CASE REPORT

A case of uterine tumor resembling ovarian sex cord tumor with prominent myxoid features

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Running title: UTROSCT with prominent myxoid features

ABSTRACT

Uterine tumor resembling ovarian sex cord tumor (UTROSCT) is a rare tumor with low malignant potential that commonly occurs in middle age. Although more than 100 cases have been reported to date, its myxoid morphology is not well documented. Here, we present a 75-year-old woman with abnormal vaginal bleeding, with an 8-cm mass in the uterine corpus detected by irregular, high-intensity signaling on T2-weighted imaging. The uterine mass had a glistering mucinous appearance on gross examination. Microscopically, most of the tumor cells were floating in the myxoid stroma. The tumor cells formed clusters or nests with abundant cytoplasm, while some exhibited trabecular or rhabdoid appearances. Immunohistochemically, tumor cells were positive for pancytokeratin (AE1/AE3), α-smooth muscle actin (SMA), CD10, progesterone receptor (PgR), and some sex cord markers such as calretinin, inhibin, CD56, steroidogenic factor 1 (SF1). Electron microscopy demonstrated epithelial and sex cord differentiation. This case was negative for *JAZF1–JJAZ1* fusion gene that is frequently found in low-grade endometrial stromal sarcoma. Fusion genes related to UTROSCT, including *NCOA2/3*, were not detected by reverse transcription polymerase chain reaction (RT-PCR). The present case suggests that UTROSCT should be raised for differential diagnosis of myxoid uterine tumors.

KEYWORDS

Carcinoma, Endometrioid; Endometrial Stromal Tumors; Granulosa Cell Tumor; Leiomyosarcoma, Myxoid; Sex Cord-Gonadal Stromal Tumors; Uterine Adenosarcoma; Uterine Neoplasm

DECLARATIONS

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All authors contributed to the study conception and design. Acquisition and analysis of data were performed by KI, ZT, YO, ST, HS, YI, MT, YG, KN, HY, TH, KN, and ST. The first draft of the manuscript was written by KI and revised by ZT, MT, and ST, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Ethics declarations:

The information contained in, and preparation of, this manuscript complies with the journal's ethical standards.

BACKGROUND

Uterine tumor resembling ovarian sex cord tumor (UTROSCT) was first described by Clement and Scully in 1976. They reported 14 cases of tumors of the uterine corpus similar to ovarian sex cord tumors in morphology and divided them into two groups. Group 1 tumors were endometrial stromal tumors with sex-cord-tumor-like focal epithelial differentiation, while Group 2 presented with predominant sex-cord-like features [1]. Previous Group 2 tumors correspond to the current entity of UTROSCT in the World Health Organization classification. As its diagnostic criterion, it is necessary to have sex cord patterns without a component of recognizable endometrial stromal tumor and preferable to be immunoreactive for sex cord-stromal markers [2]. UTROSCT occurs in the myometrium or submucosa of middle-aged women, exhibits various growth patterns as sheets, cords, nests, or tubules, with minimal cytological atypia and usually follows a benign course except some reported cases of recurrence or metastasis [3]. Although more than 100 cases of UTROSCT have been reported and morphological features with genetic abnormalities have been recently identified, myxoid morphology of UTROSCT is not well documented. Here, we describe a case of UTROSCT with prominent myxoid morphology analyzed by histological, immunohistochemical, electron microscopic, and molecular techniques.

CASE PRESENTATION

A 75-year-old postmenopausal woman presented with abnormal vaginal bleeding during postoperative follow-up of gastric cancer. Transvaginal ultrasonography revealed a hyperechoic solid mass, 5 cm in diameter, in the pelvic cavity. Magnetic resonance imaging (MRI) revealed a 62 × 47 × 46 mm mass that enlarged to 86 × 73 × 65 mm 6 months later. This tumor exhibited heterogeneous intensity, suggesting myxoid change, on T2-weighted imaging (Fig. 1a). ^{18}F-Fluorodeoxyglucose positron emission tomography revealed high accumulation in the periphery of the tumor. These images suggested malignancy such as leiomyosarcoma. Preoperatively, only carcinoembryonic antigen was elevated, up to 6.4 ng/mL, with postoperative decrease to 4.9 ng/mL, and carbohydrate antigens 19-9 and 125 and squamous cell carcinoma antigen were all within reference ranges. The patient underwent total hysterectomy and bilateral salpingo-oophrectomy with dissection of the pelvic lymph nodes.

Grossly, a large well-demarcated tumor, 7.4 × 7.2 × 3.8 cm, with glistering mucinous appearance was observed in the myometrium. The sectioned surface was also prominently gelatinous and exhibited a grayish-white color (Fig. 1b and 1c). Microscopically, abundant myxoid matrix was observed in about 95% of the tumor, and tumor cells seemed to float within the marked myxoid stroma and were arranged in small clusters with nests or cord-like structures (Fig. 2a). Individual tumor cells possessed round-to-oval uniform nuclei with mild nuclear atypia, inconspicuous nucleoli, and pale abundant cytoplasm. Myxoid stroma was diffusely positive for Alcian blue staining (pH 2.5) (Fig.2b). In addition, one-third of these areas exhibited high cell density, where tumor cells formed anastomosing trabeculae or sertoliform structures with rare nuclear grooves, reminiscent of

ovarian sex cord tumors. Rhabdoid cells were recognized only in the areas where tumor cells replaced the endometrium, which was about 1% of the entire tumor (Fig. 2c). Mitotic activities were different among these three morphologically distinct areas: 1/10 high-power fields (HPFs) in the hypocellular area, 2/10 HPFs in the hypercellular area, and 4/10 HPFs in the rhabdoid area (Fig. 1e). The tumor border was almost smooth on microscopic examination (Fig. 1d), but with a small tongue-like invasion of 8 mm beneath the serosal surface (Fig. 1e, 2d). Silver staining showed loose reticulin fibers around the tumor cell nests. Some of the stroma in the hypocellular area exhibited hyalinization and fibrosis (Fig. 1e). Immunohistochemically, tumor cells were positive for pancytokeratin (AE1/AE3), α-smooth muscle actin (SMA), desmin, HHF-35, CD10, progesterone receptor (PgR), and some sex cord markers such as inhibin α, CD56, and steroidogenic factor-1 (SF1) (Fig. 3a–3g). Tumor cells showed weak and focal immunoreactivity for calretinin (Fig. 3h) and were negative for cytokeratin (CK) 7, CK20, estrogen receptor (ER), HMB45, Melan A, CD99, FOXL2 (Fig. 3i), anaplastic lymphoma kinase (ALK). Coagulated necrosis was absent. Venous or lymphatic vessel invasion was not observed. No metastasis was observed in the dissected lymph nodes. There were two intramural leiomyomata separately from the main tumor (Fig.1e).

Transmission electron microscopy (TEM) showed desmosome-like junctions (Fig. 3j) and duct formation, which suggested epithelial differentiation. Nuclear indentation and intracytoplasmic lipid droplets were recognized (Fig. 3k and 3l), which were features of sex cord differentiation. Aggregated fibers or tonofilaments were not observed. Fluorescence *in situ* hybridization (FISH) was performed using split apart probes of *JAZF1*, *JJAZ1*, and *NCOA2*, and the split signal was 0%, 2%, and 0%, respectively, suggesting there was no *JAZF1*–

JJAZ1 or *NCOA2*-related fusion gene. For detection of UTROSCT-related fusion genes, including *ESR1–NCOA1/2/3* and *GREB1–NCOA1/2/3*, 16 primers were designed for *ESR1* exon 3; *GREB1* exons 2, 5, and 7; *NCOA1* exons 13–15; *NCOA2* exons 13 and 15; and *NCOA3* exons 14–16. Reverse transcription polymerase chain reaction (RT-PCR) analysis was performed using these primers but none of the fusion genes was detected. Clinically, there was no evidence of recurrence or metastasis after a follow-up of 2 years.

DISCUSSION AND CONCLUSIONS

In this report, we have presented a case of UTROSCT with a distinctive myxoid component that accounts for about 95% of the tumor. To date, the hyalinized stroma of UTROSCT has been well documented, but we have found few descriptions of the myxoid character of UTROSCT [4]. The term “myxoid” refers to the presence of glycosaminoglycans and proteoglycans in the extracellular matrix [5]. Histologically, the myxoid matrix shows pale blue color on hematoxylin and eosin (H&E) staining and blue color on Alcian blue staining [6]. Edema and hyalin change can mimic the morphology of the myxoid matrix, but the color of stroma shown by H&E and Alcian blue staining suggests that they are unlikely to be edematous or hyalinized in the present case.

For myxoid uterine tumors, the following four entities may be the major differential diagnoses [6]. Endometrial stromal tumor may partly exhibit sex-cord-like differentiation corresponding to Group 1 tumors defined by Clement and Scully, but should exhibit permeative growth. Our case was mostly well-demarcated and only a focal tongue-like invasion was observed without spindle cells. Myxoid leiomyosarcoma/leiomyoma are hypocellular because of the myxoid stroma, but they usually do not form epithelioid structures. Inflammatory myofibroblastic tumors may have a tissue-culture-like appearance of spindle cells with positivity for ALK.

The following five tumors should be discriminated by sex cord morphology [7]. Endometrioid carcinoma may possess sertoliform tubules positive for CK7 and negative for α-SMA. Adenosarcoma has a partial sex-cord-like appearance in the stromal elements. Mesonephric adenocarcinoma typically arises from the uterine cervix and is characterized by positivity for CD10 along the luminal border. A few case reports are describing perivascular epithelioid cell tumors with sex-cord morphology that were recognized by expression of HMB45 [8].

Metastatic ovarian sex cord tumors are ruled out by the absence of any tumor in both ovaries.

The immunohistochemical profile of the present case was consistent with previous reports of UTROSCT that showed diverse immunophenotypes and met the desirable diagnostic criteria for UTROSCT from the positivity of multiple sex cord markers [2]. It has been reported that calretinin, inhibin, CD99, and Melan A can be sex cord markers [9]. Recently, SF1 and FOXL2 have been confirmed to be UTROSCT [10]. It was noteworthy that SF1 was negative for the mimics of UTROSCT such as low grade endometrial stromal sarcomas, adenosarcomas, etc [11]. In this case, inhibin and SF1 positivity suggested reliable sex cord differentiation. Unlike most of the cases, tumor cells showed only weak and focal immunoreactivity for calretinin. This may be related to the abundant mucinous component of the present case.

In our case, TEM also indicated epithelial and sex-cord-like features, including desmosome-like junctions, duct formation, intracytoplasmic lipid droplets, and nuclear indentation. It has been reported in 13 cases that tonofilaments, desmosome-like junctions, duct formation, and basal lamina are indicative of epithelial differentiation, and intracytoplasmic lipid droplets and nuclear indentation are indicative of sex cord differentiation [12]. Smooth muscle differentiation has not been confirmed.

In the present case, the FISH analysis indicated the absence of *JAZF1–JJAZ1* fusion frequently detected in low-grade endometrial stromal sarcoma. It is known that UTROSCT does not harbor *JAZF1–JJAZ1* translocation [13]. We did not check molecular alterations useful for differential diagnosis of myxoid uterine tumors such as *PLAG1*, *YWHAE*, *BCOR*, and *ALK* [2]. Recently, fusion genes including *ESR1–NCOA2/3* and *GREB1–NCOA1/2* were detected for UTROSCT and related sarcomas [14,15] (Supplementary Table). We

investigated the reported fusion genes, but we failed to detect any. Next generation sequencing-based RNA analysis may reveal novel gene alterations in UTROSCT in the future.

We have reported a case of UTROSCT with prominent myxoid features. UTROSCT can be a differential diagnosis for myxoid tumors, thus one should carefully investigate the presence of sex-cord-like structures in cases of myxoid uterine tumors.

ABBREVIATIONS

ALK: anaplastic lymphoma kinase

CK: cytokeratin

CT: computed tomography

ER: estrogene receptor

FISH: fluorescence *in situ* hybridization

HPF: high-power field

H&E: hematoxylin and eosin

IHC: immunohistochemistry

MRI: magnetic resonance imaging

PgR: progesterone receptor

RT-PCR: reverse transcription polymerase chain reaction

SF1: Steroidogenic factor-1

SMA: smooth muscle actin

TEM: transmission electron microscopy

UTROSCT: uterine tumor resembling ovarian sex cord tumor

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FIGURE LEGENDS

Figure 1

(**a**) Sagittal T2-weighted image of pelvic magnetic resonance imaging (MRI) one month before the operation. White arrowheads indicate the entire tumor mass. (**b**) Gross appearance of the resected uterine tumor. The anterior wall of the uterus was sectioned. (**c**) Gross appearance of the sectioned surface. (**d**) Semi-macroscopic image of hematoxylin and eosin (H&E)-stained slides of the corresponding region in the gross section. (**e**) Schematic representation of the semi-macroscopic image. “Hypocellular” means the area where the ratio of tumor cells to stroma is less than one; “hypercellular” means the ratio greater than one. Blue, “hypocellular” areas with myxoid stroma; green, “hypercellular” areas with myxoid stroma; red, areas consisted of rhabdoid tumor cells; yellow, tumor areas with fibrosis; pink, intramural leiomyomata; dark blue line, endometrium; asterisk, endometriosis. Arrow shows the tongue-like invasion. Each scale bar shows (**a, b**) 2 cm, (**c-e**) 1 cm.

Figure 2

(**a, b**) Microscopic images of H&E staining (**a**) and Alcian blue staining at pH 2.5 (**b**) of the myxoid area. (**c**) H&E staining of the rhabdoid area. Yellow arrowhead indicates mitosis. (**d**) Microscopic image of focal irregular border indicated by the arrow in Fig. 1e. Each scale bar shows (**a, b, d**) 500 μm, (**c**) 50 μm.

Figure 3

(**a–i**) Immunohistochemistry (IHC) was performed for (**a**) keratin, demonstrated by pancytokeratin (AE1/AE3)

antibody, (**b**) α-smooth muscle actin, (**c**) CD10, (**d**) progesterone receptor (PgR), (**e**) inhibin α, (**f**) Steroidogenic factor 1 (SF1), (**g**) CD56, (**h**) calretinin, (**i**) FOXL2. Scale bar shows 100 μm. (**j, k, l**) Electron microscopy of tumor tissue. (**j**) Arrows indicate desmosome-like junctions, (**k**) nuclear indentation, (**l**) arrow heads indicate intracytoplasmic lipid droplets. Each scale bar shows 1 μm (**j**), 0.5 μm (**k**), and 2 μm (**l**).

Figure 1

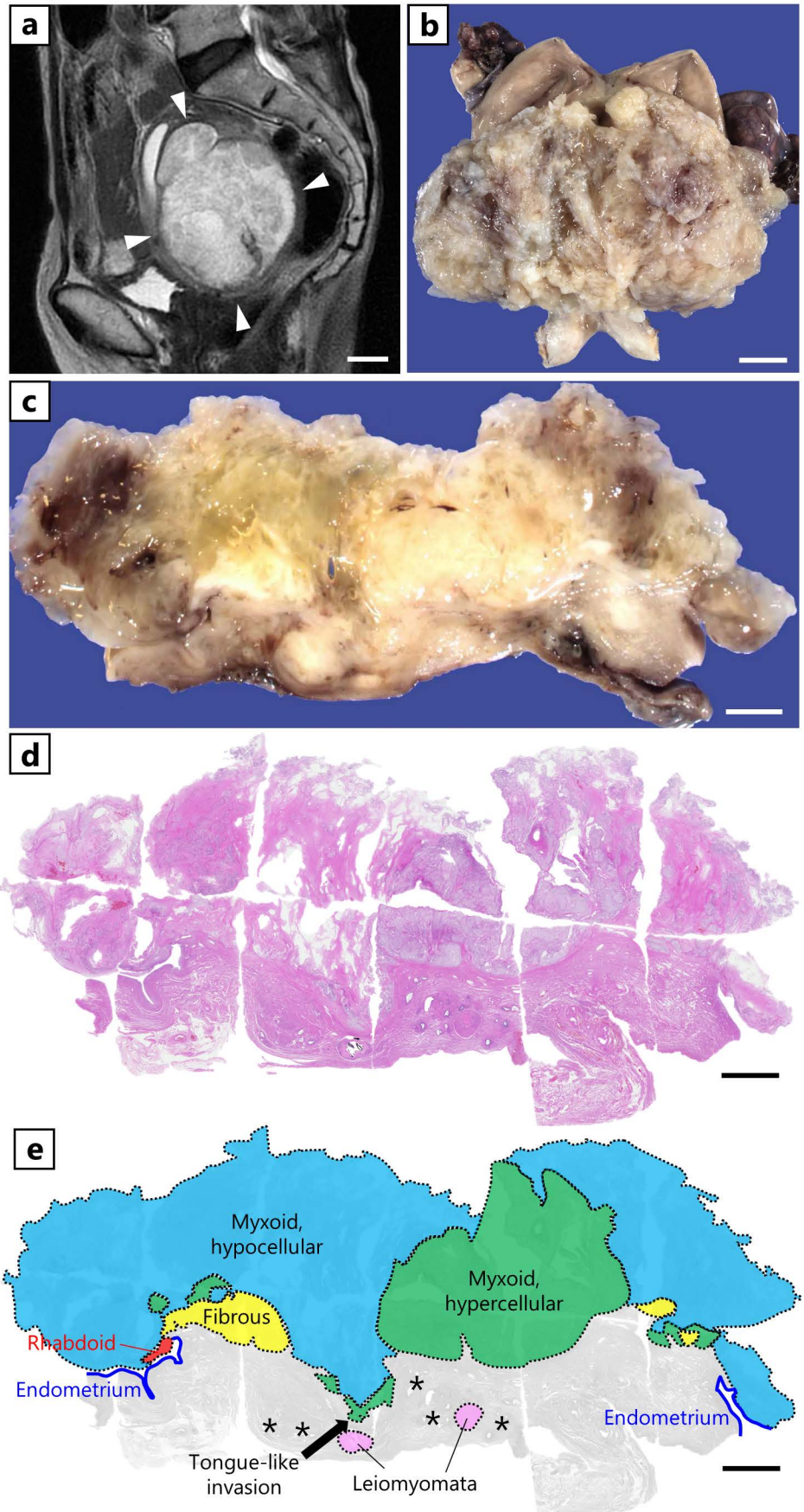
a
b
c
d
e
Myxoid,
hypocellular
Myxoid,
hypercellular
Fibrous
Rhabdoid
Endometrium
Endometrium
Tongue-like
invasion
Leiomyomata

Figure 2

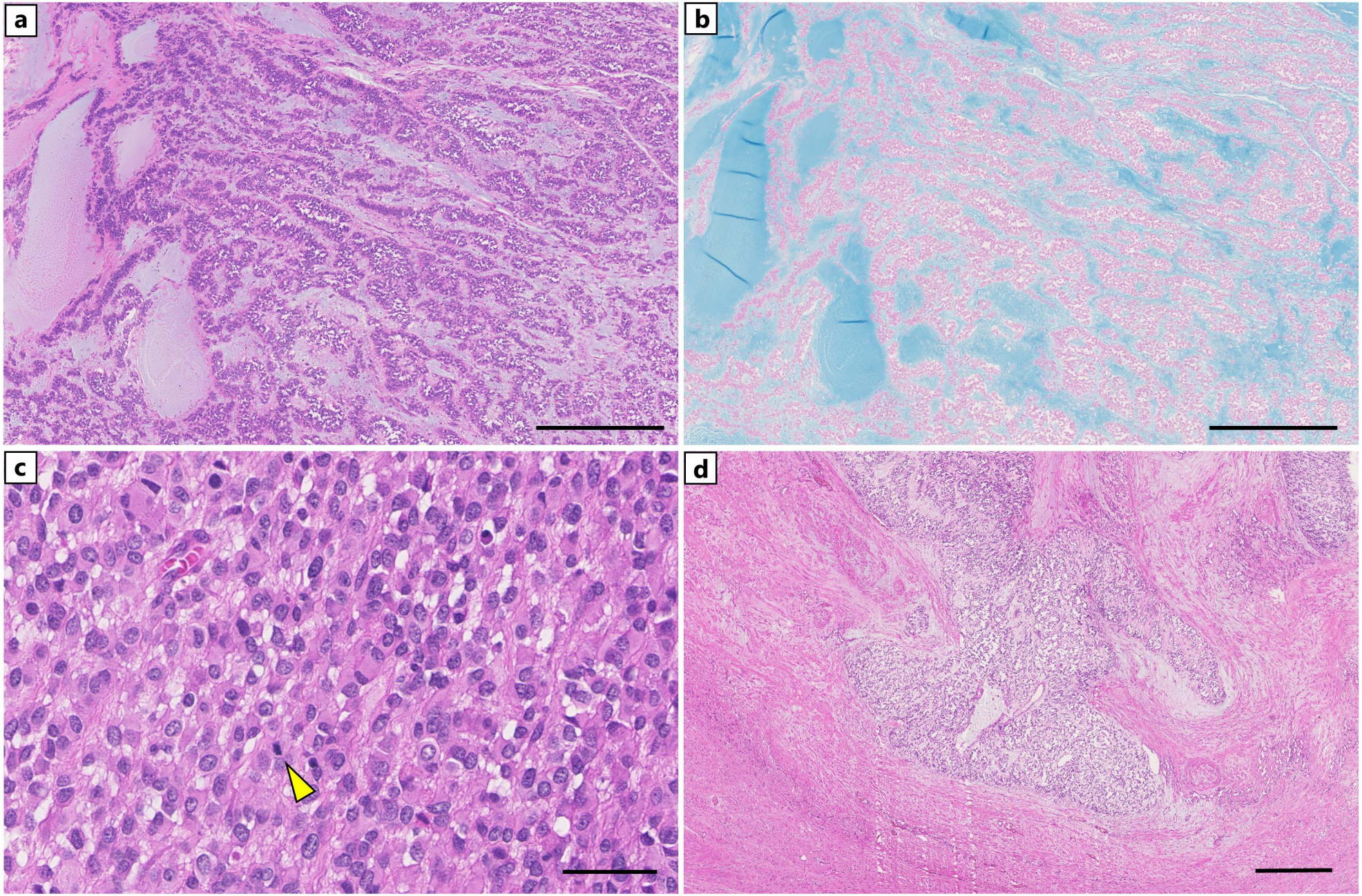

Figure 3