatment were delayed, as it remained unclear whether immunotherapy caused hyper-progression of the disease. In addition, the specific cause of death in the patient was not determined due to the absence of autopsy confirmation.

In conclusion, the present study reported a rare case of SMARCA4-DUC in the gastrointestinal tract, which provides a theoretical basis for the clinical management of this disease. SMARCA4-DUC often affects elderly male patients and imaging often reveals large lesions, invasion of surrounding tissues and metastasis to lymph nodes and distant organs. Definitive diagnosis of the disease relies on pathological examination, immunohistochemistry and molecular testing. A diagnosis of SMARCA4-DUC should be considered following the observation of solid high-grade undifferentiated morphology of cells and negative expression of genes used for conventional staging. Thus, appropriate immunohistochemical and molecular tests should be carried out to aid in early diagnosis and effective treatment.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author. The raw sequence data generated in the present study may be found in the Genome Sequence Archive (GSA) (14) in National Genomics Data Center (15), China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences, under accession number (accession no. HRA011751) or at the following URL: ngdc.cncb.ac.cn/gsa-human/browse/HRA011751.

Authors' contributions

MQ, LL, BY, and YZ analyzed data. BY and XY designed the study protocol. XC and SL were the primary care physicians of the patient and developed and implemented the treatment plan. YW, QG and ZC performed the literature review and analyzed and interpreted the data in the paper. XY drafted the work and critically revised intellectual content. BY and XY confirm the authenticity of all the raw data. All authors commented on the manuscript and agreed with the conclusions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present case report was approved by the Ethics Committee of the Weifang No. 2 People's Hospital (approval no. KY2023-055-01; Weifang, China) and was performed in accordance with the Declaration of Helsinki.

Patient consent for publication

The patient's family member provided written informed consent for the publication of the manuscript including any identifying images or data.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA and Bray F: Global burden of 5 major types of gastrointestinal cancer. Gastroenterology 159: 335-349.e15, 2020.
3. Zhan T, Betge J, Schulte N, Dreikhausen L, Hirth M, Li M, Weidner P, Leipertz A, Teufel A and Ebert MP: Digestive cancers: Mechanisms, therapeutics and management. Signal Transduct Target Ther 10: 24, 2025.
4. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F and Cree IA; WHO Classification of Tumours Editorial Board: The 2019 WHO classification of tumours of the digestive system. Histopathology 76: 182-188, 2020.
5. Zhu PP, Li XX, Liu JH, Du XL, Su HY and Wang J: SMARCA4-deficient undifferentiated carcinoma of the gastrointestinal tract: a clinicopathological and immunohistochemical study of nine cases. Zhonghua Bing Li Xue Za Zhi 51: 868-874, 2022 (In Chinese).
6. Tian Y, Xu L, Li X, Li H and Zhao M: SMARCA4: Current status and future perspectives in non-small-cell lung cancer. Cancer Lett 554: 216022, 2023.
7. Lombardi M, D'Ercole M, Midolo De Luca V, Chiari M, Spaggiari L and Bertolaccini L: The impact of SMARCA4 loss in non-small cell lung cancer therapy. Heliyon 11: e41128, 2024.
8. Shi M, Pang L, Zhou H, Mo S, Sheng J, Zhang Y, Liu J, Sun D, Gong L, Wang J, *et al*: Rare SMARCA4-deficient thoracic tumor: Insights into molecular characterization and optimal therapeutics methods. Lung Cancer 192: 107818, 2024.
9. Xue Y, Morris JL, Yang K, Fu Z, Zhu X, Johnson F, Meehan B, Witkowski L, Yasmeen A, Golenar T, *et al*: SMARCA4/2 loss inhibits chemotherapy-induced apoptosis by restricting IP3R3-mediated Ca^{2+} flux to mitochondria. Nat Commun 12: 5404, 2021.
10. Kim J, Jang G, Sim SH, Park IH, Kim K and Park C: SMARCA4 depletion induces cisplatin resistance by activating YAP1-mediated epithelial-to-mesenchymal transition in triple-negative breast cancer. Cancers (Basel) 13: 5474, 2021.
11. Edge SB and Compton CC: The American joint committee on cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17: 1471-1474, 2010.
12. Locher C, Batumona B, Afchain P, Carrère N, Samalin E, Cellier C, Aparicio T, Becouarn Y, Bedenne L, Michel P, *et al*: Small bowel adenocarcinoma: French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO). Dig Liver Dis 50: 15-19, 2018.
13. Kelly RJ, Bever K, Chao J, Ciombor KK, Eng C, Fakih M, Goyal L, Hubbard J, Iyer R, Kemberling HT, *et al*: Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of gastrointestinal cancer. J Immunother Cancer 11: e006658, 2023.
14. Liu H, Hong Q, Zheng S, Zhang M and Cai L: Effective treatment strategies and key factors influencing therapeutic efficacy in advanced SMARCA4-deficient non-small cell lung cancer. Lung Cancer 198: 108022, 2024.
15. Chen T, Chen X, Zhang S, Zhu J, Tang B, Wang A, Dong L, Zhang Z, Yu C, Sun Y, *et al*: The genome sequence archive family: Toward explosive data growth and diverse data types. Genomics Proteomics Bioinformatics 19: 578-583, 2021.
16. CNCB-NGDC Members and Partners: Database resources of the national genomics data center, china national center for bioinformation in 2022. Nucleic Acids Res 50 (D1): D27-D38, 2022.
17. Saura C, Roda D, Roselló S, Oliveira M, Macarulla T, Pérez-Fidalgo JA, Morales-Barrera R, Sanchis-García JM, Musib L, Budha N, *et al*: A First-in-human phase I study of the ATP-competitive AKT inhibitor ipatasertib demonstrates robust and safe targeting of AKT in patients with solid tumors. Cancer Discov 7: 102-113, 2017.
18. Therkildsen C, Bergmann TK, Henrichsen-Schnack T, Ladelund S and Nilbert M: The predictive value of KRAS, NRAS, BRAF, PIK3CA and PTEN for anti-EGFR treatment in metastatic colorectal cancer: A systematic review and meta-analysis. Acta Oncol 53: 852-864, 2014.
19. Wang ZH, Gao QY and Fang JY: Loss of PTEN expression as a predictor of resistance to anti-EGFR monoclonal therapy in metastatic colorectal cancer: Evidence from retrospective studies. Cancer Chemother Pharmacol 69: 1647-1655, 2012.
20. Forster MD, Dedes KJ, Sandhu S, Frentzas S, Kristeleit R, Ashworth A, Poole CJ, Weigelt B, Kaye SB and Molife LR: Treatment with olaparib in a patient with PTEN-deficient endometrioid endometrial cancer. Nat Rev Clin Oncol 8: 302-306, 2011.
21. Koehler K, Liebner D and Chen JL: TP53 mutational status is predictive of pazopanib response in advanced sarcomas. Ann Oncol 27: 539-543, 2016.
22. Chalhoub N and Baker SJ: PTEN and the PI3-kinase pathway in cancer. Annu Rev Pathol 4: 127-150, 2009.
23. Milella M, Falcone I, Conciatori F, Cesta Incani U, Del Curatolo A, Inzerilli N, Nuzzo CM, Vaccaro V, Vari S, Cognetti F and Ciuffreda L: PTEN: Multiple functions in human malignant tumors. Front Oncol 5: 24, 2015.
24. Seshacharyulu P, Ponnusamy MP, Haridas D, Jain M, Ganti AK and Batra SK: Targeting the EGFR signaling pathway in cancer therapy. Expert Opin Ther Targets 16: 15-31, 2012.
25. Sigismund S, Avanzato D and Lanzetti L: Emerging functions of the EGFR in cancer. Mol Oncol 12: 3-20, 2018.
26. Bendell JC, Rodon J, Burris HA, de Jonge M, Verweij J, Birle D, Demanse D, De Buck SS, Ru QC, Peters M, *et al*: Phase I, dose-escalation study of BKM120, an oral pan-class I PI3K inhibitor, in patients with advanced solid tumors. J Clin Oncol 30: 282-290, 2012.
27. Weber J and McCormack PL: Panitumumab: In metastatic colorectal cancer with wild-type KRAS. BioDrugs 22: 403-411, 2008.
28. Sørensen SG, Shrikhande A, Poulsgaard GA, Christensen MH, Bertl J, Laursen BE, Hoffmann ER and Pedersen JS: Pan-cancer association of DNA repair deficiencies with whole-genome mutational patterns. Elife 12: e81224, 2023.
29. Kassem PH, Montasser IF, Mahmoud RM, Ghorab RA, AbdelHakam DA, Fathi MESA, Wahed MAA, Mohey K, Ibrahim M, Hadidi ME, *et al*: Genomic landscape of hepatocellular carcinoma in Egyptian patients by whole exome sequencing. BMC Med Genomics 17: 202, 2024.
30. Watanabe T, Semba S and Yokozaki H: Regulation of PTEN expression by the SWI/SNF chromatin-remodelling protein BRG1 in human colorectal carcinoma cells. Br J Cancer 104: 146-154, 2011.
31. Gouda MA, Janku F, Wahida A, Buschhorn L, Schneeweiss A, Abdel Karim N, De Miguel Perez D, Del Re M, Russo A, Curigliano G, *et al*: Liquid biopsy response evaluation criteria in solid tumors (LB-RECIST). Ann Oncol 35: 267-275, 2024.

32. Ebner L, Christodoulidis S, Stathopoulou T, Geiser T, Stalder O, Limacher A, Heverhagen JT, Mougiakakou SG and Christe A: Meta-analysis of the radiological and clinical features of usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). PLoS One 15: e0226084, 2020.
33. Zeng X, Yao B, Liu J, Gong GW, Liu M, Li J, Pan HF, Li Q, Yang D, Lu P, *et al*: The SMARCA4^{R1157W} mutation facilitates chromatin remodeling and confers PRMT1/SMARCA4 inhibitors sensitivity in colorectal cancer. NPJ Precis Oncol 7: 28, 2023.
34. Liang X, Gao X, Wang F, Li S, Zhou Y, Guo P, Meng Y and Lu T: Clinical characteristics and prognostic analysis of SMARCA4-deficient non-small cell lung cancer. Cancer Med 12: 14171-14182, 2023.
35. Witkowski L, Nichols KE, Jongmans M, van Engelen N, de Krijger RR, Herrera-Mullar J, Tytgat L, Bahrami A, Mar Fan H, Davidson AL, *et al*: Germline pathogenic SMARCA4 variants in neuroblastoma. J Med Genet 60: 987-992, 2023.
36. Neil AJ, Zhao L, Isidro RA, Srivastava A, Cleary JM and Dong F: SMARCA4 mutations in carcinomas of the esophagus, esophagogastric junction, and stomach. Mod Pathol 36: 100183, 2023.
37. Pors J, Devereaux KA, Hildebrandt D and Longacre TA: Primary uterine synovial sarcoma with SMARCA4 loss. Histopathology 80: 1135-1137, 2022.
38. Koyasu S, Sugimoto A, Matsubara J, Muto M and Nakamoto Y: SMARCA4-deficient poorly differentiated adenocarcinoma of the gallbladder. Clin Nucl Med 49: 688-689, 2024.
39. Akunuru S, James Zhai Q and Zheng Y: Non-small cell lung cancer stem/progenitor cells are enriched in multiple distinct phenotypic subpopulations and exhibit plasticity. Cell Death Dis 3: e352, 2012.
40. Xu J and Chi Z: Esophageal carcinoma with SMARCA4 mutation: A narrative review for this rare entity. Transl Gastroenterol Hepatol 9: 24, 2024.
41. Chang B, Sheng W, Wang L, Zhu X, Tan C, Ni S, Weng W, Huang D and Wang J: SWI/SNF complex-deficient undifferentiated carcinoma of the gastrointestinal tract: Clinicopathologic study of 30 cases with an emphasis on variable morphology, immune features, and the prognostic significance of different SMARCA4 and SMARCA2 subunit deficiencies. Am J Surg Pathol 46: 889-906, 2022.
42. Wang Y, Meraz IM, Qudratullah M, Kotagiri S, Han Y, Xi Y, Wang J and Lissanu Y: SMARCA4 mutation induces tumor cell-intrinsic defects in enhancer landscape and resistance to immunotherapy. bioRxiv: Jun 22, 2024 (Epub ahead of print).
43. Shi YN, Zhang XR, Ma WY, Lian J, Liu YF, Li YF and Yang WH: PD-1 antibody in combination with chemotherapy for the treatment of SMARCA4-deficient advanced undifferentiated carcinoma of the duodenum: Two case reports. World J Clin Oncol 15: 456-463, 2024.
44. Schoenfeld AJ, Bandlamudi C, Lavery JA, Montecalvo J, Namakydoust A, Rizvi H, Egger J, Concepcion CP, Paul S, Arcila ME, *et al*: The genomic landscape of SMARCA4 alterations and associations with outcomes in patients with lung cancer. Clin Cancer 26: 5701-5708, 2020.
45. Agaimy A, Daum O, Märkl B, Lichtmannegger I, Michal M and Hartmann A: SWI/SNF complex-deficient undifferentiated/rhabdoid carcinomas of the gastrointestinal tract: A series of 13 cases highlighting mutually exclusive loss of SMARCA4 and SMARCA2 and frequent co-inactivation of SMARCB1 and SMARCA2. Am J Surg Pathol 40: 544-553, 2016.
46. Liu J, Song L and Wang J: Primary SMARCA4-deficient undifferentiated sarcomatoid tumor of the gastroesophageal junction. Hum Pathol Case Rep 22: 200432, 2020.
47. Wong AK, Shanahan F, Chen Y, Lian L, Ha P, Hendricks K, Ghaffari S, Iliev D, Penn B, Woodland AM, *et al*: BRG1, a component of the SWI-SNF complex, is mutated in multiple human tumor cell lines. Cancer Res 60: 6171-6177, 2000.
48. Ankoh K, Shinji S, Yamada T, Matsuda A, Ohta R, Sonoda H, Hotta M, Takahashi G, Kaneya Y, Iwai T, *et al*: A rapidly growing small-intestinal metastasis from lung cancer. J Nippon Med Sch 89: 540-545, 2022.
49. Xu Y, Zhang B and Wang J: Gastrointestinal stromal tumour with liver metastasis presenting as gastric cancer. Diagnostics (Basel) 13: 376, 2023.
50. Altaf K, Mckernan G, Skaife P and Slawik S: Splenic metastasis in colorectal cancer. Tech Coloproctol 20: 795-796, 2016.
51. Li X, Tian S, Shi H, Ta N, Ni X, Bai C, Zhu Z, Chen Y, Shi D, Huang H, *et al*: The golden key to open mystery boxes of SMARCA4-deficient undifferentiated thoracic tumor: Focusing immunotherapy, tumor microenvironment and epigenetic regulation. Cancer Gene Ther 31: 687-697, 2024.
52. Kakkar A, Ashraf SF, Rathor A, Adhya AK, Mani S, Sikka K and Jain D: SMARCA4/BRG1-deficient sinonasal carcinoma. Arch Pathol Lab Med 146: 1122-1130, 2022.
53. Nambirajan A, Singh V, Bhardwaj N, Mittal S, Kumar S and Jain D: SMARCA4/BRG1-deficient non-small cell lung carcinomas: A case series and review of the literature. Arch Pathol Lab Med 145: 90-98, 2021.
54. Zhou P, Fu Y and Wang W: Case report: Gastrointestinal neuroendocrine carcinoma with SMARCA4 deficiency: A clinicopathological report of two rare cases. Front Oncol 13: 1290717, 2023.
55. Yu L and Wu D: SMARCA2 and SMARCA4 participate in DNA damage repair. Front Biosci (Landmark Ed) 29: 262, 2024.
56. Berezowska S, Maillard M, Keyter M and Bisig B: Pulmonary squamous cell carcinoma and lymphoepithelial carcinoma-morphology, molecular characteristics and differential diagnosis. Histopathology 84: 32-49, 2024.
57. Affandi KA, Tizen NMS, Mustangin M and Zin RRMRM: p40 immunohistochemistry is an excellent marker in primary lung squamous cell carcinoma. J Pathol Transl Med 52: 283-289, 2018.
58. Garcia-Porrero G, Wood F, Faria S, Kelly PJ and McCluggage WG: 'Aberrant' expression of skeletal muscle markers in neuroendocrine carcinomas: A significant diagnostic pitfall. Virchows Arch 485: 625-629, 2024.
59. Vocino Trucco G, Righi L, Volante M and Papotti M: Updates on lung neuroendocrine neoplasm classification. Histopathology 84: 67-85, 2024.
60. Watter H, Milkins R, Chambers C and O'Brien B: Melanoma with rhabdomyosarcomatous features: A potential diagnostic pitfall. BMJ Case Rep 16: e256427, 2023.
61. Tran TAN, Linos K, de Abreu FB and Carlson JA: Undifferentiated sarcoma as intermediate step in the progression of malignant melanoma to rhabdomyosarcoma: Histologic, histologic, immunohistochemical, and molecular studies of a new case of malignant melanoma with rhabdomyosarcomatous differentiation. Am J Dermatopathol 41: 221-229, 2019.
62. Tuohy JL, Byer BJ, Royer S, Keller C, Nagai-Singer MA, Regan DP and Seguin B: Evaluation of myogenin and MyoD1 as immunohistochemical markers of canine rhabdomyosarcoma. Vet Pathol 58: 516-526, 2021.
63. Agard H, Clark C, Massanyi E, Steele M and McMahon D: Chemoradiotherapy-induced cytodifferentiation in bladder/prostate rhabdomyosarcoma with genetic downregulation of myogenin and MyoD1 gene expression: A case study and review of the literature. Urology 137: 173-177, 2020.
64. Mishra P, Patra S, Srinivasan A, Padhi S, Sable MN, Samal SC and Mohapatra S: Primary gastrointestinal anaplastic large cell lymphoma: A critical reappraisal with a systematic review of the world literature. J Cancer Res Ther 17: 1307-1313, 2021.
65. Radha S, Afroz T and Reddy R: Primary anaplastic large cell lymphoma of caecum and ascending colon. Indian J Pathol Microbiol 64: 168-170, 2021.
66. Hasegawa T, Matsuno Y, Shimoda T, Umeda T, Yokoyama R and Hirohashi S: Proximal-type epithelioid sarcoma: A clinicopathologic study of 20 cases. Mod Pathol 14: 655-663, 2001.
67. Echchaoui A, Sadrati Y, Elbir Y, Elktaibi A, Benyachou M, Mazouz SE, Gharib NE and Abbassi A: Proximal-type epithelioid sarcoma: A new case report and literature review. Pan Afr Med J 24: 238, 2016.
68. Quintanal-Villalonga Á, Costa E, Wohlheiter C, Tischfield S, Redin E, Sridhar H, Funnel A, Poirier JT, Hao Y, Kinyua D, *et al*: 228P SMARCA4 inactivation drives aggressiveness in STK11/KEAP1 co-mutant lung adenocarcinomas through the induction of TGFβ signaling. ESMO Open 9 (Suppl 3): S102878, 2024.
69. An HR, Kim HD, Ryu MH and Park YS: SMARCA4-deficient undifferentiated gastric carcinoma: A case series and literature review. Gastric Cancer 27: 1147-1152, 2024.
70. Wilson BG and Roberts CWM: SWI/SNF nucleosome remodellers and cancer. Nat Rev Cancer 11: 481-492, 2011.
71. Liu L, Ahmed T, Petty WJ, Grant S, Ruiz J, Lycan TW, Topaloglu U, Chou PC, Miller LD, Hawkins GA, *et al*: SMARCA4 mutations in KRAS-mutant lung adenocarcinoma: A multi-cohort analysis. Mol Oncol 15: 462-472, 2021.
72. Alessi JV, Ricciuti B, Spurr LF, Gupta H, Li YY, Glass C, Nishino M, Cherniack AD, Lindsay J, Sharma B, *et al*: SMARCA4 and other SWItch/sucrose nonfermentable family genomic alterations in NSCLC: Clinicopathologic characteristics and outcomes to immune checkpoint inhibition. J Thorac Oncol 16: 1176-1187, 2021.

73. Cui M, Lemmon K, Jin Z and Uboha NV: Esophageal carcinoma with SMARCA4 mutation: Unique diagnostic challenges. Pathol Res Pract 248: 154692, 2023.
74. Yin C, Liu ZJ, He C and Yu HX: A case of surgically treated non-metastatic SMARCA4-deficient undifferentiated thoracic tumor: A case report and literature review. Front Oncol 14: 1399868, 2024.
75. Bell EH, Chakraborty AR, Mo X, Liu Z, Shilo K, Kirste S, Stegmaier P, McNulty M, Karachaliou N, Rosell R, *et al*: SMARCA4/BRG1 is a novel prognostic biomarker predictive of cisplatin-based chemotherapy outcomes in resected non-small cell lung cancer. Clin Cancer Res 22: 2396-2404, 2016.
76. Dagogo-Jack I, Schrock AB, Kem M, Jessop N, Lee J, Ali SM, Ross JS, Lennerz JK, Shaw AT and Mino-Kenudson M: Clinicopathologic characteristics of BRG1-deficient NSCLC. J Thorac Oncol 15: 766-776, 2020.
77. Naito T, Umemura S, Nakamura H, Zenke Y, Udagawa H, Kirita K, Matsumoto S, Yoh K, Niho S, Motoi N, *et al*: Successful treatment with nivolumab for SMARCA4-deficient non-small cell lung carcinoma with a high tumor mutation burden: A case report. Thorac Cancer 10: 1285-1288, 2019.
78. Skoulidis F, Goldberg ME, Greenawalt DM, Hellmann MD, Awad MM, Gainor JF, Schrock AB, Hartmaier RJ, Trabucco SE, Gay L, *et al*: STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma. Cancer Discov 8: 822-835, 2018.
79. Leinonen HM, Kansanen E, Pölönen P, Heinäniemi M and Levonen AL: Dysregulation of the keap1-Nrf2 pathway in cancer. Biochem Soc Trans 43: 645-649, 2015.
80. Gatalica Z, Xiu J, Swensen J and Vranic S: Comprehensive analysis of cancers of unknown primary for the biomarkers of response to immune checkpoint blockade therapy. Eur J Cancer 94: 179-186, 2018.
81. Concepcion CP, Ma S, LaFave LM, Bhutkar A, Liu M, DeAngelo LP, Kim JY, Del Priore I, Schoenfeld AJ, Miller M, *et al*: Smarca4 inactivation promotes lineage-specific transformation and early metastatic features in the lung. Cancer Discov 12: 562-585, 2022.
82. Han XJ, Alu A, Xiao YN, Wei YQ and Wei XW: Hyperprogression: A novel response pattern under immunotherapy. Clin Transl Med 10: e167, 2020.
83. Misra S, Szeto W, Centeno L, Castillo D, Rucker A, Rahmanuddin S and Mannan R: SMARCA4 deficient gastric carcinoma with squamous differentiation in a young patient with aggressive clinical course. Int J Surg Pathol 33: 1016-1021, 2025.
84. Bhat V, Koneru M, Knapp K, Joneja U, Morrison J and Hong YK: Identification and treatment of SMARCA4 deficient poorly differentiated gastric carcinoma. Am Surg 89: 4987-4989, 2023.
85. Kido K, Nojima S, Motooka D, Nomura Y, Kohara M, Sato K, Ohshima K, Tahara S, Kurashige M, Umeda D, *et al*: Ovarian high-grade serous carcinoma cells with low SMARCA4 expression and high SMARCA2 expression contribute to platinum resistance. J Pathol 260: 56-70, 2023.
86. Mokashi A and Bhatia NM: Integrated network ethnopharmacology, molecular docking, and ADMET analysis strategy for exploring the anti-breast cancer activity of ayurvedic botanicals targeting the progesterone receptor. BIO Integr 5: 1-17, 2024.
87. Ji X, Tian X, Feng S, Zhang L, Wang J, Guo R, Zhu Y, Yu X, Zhang Y, Du H, *et al*: Intermittent F-actin perturbations by magnetic fields inhibit breast cancer metastasis. Research (Wash DC) 6: 0080, 2023.
88. Guo XF, Gu SS, Wang J, Sun H, Zhang YJ, Yu PF, Zhang JS and Jiang L: Protective effect of mesenchymal stem cell-derived exosomal treatment of hippocampal neurons against oxygen-glucose deprivation/reperfusion-induced injury. World J Emerg Med 13: 46-53, 2022.
89. Luo Z, Mei J, Wang X, Wang R, He Z, Geffen Y, Sun X, Zhang X, Xu J, Wan R, *et al*: Voluntary exercise sensitizes cancer immunotherapy via the collagen inhibition-orchestrated inflammatory tumor immune microenvironment. Cell Rep 43: 114697, 2024.