

Histopathological Features and Immunophenotype of Primary Gastric Invasive Fibromatosis

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Abstract

Background To investigate the histopathological characteristics, immunophenotype and differential diagnosis of primary gastric invasive fibromatosis.

Methods The clinical manifestations, histological morphology and immunophenotype of 4 cases of primary gastric invasive fibromatosis were observed and related literatures were reviewed.

Results Among the 4 patients, 2 were males and 2 were females, aged 28 and 47 years, respectively. The lesions were located in the stomach in 2 cases, the gastric antrum in 1 case and cardia in 1 case. Under the microscope, the tumor was located in the submucosa, growing infiltratingly, and infiltrating into the gastric wall muscularis, serous membrane and extraserosal fatty tissue. Tumor cells were rich in cytoplasm, with unclear cell boundaries, long rod-shaped nuclei, deep chromatin, no atypia, and rare mitotic figures. The tumor tissue was composed of proliferating spindle-shaped fibroblasts and collagen fibers, and the cell morphology was relatively uniform, arranged in parallel bundles or staggered weaves. Tumor tissue invaded and destroyed smooth muscle, blood vessels, nerve tissue and adipose tissue of the gastric wall. Immunophenotype: positive expression of vimentin, β -catenin, SMA positive expression; CKpan, EMA, S-100 protein, desmin, CD99, Bcl-2, ALK, CD34, CD117, DOG1, hormone receptors were all negative; The cell proliferation index ki-67 positive cells were 3–5%.

Conclusion Primary invasive fibromatosis of the stomach is a relatively rare spindle cell tumor, which needs to be differentiated from tumors and pathological lesions such as inflammatory myofibroblastic tumor, plexiform mucinous fibroma, gastrointestinal stromal tumor, etc.

Background

Invasive fibromatosis usually occurs in the fibroids of the abdominal muscle layer and fascia sheath, so it is also called abdominal wall ligamentoid fibroids, band tumors, and fibromatosis. Because the growth of the tumor is invasive, recurring and locally destructive, it is also known as invasive fibromatosis, fibroid hyperplasia, recurrent abdominal wall fibroids and abdominal wall fibroblasts. Invasive fibromatosis has no signs of malignancy in cytological morphology, no lymphatic and blood tract metastasis, but it is invasive, recurring, and locally destructive, which is different from benign and malignant tumors [1–4]. WHO (1994) defines it as differentiated fibroblast tumors, whose biological characteristics are between benign fibroblast tumors and fibrosarcomas, and are recognized by more and more scholars [5–8]. Primary invasive fibromatosis of the stomach is rare. 3 cases are reported in this article. The clinicopathological features, diagnosis and differential diagnosis are analyzed, and relevant literatures are reviewed.

Methods

1.1 Clinical data collection From December 2017 to December 2019, the external examination and consultation cases of the Department of Pathology, Shenzhen Hospital of Southern Medical University

and the Department of Pathology of the 159th Hospital of the PLA, a total of 4 cases, were enrolled, including 2 males and 2 females, aged 28 to 47, with an average of 38.6 years old.

1.2 Methods After surgery, the specimens were fixed within 30 minutes, and fixed with freshly prepared 10% neutral buffered formalin solution (NBF) for 8–48 hours, and the volume ratio of fixative to tissue was 10:1. The tissues of the tumor area were fully collected, and the samples were routinely collected according to the depth of invasion, different colors, and different textures, and stained with HE and immunohistochemical En Vision methods. The primary antibodies vimentin, β -catenin, ALK, EMA, CKpan, SMA, S-100 protein, desmin, CD99, Bcl-2, CD34, CD117, DOG1, ki-67, hormone receptors, and working solutions were all purchased from Fuzhou Maixin Biotechnology Development Co., Ltd., the operation steps strictly follow the kit instructions.

Results

2.1 Clinical data There was no obvious cause for upper abdominal pain and discomfort in 4 cases, which was intermittent dull pain, every 2 days or 3 days, the dull pain lasted between 1 hour and 1.5 hours. No discomfort such as acid reflux, heartburn, nausea, vomiting, diarrhea, constipation, etc. No fever, cough, sputum, palpitation, chest tightness, shortness of breath and other discomforts. There were 2 males, one of whom had a history of smoking for 35 years, 15 cigarettes per day, which lasted until hospitalization in 2018. Two females were married at the right age, each had a son, and were healthy. None of the 4 patients had a family history of genetic disease. Admission check: consciousness, good spirits, normal development, and cooperative physical examination. There was no yellowing of skin and mucous membranes, and no swelling of superficial lymph nodes. The thorax was symmetrical and had no deformities, no local bulges and depressions, heart rate 77 to 86 beats per minute, regular rhythm, and normal heart sounds. Specialist examination: flat abdomen, tenderness, rebound pain and muscle tension. ECG: Sinus rhythm, normal ECG. Various laboratory tests showed no abnormalities. Two cases of abdominal CT showed a huge soft tissue mass between the gastric body and the gastric wall. The lesion was closely attached to the mucosal layer, and the gastric mucosa was damaged locally. The liver shape and size were normal, the intrahepatic bile ducts were not significantly dilated, the gallbladder was normal in size, the pancreas was normal in shape and size, there was no obvious abnormal density in it, and the spleen was normal in size. CT suggested the possibility of gastrointestinal stromal tumors, admitted to surgery with "gastric space occupying" by the outpatient department. Intraoperative frozen rapid pathological diagnosis: (2 cases of gastric body) spindle cell tumor, morphology consistent with invasive fibromatosis. (1 case of gastric antrum) the hyperplastic fibrous tissue showed low-grade intraepithelial tumor changes.

2.2 Pathological examination

2.2.1 Eye view 2 cases are proximal partial gastrectomy specimens, and 2 cases are distal partial gastrectomy specimens. The cut surface of the tumor is gray-white, hard, and the boundary is unclear. No bleeding, necrosis, or cystic change is seen.

2.2.2 Microscopic examination Under the microscope, the tumor is found in the submucosa and shows invasive growth. The tumor tissue invades the gastric mucosa layer, destroying the mucosal layer structure (Figure 1), the mucosal muscle layer mostly disappears, the proper glands are atrophy, hyperplasia, and heterogeneity, forming a disordered shape, the tumor tissue can eventually completely replace the gastric mucosa layer, and the gastric mucosa necrotizes and forms ulcers. The tumor tissue invades the muscular layer of the gastric wall, and the smooth muscle tissue of the muscular layer of the gastric wall is divided into nest-like or disordered pieces of different sizes, especially in the outer muscle layer of the gastric wall, this smooth muscle piece may be pushed by tumor tissue to 10mm away (Figure 2), indicates that the invasion of the tumor is not only strong, but also has a certain directionality. The smooth muscle fragments destroyed by tumor invasion gradually become smaller, disappear uniformly, and finally are completely replaced by tumor tissue. The tumor tissue invaded the serosal layer to widen the serous membrane, and the tumor tissue divided the fat tissue into irregular pieces of fat. The tumor tissue continued to grow in the adipose tissue outside the serous membrane of the gastric wall, showing a crab-food-like growth (Figure 3). The directional and invasive destruction of the morphological features of smooth muscle, blood vessels and nerve tissue by tumor tissue is one of the key points in the diagnosis of gastric primary fibromatosis (Figure 4). The tumor tissue is mainly composed of proliferating spindle fibroblasts and collagen fibers, and the morphology of tumor cells is relatively consistent. The arrangement of tumor tissue growth is mainly in bundles (parallel bundles or cross bundles), and can also form a staggered weave-like arrangement. The collagen fibers form a wide and long ribbon, sometimes very eye-catching (Figure 5). The density of cells near the muscularis of the gastric wall is slightly higher, and the density of adipose tissue tumor cells near the serosa is lower, which may be related to the density of the original tissue. There is no necrosis of tumor tissue. In tumor cytology, the tumor cells are long spindle-shaped, with rich and lightly stained cytoplasm, unclear cell boundaries, and elongated spindle-shaped or rod-shaped nuclei with deep staining. The tumor cells have no atypia, with 0 to 3 mitotic figures/50HPF. Ganglion-like myofibroblasts can be seen in the tumor tissues, the nucleus is vacuolated, with or without eosinophilic nucleoli, and the cytoplasm is rich and double stained. The accumulation of lymphocytes is often seen in tumor tissues. The main composition is small lymphocytes with no lymph node structure, no germinal center, no envelope structure, and the size is 0.5 to 1.0 mm.

2.3 Immunophenotype Immunophenotype: tumor cell vimentin, β -catenin diffuse and strong positive expression, cell proliferation index ki-67 positive cell number 3%~5% (Figure 6), SMA negative or focal positive expression; broad spectrum cells keratin (CKpan), EMA, S-100 protein, desmin, CD99, Bcl-2, ALK, CD34, CD68, CD163, CD21, CD23, CD117, DOG1, hormone receptors are all negative.

2.4 Follow-up The deadline of follow-up was April 1, 2020. There was no recurrence during the follow-up period of 4-28 months.

Discussion

Invasive fibromatosis or ligament-like fibromatosis is the abnormal proliferation of clonal fibroblasts and/or myofibroblasts that occur in deep soft tissues, and has the characteristics of infiltrating growth into surrounding soft tissues and high local recurrence tendency. The etiology of the disease is currently controversial. The literature puts forward three hypotheses [5]: (1) Injury factors, pregnancy, childbirth, abdominal wall muscle fiber injury and bleeding, and hematoma formation provide conditions for tumor occurrence; (2) Endocrine disorders, taking estrogen drugs; (3) Chromosomal abnormalities, that is, the Y chromosome corresponding to chromosome 8 / 20 has a triploid. According to the WHO classification of soft tissue tumors in 2013, it belongs to intermediate local invasive tumors ^[1-3]. The peak age of onset is between 10 and 40 years old, and there is no obvious gender difference. According to the location of the tumor, it can be divided into three types: abdominal wall fibromatosis, extra-abdominal fibromatosis, intra-abdominal and mesenteric fibromatosis. Extra-abdominal ligamentoid fibromatosis mainly affects the skeletal muscle system of the neck, shoulders, and limbs, and a small number of cases involve the intracranial, thoracic cavity, breast, thyroid, liver, etc. ^[2-4]. Primary gastric invasive fibromatosis is rare, and the clinical manifestations are upper abdominal discomfort. This study found that the age of onset was 28 to 46 years old, with an average of 37.3 years old. The tumor is located in the submucosa and grows invasively. Key points of histopathological diagnosis: (1) The tumor has no envelope and has the characteristics of strong invasion and destruction of surrounding tissues without causing tissue necrosis; (2) The tumor cell nucleus is elongated, spindle-shaped or rod-shaped, and the cell morphology is relatively consistent, no atypia, mitosis is rare, cell proliferation index is low; (3) The density of tumor cells that invade the smooth muscle tissues of the gastric wall is high, and the density of tumor cells that invade the fat tissues outside the serosal membrane is low; (4) Directional destruction invades smooth muscles and blood vessels and nerve tissue; (5) The tumor tissue is rich in collagen fibers, less inflammatory cell infiltration, and there may be lymphocyte aggregation, about 0.5-1.0 mm in size.

Differential diagnosis: (1) Inflammatory fibrous polyps are interstitial hyperplasia composed of spindle cells, small blood vessels and inflammatory cells, especially eosinophils. The age of onset is older, usually 60 to 75 years old, and it is a sessile polypoid mass with an average diameter of 1.5 cm. Histologically, inflammatory fibrous polyps are composed of loose connective tissue, and are mixed with more inflammatory cells and proliferating thin-walled blood vessels, regional edema or mucus-like background. Inflammatory cells are mainly lymphocytes and eosinophils, and sometimes eosinophils are the main component of inflammation, often surrounding blood vessels. Sometimes proliferating mesenchymal cells surround the small and medium-sized blood vessels, forming a concentric structure. The immunophenotype is positive for vimentin and CD34, focally expressing SMA, and negative for β -catenin and ALK ^[9]. (2) Gastrointestinal stromal tumor (GIST): GIST is the most common mesenchymal tumor of the gastrointestinal tract, which usually occurs in the elderly, with a median age ranging from 60 to 65 years. Gastric GIST can occur in any part of the stomach, from the smallest mural nodules to large complex masses with intracavity and extracavity. The histology of gastric GIST is diverse, most of which are spindle cell type, a few are epithelioid cell type, and mixed type of spindle cell epithelioid cell, and there are a few special morphology, showing sarcomatoid features, accompanied by a large number of nuclear atypia and mitosis, which are pleomorphic cell type. Most gastric GISTs positively express CD117

and DOG1; some positively express CD34 and S100 proteins. The KIT or PDGFRA gene mutation can be detected by molecular method^[10, 11]. (3) Invasive fibromatosis in the abdominal cavity involving the stomach: it can be distinguished by the combination of surgical findings, gross specimen examination and imaging examination. Histologically, invasive fibromatosis has the characteristics of directional invasion and destruction of smooth muscle, blood vessels and nerve tissues, which can exclude gastric involvement in abdominal invasive fibromatosis^[12, 13]. (4) Gastric plexiform fibromyxoma: it is a rare gastric mesenchymal tumor with unique histological characteristics, which mostly occurs in the antrum of the stomach. Tumors grow in clusters or multiple nodules of varying sizes between the gastric wall, staggered with the smooth muscle of the gastric wall. The tumors are rich in small, thin-walled blood vessels, and the cells are rich in mucin-like or fibromycin-like stroma; the tumor cell nuclei are spindle-shaped or oval, nucleolus is not obvious, cytoplasm is slightly eosinophilic, and cell atypia is not obvious. The immunophenotypic spindle cells mainly express α -SMA and muscle-specific actin (MSA), while β -catenin is negative. Electron microscopy shows that the tumor has myofibroblast differentiation^[14]. (5) Schwannoma rarely occurs in the stomach, and its frequency is similar to that of gastric leiomyoma. The tumor often occurs in the elderly, and generally forms a mass of 2 cm to 5 cm in the stomach wall. The clinical manifestations, including general features, are similar to those of GIST. The biological behavior of the tumor is benign and recurrence is rare. Tumor cells are composed of spindle-shaped cells, arranged in a cross-bundle shape, and the nuclei can be arranged in a fence shape. Different amount of collagen fibers can be seen between the cells. Immunophenotypic tumor cells strongly express S-100 protein diffusely, and some cases express CD34; they do not express CD117, DOG1, ALK, β -catenin, desmin, SMA^[15]. (6) Inflammatory myofibroblastic tumors: mostly occur in children under 10 years of age, mainly composed of proliferating obese spindle-shaped fibroblasts or myofibroblasts, with a large number of inflammatory cell infiltration in the interstitium, mostly mature plasma cells, lymphocytes and eosinophils, a few are neutrophils, and regional lymphocytes aggregate. In addition to the spindle cells, round-shaped histiocyte-like cells can be seen in the lesions. In some cases, some irregular, polygonal or odd-shaped cells can be seen. Eosinophilic or basophilic inclusions can be seen in the nucleus, similar to ganglion cells or R-S cells. The immunophenotype is positive for vimentin and SMA, and desmin and MSA are focally positive. 50% of the cases are positive for ALK, and CD117. DOG1, β -catenin, and S-100 protein are not expressed^[16]. (7) Synovial sarcoma: it is a malignant mesenchymal tumor showing epithelioid differentiation to varying degrees, with characteristic chromosomal translocation t(X;18)(p11;q11) and the resulting SS18-SSX gene fusion. Mainly occurring in the limbs of young people, gastric synovial sarcoma is very rare, and 24 cases have been reported in the English literature^[17]. A typical synovial sarcoma is composed of cancer-like epithelioid cells and fibrosarcoma-like spindle cells mixed in different proportions to form a biphasic structure. Gross examination, usually occurs in the gastric body and bottom of the stomach, and occasionally occurs in the gastric antrum or gastroesophageal junction. The tumor is 0.8–16.0 cm in diameter, with multiple or single nodules, uneven surface, and ulcer formation. The section is grayish white, grayish red, fish like, with or without necrosis. Histologically, 22 cases of gastric synovial sarcoma were reported in the literature as monophasic type and 2 cases were biphasic type. Immunohistochemistry shows positive expression of CK and EMA, molecular detection of

SYT-SST gene fusion. (8) Myofibroma/myofibromatosis: refers to benign tumors formed by muscle-like cells with contractile function arranged around thin-walled blood vessels. The isolated ones are called myofibromatosis, and the multiple ones are myofibromatosis. It can occur from newborns to the elderly, but many are seen at birth and in infants and children under 2 years of age. Men are more common. It mainly occurs in the head and neck, trunk and limbs, as well as skeletal muscle and aponeurosis. 15–20% occurs in internal organs, such as lung, heart, gastrointestinal tract, liver, kidney, pancreas, etc. Myofibroblasts are spindle-shaped, with pale pink cytoplasm, long spindle-shaped nucleus, vacuolated chromatin, with 1 to 2 small nucleoli, and the cell atypia and pleomorphism are not obvious. Round and polygonal cells with slightly larger nuclei can also be seen. The tumor cells are arranged around the irregularly branched perivascular tumor-like thin-walled blood vessels, intersecting with perihemangioma, and the tumor is an image of hemangiopericytoma. Calcification, hyaline degeneration, necrosis and apoptosis are common. Generally, there are not many lymphocytes and plasma cells. Immunophenotype: positive expression of vimentin and SMA, stronger positive for whole actin HHF35, negative for CK, EMA, ALK, β -catenin, and S-100 protein ^[18, 19]. (9) Gastric malignant solitary fibrous tumor (SFT): the tumor is a non-fixed tissue structure, and its histological characteristics are the irregular distribution of areas with few tumor cells and areas with rich tumor cells. There are more dense scar-like collagen fiber deposits and branched perivascular tumor-like vascular separation between the two (hemangiopericytoma-like areas). Gastric malignant SFT tumor cells are abundant, and the tumor cells are at least moderately to severely atypia, with tumor tissue necrosis. Lymph node metastasis occurred in gastric malignant SFT. Immunophenotype: tumor cells CD99, CD34, Bcl-2, vimentin positive expression; CKpan, EMA, SMA, S-100 protein, desmin focal weak positive expression, no express of ALK, β -catenin, CD68, CD163, CD21, CD23, CD117, DOG1 ^[20]. Other tumors that require differential diagnosis include spindle cell hyperplastic nodules, leiomyosarcoma, and epithelioid sarcoma after gastric surgery.

Treatment and prognosis: Invasive fibromatosis is a locally aggressive tumor, and surgical resection is the main method of treatment. Because the disease has a very high recurrence rate, no distant metastasis and low fatality rate, close follow-up is often used in clinical practice. Sometimes the pathology and clinical manifestations are special and must be differentiated from other spindle cell tumors and tumor-like lesions.

Conclusion

Primary invasive fibromatosis of the stomach is a relatively rare spindle cell tumor, which needs to be differentiated from tumors and pathological lesions such as inflammatory myofibroblastic tumor, plexiform mucinous fibroma, gastrointestinal stromal tumor, etc.

Abbreviations

SMA

Smooth muscle actin

EMA

Epithelial membrane antigen
ALK
Anaplastic lymphoma kinase
WHO
World Health Organization
NBF
neutral buffered formalin solution
CT
Computed Tomography
GIST
Gastrointestinal stromal tumor
SFT
solitary fibrous tumor

Declarations

Ethics approval and consent to participate:

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Shenzhen Polytechnic.

Written informed consent was obtained from all participants.

Consent to publication:

Not Applicable.

Availability of data and materials:

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

All of the authors had no any personal, financial, commercial, or academic conflicts of interest separately.

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Authors' Contribution

Conception and design of the research: YK Wang, ZS Zhang. Acquisition of data: B Jiang. Analysis and interpretation of the data: CY Zhu. Statistical analysis: B Jiang, G Zhao. Obtaining financing: None. Writing of the manuscript: YK Wang, ZS Zhang, SN Wang. Critical revision of the manuscript for intellectual content: YK Wang, SN Wang.

All authors have read and approved the manuscript.

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Figures

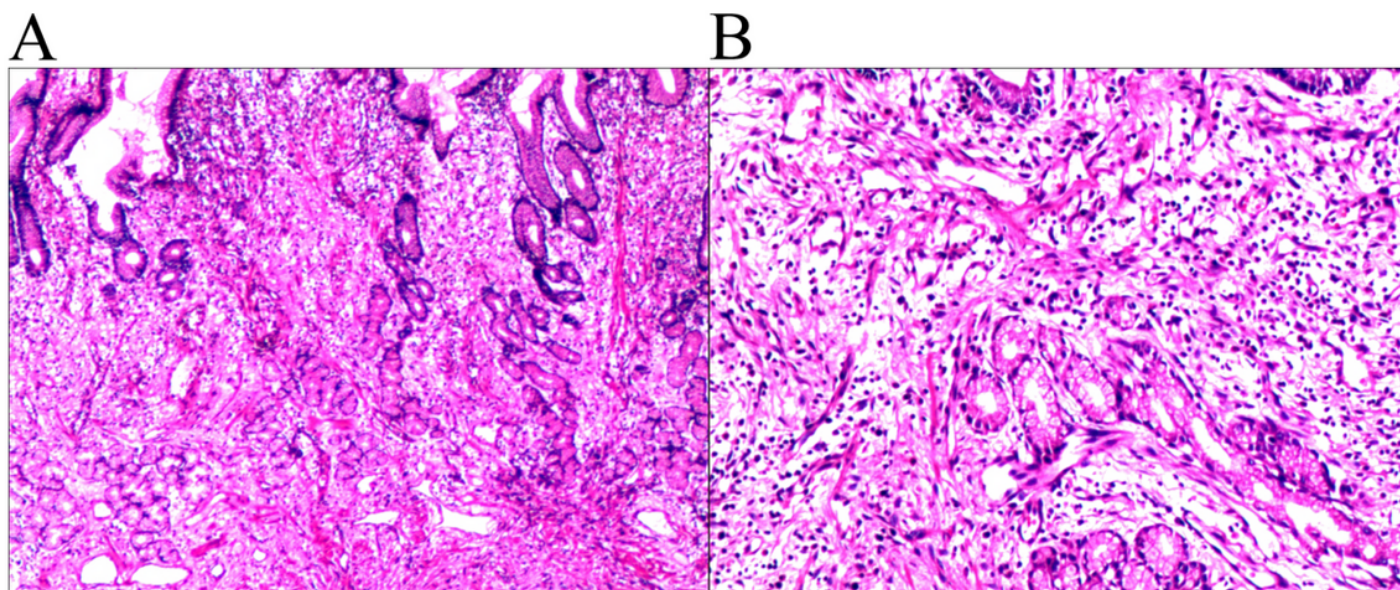


Figure 1

tumor tissue invades mucosal layer :A. The mucosal muscularis disappears, and the tumor tissue invades mucosal layer and causes the glands of lamina propria to atrophy, proliferate, and change,

forming A disordered form; B. Tumor tissue separates the lamina propria glands from the variegated lamellar structures.

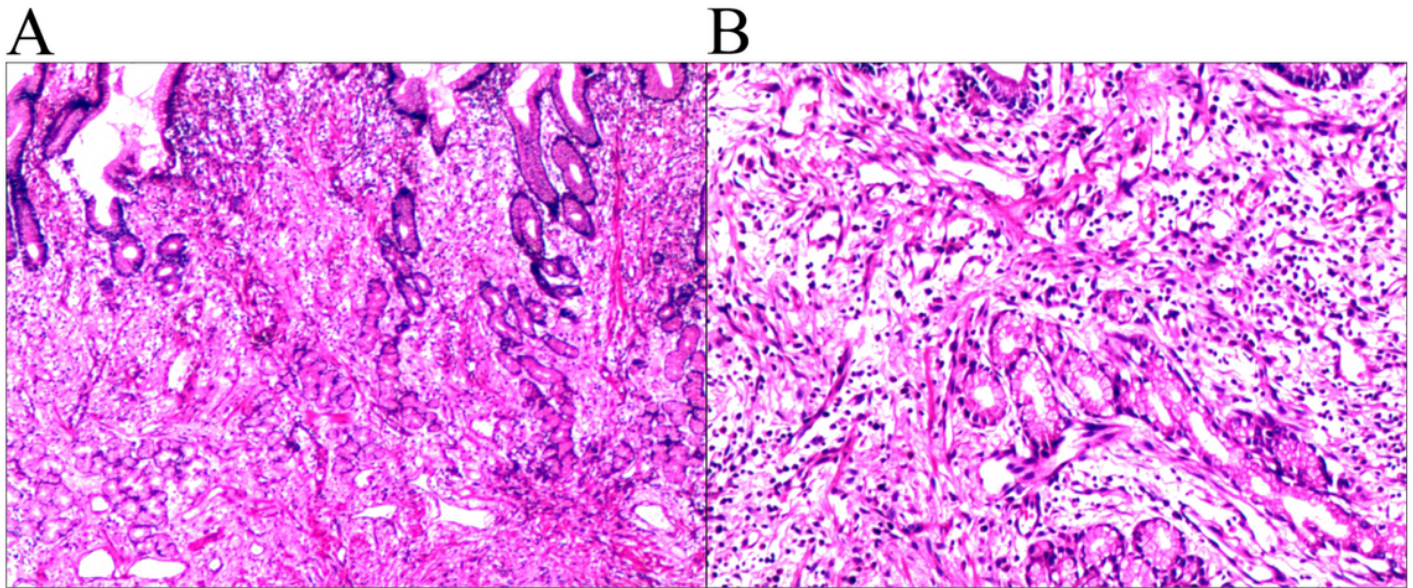


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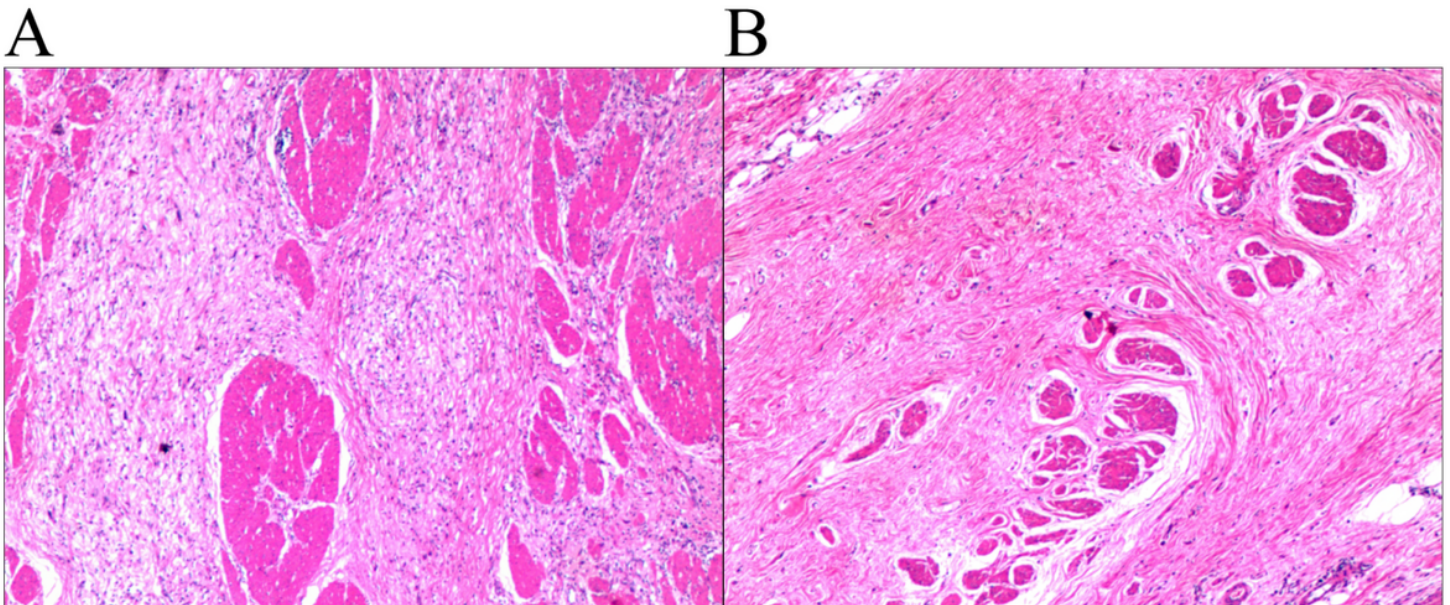


Figure 2

Tumor tissue invades the muscular layer of gastric wall: A. The smooth muscle tissue of the muscular layer of gastric wall is separated into disorganized pieces of different sizes, lumps and nests; B. A

smooth muscle mass is visible as the invasion pushes out, up to 10mm away from the musculature.

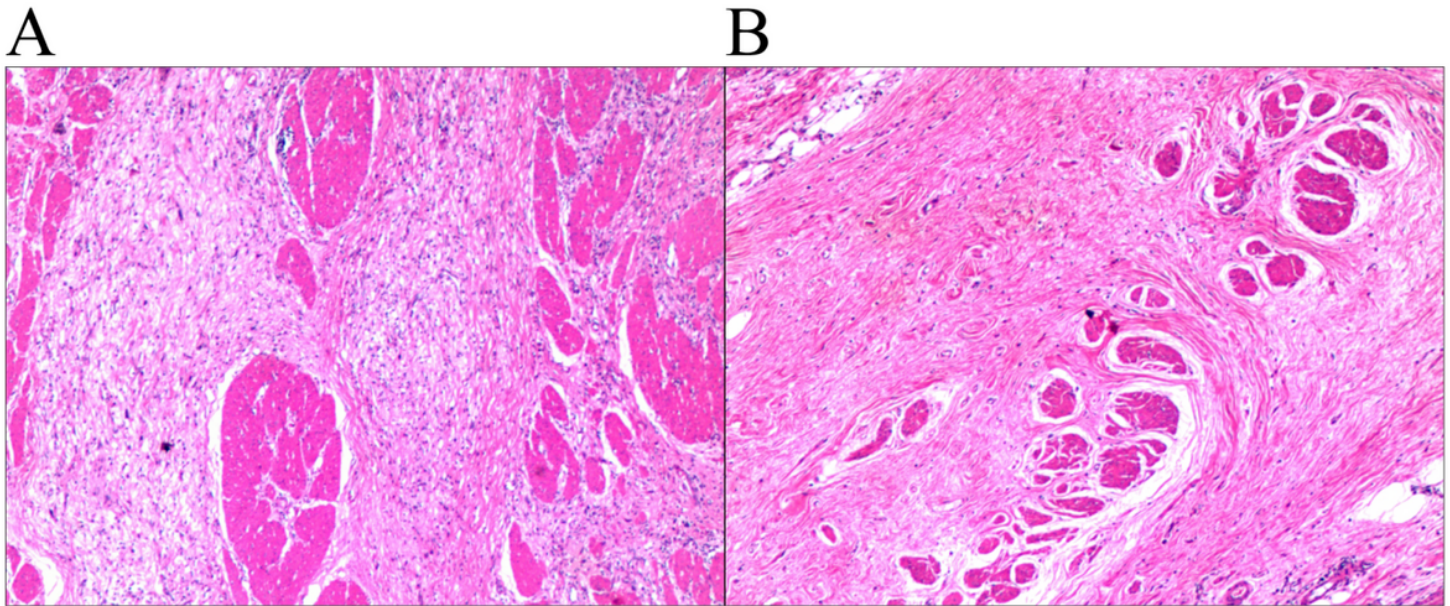


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Tumor tissue invades the muscular layer of gastric wall: A. The smooth muscle tissue of the muscular layer of gastric wall is separated into disorganized pieces of different sizes, lumps and nests; B. A smooth muscle mass is visible as the invasion pushes out, up to 10mm away from the musculature.

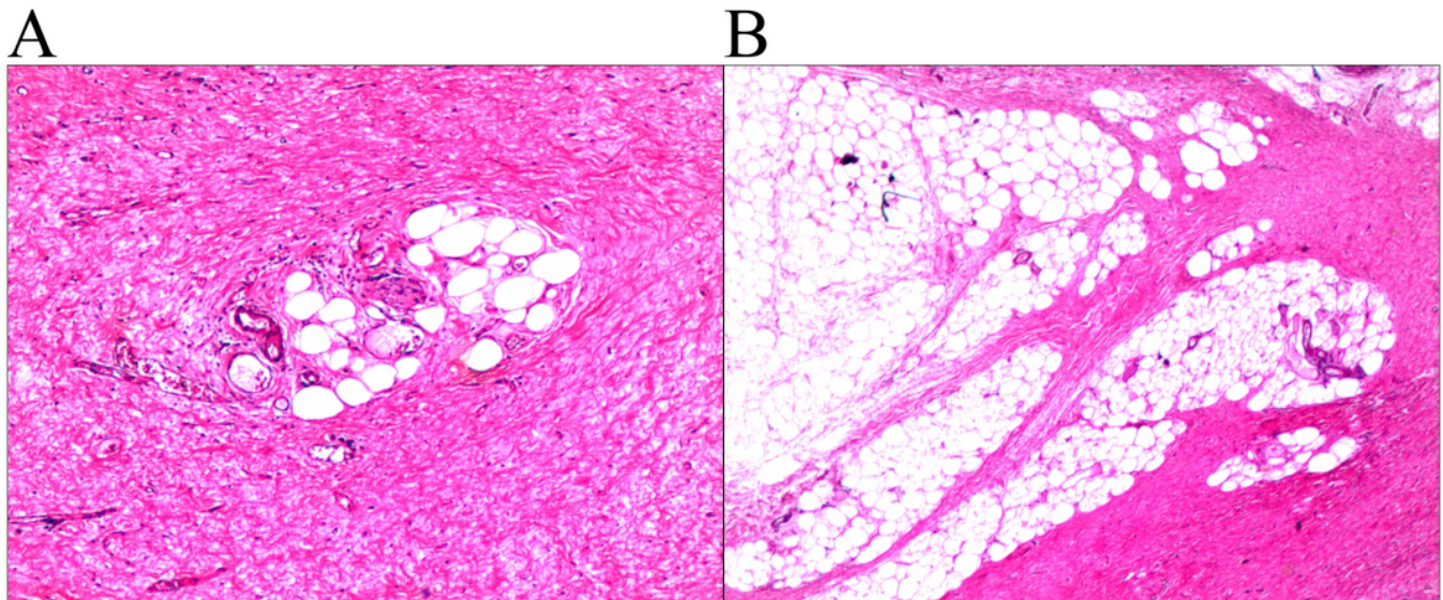


Figure 3

Tumor tissue invades the serosal layer; A. Tumor tissue divides adipose tissue into patches; B. Crab-like growth continued to occur between adipose tissues.

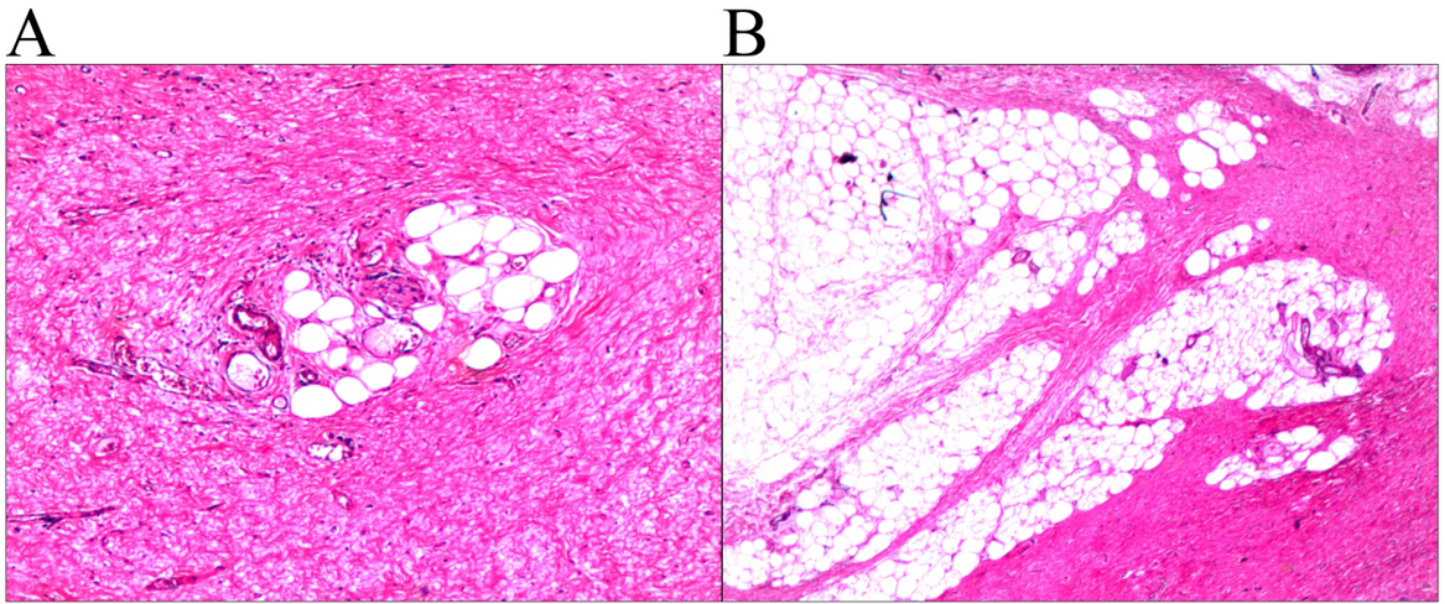


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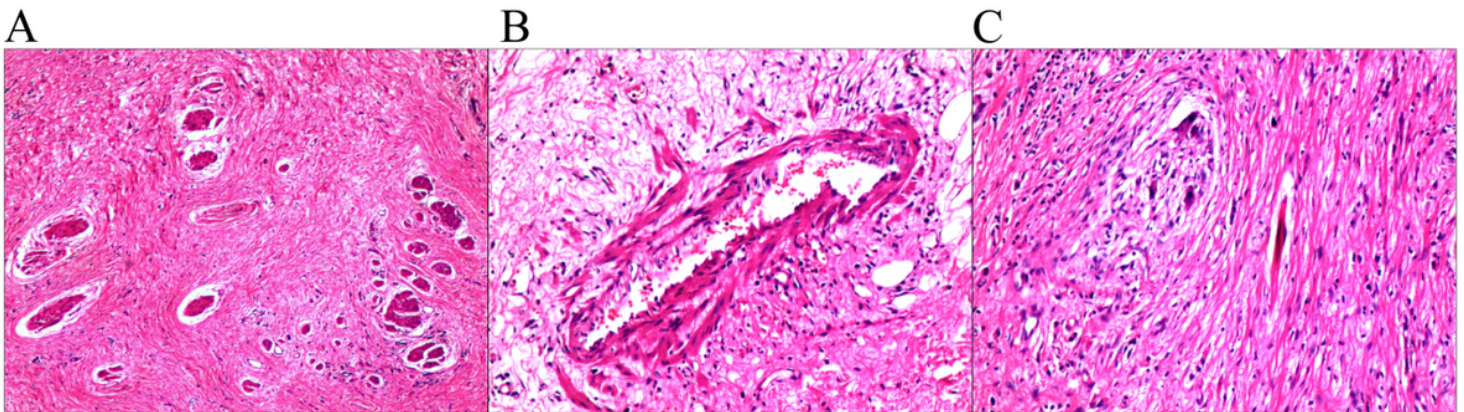


Figure 4

Morphological characteristics of directional invasive destruction of smooth muscle, blood vessels, lymphatic vessels and nerve tissues of tumor tissues: A. Neoplastic tissue invades and destroys the smooth muscle tissue, and the smooth muscle fibers are separated from the fast slice structure of different size. B. Neoplastic tissue showed invasion and destruction of blood vessels in one direction; C. Neoplastic tissue invades and destroys nerve tissue, leaving only incomplete ganglion cells.

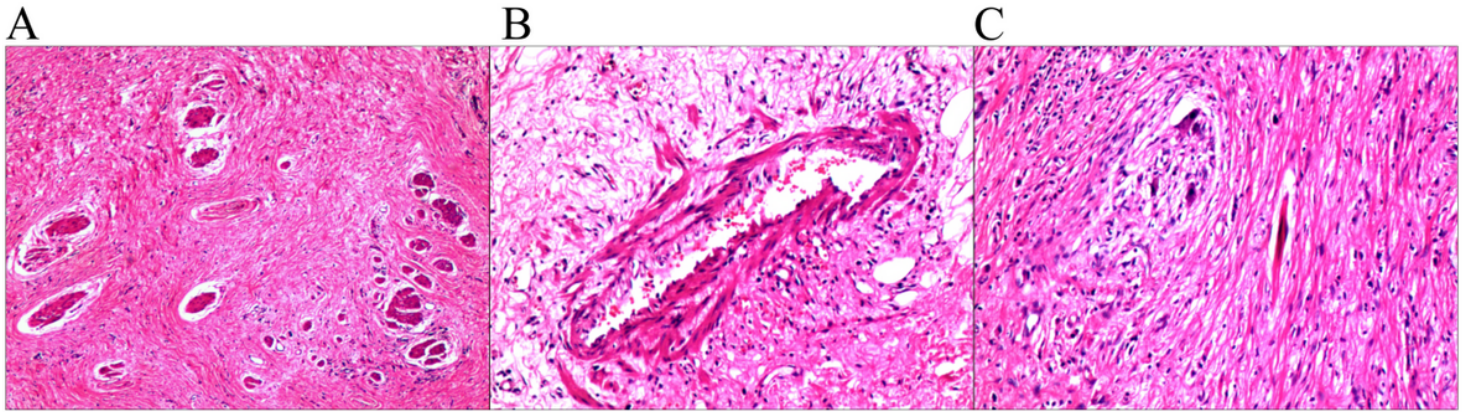


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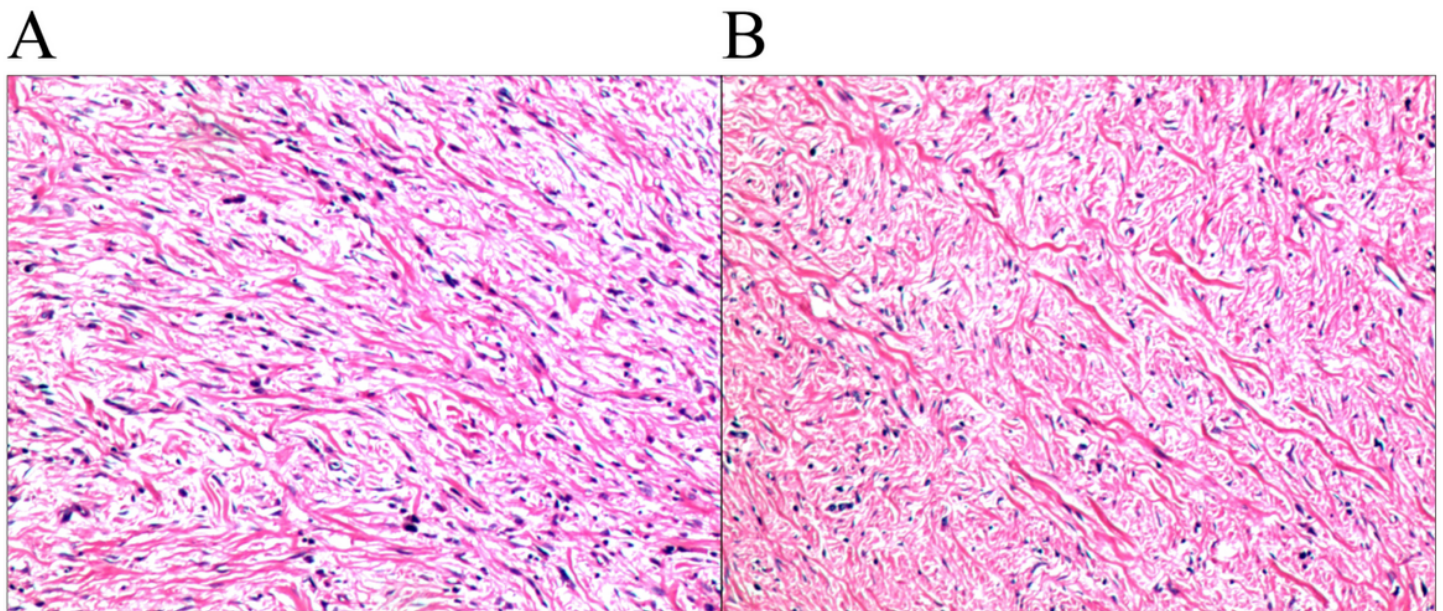


Figure 5

The composition of tumor tissues is mainly composed of proliferating spindle fibroblasts and collagen fibers. The morphology of tumor cells is relatively consistent: A. The arrangement of tumor tissue growth is mainly interlaced bundles. B. Collagen fibers form wide and long bands with prominent regions

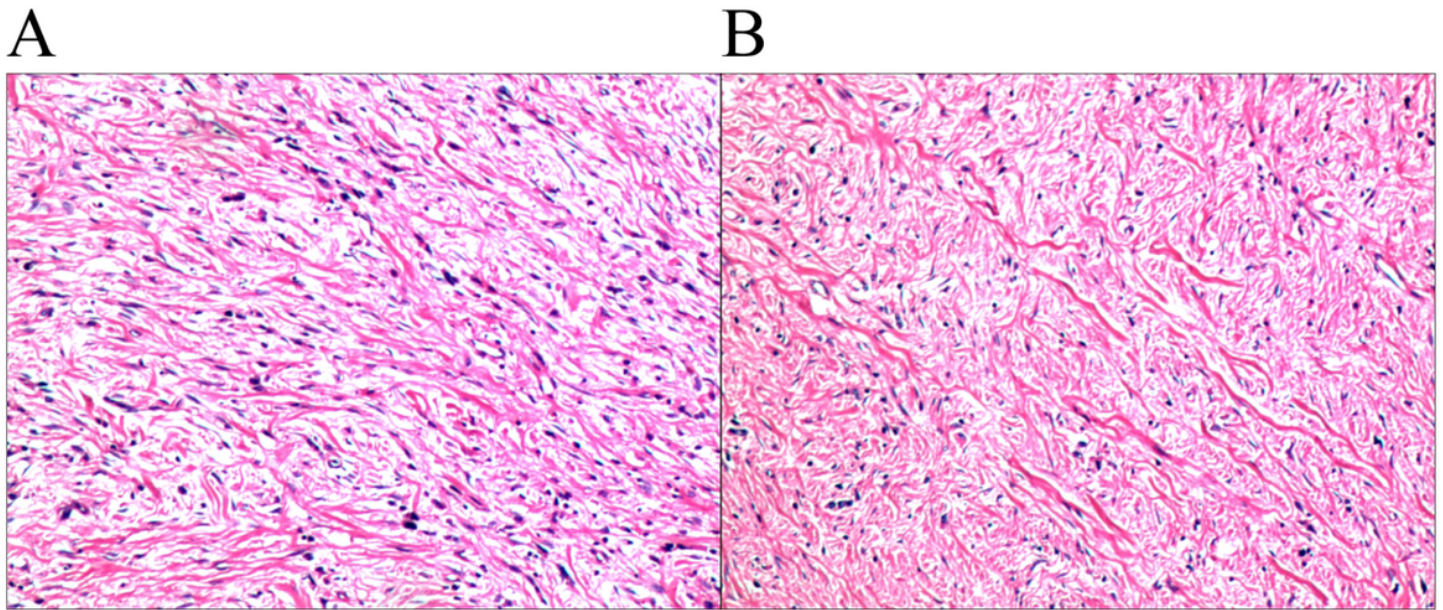


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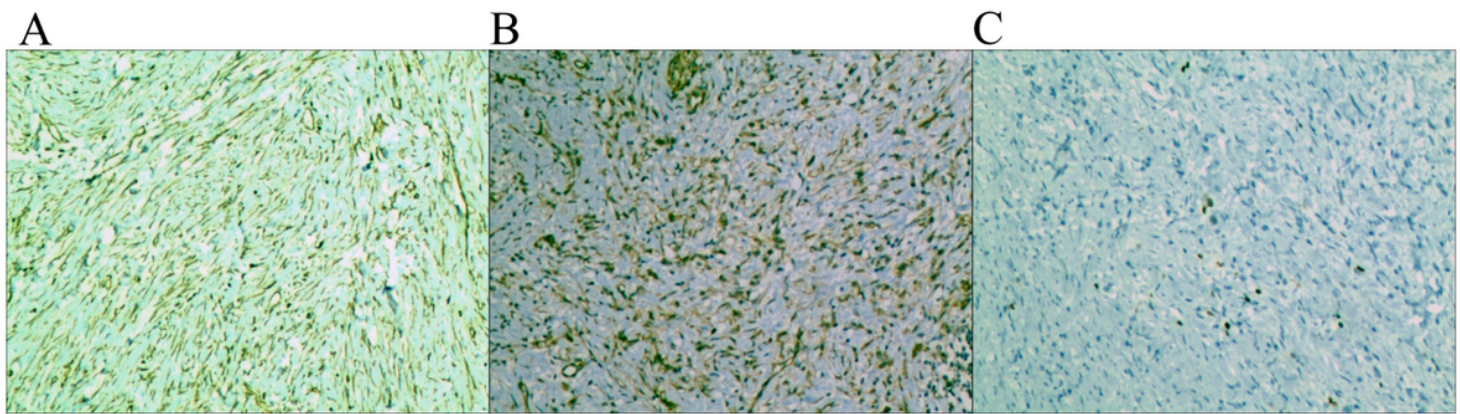


Figure 6

Immunophenotype of gastrofibromatosis, En Vision method: a. positive expression of vimentin; Positive expression of β -catenin; The number of ki-67 positive cells was 3% ~ 11%.

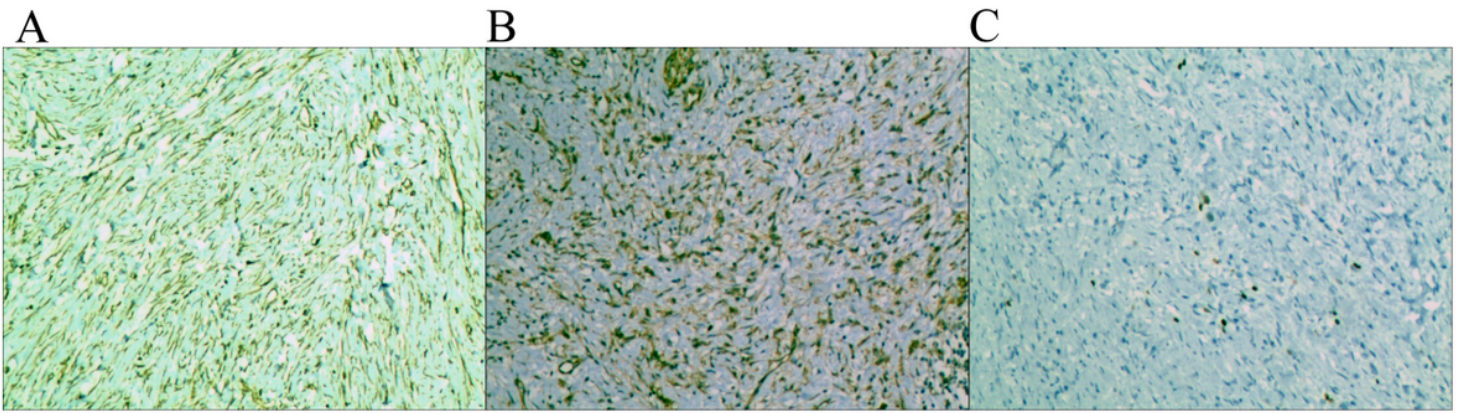


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