Carcinoma ex pleomorphic adenoma in minor salivary glands of the anterior tongue: a case report

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ABSTRACT

Carcinoma ex pleomorphic adenoma (CEPA) is defined as a pleomorphic adenoma from which an epithelial malignancy is derived. Most cases of CEPA occur in parotid glands, and CEPA arising in minor salivary glands is rare. We report an extremely rare case of CEPA arising in the minor salivary glands of the anterior tongue in a 64-year-old man. The mass of the left anterior surface of tongue was a 30×20×20 mm, relatively well-defined, elastic, hard, and tender. Biopsy was performed and the histological diagnosis was adenocarcinoma, not otherwise specified(NOS). Benign PA was not included in the biopsy specimen. A wide local excision of the tongue, with left upper neck dissection, and local flap repair were performed. The removed tumor was composed of adenocarcinoma, NOS accompanied with small foci of pre-existing chondroid areas of PA. A diagnosis of CEPA was finally made. There were no signs of recurrence and metastasis 22 months after the surgery.

1. INTRODUCTION

Carcinoma ex pleomorphic adenoma (CEPA) is defined as the pleomorphic adenoma from which an epithelial malignancy is derived [1]. CEPA comprises approximately 3.6% of all salivary gland tumors, 12% of all salivary gland malignancies, and 6.2% of all PAs[1]. CEPA is usually seen in the 6th or 7th decade, approximately one decade later than PA [1]. Most CEPA arise in the major salivary glands, such as the parotid glands[1]. Gnepp described that the frequencies of malignant mixed tumor in the parotid, submandibular, sublingual, and minor glands are 67%, 15%, less than 1%, and 18%, respectively [1]. In the minor salivary glands, CEPA appears most commonly in palatal gland, whereas the minor glands of the anterior tongue are an extremely rare site[2]. In this report, we describe a first case of CEPA arising in the minor salivary glands of the anterior tongue.

2. Caes Reports

A 64-year-old man was referred for diagnosis and treatment of a painless mass on the left anterior surface of the tongue, which had been present for 20 years. The mass had slowly increased in size for the last 3 months. At the time of the first visit, the patient's medical history included diagnoses of hypertension 10 years ago and diabetes 2 years ago. Intraoral examination revealed a 30×20×20 mm, relatively well-defined, elastic, hard, and tender mass on the left anterior surface of the tongue (Fig. 1). The overlying mucosal surface was partially ulcerated. The submandibular and cervical lymph nodes were not palpable. Computed tomography scan (CT) and magnetic resonance imaging (MRI) were performed to assess the extent of the tumor and determine possible involvement of regional lymph nodes. Enhanced CT revealed a slightly enhanced heterogeneous lesion and enhanced MRI revealed a 20 x 20 x 18 mm, relatively well-defined, rounded lesion with heterogeneous hypointensity on T1-weighted (T1W) and hyperintensity on T2-weighted (T2W) images at the left of the tongue (Fig. 2A,B). No enlarged regional lymph nodes were found upon CT and MRI examinations. Clinically and radiographically, a diagnosis of tongue cancer (T2N0N0) was made. Biopsy was performed under local anesthesia. Histological examination of the biopsy specimen revealed submucosal nodular epithelial tumors including ductal, cribriform-like and solid patterns without connection with mucosal epithelium (Fig. 3A).

Cellular details revealed nuclear pleomorphism, hyperchromatism, and high mitotic activity. The neoplastic ducts showed single cell-layered structures (Fig. 3B). The cribriforme patterns contained necrotic debris (Fig. 3B) and PAS-positive materials in the cystic lumens (Fig. 3C). Benign area such as PA was not included in the biopsy specimen. Immunohistochemically, most tumor cells of the duct or cribriform nests were positive for EMA (Fig. 3D). Although S-100 protein was expressed in scattered cells in the tumor(Fig. 3E), vimentin was throughout negative (Fig. 3F). The cribriform-like patterns were suggestive of adenoid cystic carcinoma, but they did not contain amorphous basophilic materials in the cystic spaces, and ducts exhibited single cell-layered unlike adenoid cystic carcinoma. Immunohistochemistry indicated the tumor was comprised of duct luminal cells rather than modified myoepithelial cells. For the differential diagnosis from polymorphous low-grade adenocarcinoma (PLGA), bcl-2 and MIB-1 antibodies were also employed. Although bcl-2 is overexpressed in most cases of PLGA[3,4], no expression of bcl-2 was observed in the present tumor. MIB-1 labeling index was 46%. Therefore, we made a histological diagnosis of adenocarcinoma, NOS.

After the establishment of the histopathological diagnosis, a wide local excision of the tongue, with the left upper neck dissection, and local flap repair were performed under general anesthesia. The cut surface of the tumor showed a nodule with

a peripheral yellowish-white band-like zone and inner white fibrous or necrotic area (Fig. 4). Microscopically, the tumor had no fibrous capsule. The tumor infiltrating into the muscle and adjacent to the mucosal epithelium was composed of trabecular and ductal patterns (Fig. 5A). Cribriform structure was scant. Most ductal structures were adenocarcinoma, NOS (Fig. 5B). Moreover, clear cells with broad cytoplasm were also included (Fig. 5B). The tumor contained nodular necrotic foci (Fig. 5C) and invaded perineural area (Fig. 5D). We could find some small cartilaginous nodules circumscribed by atypical cell nests (Fig. 5E). The chondroid cells exhibited no cellular atypia but merged into the surrounding malignant cell nests. Although the cells embedded in the cartilaginous matrix were immunohistochemically positive for α-SMA, the surrounding atypical cells and adenocarcinoma, NOS component were negative (Fig. 5F). We could not detect tubular structures composed of double cell-layered, i.e. outer myoepithelial cell and inner luminal cell. But immunohistochemistry for α-SMA demonstrated myoepithelial proliferation in the extracellular matrix like PA. Cosidering the clinical history, we believed that the neoplastic chondroid areas were part of pre-existing benign PA. Thus the lesion was histopathologically diagnosed as CEPA. The margin of the resected tumor was free of tumor and no metastatic lymph nodes were seen. No signs of recurrence and metastasis have been observed 22 months after surgery.

3. DISCUSSION

Of the malignant derivatives from PA of the salivary glands, CEPA is the most common, whereas carcinosarcoma (true malignant mixed tumor) and metastasizing PA are less common [5]. The CEPA is a mixed tumor (PA) in which a second neoplasm that fulfils the criteria for malignancy develops from the epithelial component [5]. In the minor salivary glands, CEPA occurs in palatal gland as the distribution of benign PA [2]. Yih et al [6]. and Piers et al [7]. clinicopathologically examined 213 and 546 cases of minor salivary gland tumors, respectively. They described that frequencies of CEPA were 0.9% (2 cases) and 0.4% (2 cases), respectively, and the occurrence sites of CEPA did not include the minor glands of the anterior tongue. In other previous cases, CEPAs arising in the buccal mucosa [8,9], palate [10-12], and lip [13] have been reported. According to these data, it may be concluded that CEPA arising in the minor salivary glands of the anterior tongue is an extremely rare entity.

A clinico-pathological review of CEPA arising in the major salivary glands reported that metastasis occurred regionally in 56% and distantly in 44% of cases [14]. The overall survival of CEPA was 39% at 3 years, and 30% at 5 years [14]. CEPA of the major salivary glands was reported to have been considered an aggressive entity with high tendency for recurrence and fatal outcome [6]. Factors such as the size, persistence, and location of the tumor are important for the prognosis [9]. Additionally, the

histopathological subclassification and grading of the tumor are also prognostic factors [7]. The CEPA is subclassified into non-invasive, minimally invasive (≦1.5 mm penetration of the malignant component into the extra capsular tissue), and invasive (>1.5 mm of invasion from the tumor capsule into the adjacent tissues) [1]. For these subtypes, the first two types have an excellent prognosis [1]. On the other hand, the latter has a more guarded prognosis [1]. The CEPA with capsular penetration of more than 1.5 mm is associated with a poor prognosis [1]. It is important to designate those CEPA that are confined within the capsule and those invading through the capsule as non-invasive and invasive, respectively, and to differentiate within the latter group between widely invasive and minimally invasive tumors [1]. In the present case, the tumor appeared in nodule, but did not have a fibrous capsule. It was impossible to measure the distance between the capsule and the front of invasion. Thus, we consider that this subclassification is not applicable for all cases of CEPA. However, it seems very important for the prognosis to classify CEPA according to the histopathologic feature of malignant component (ie. adenocarcinoma NOS., adenoid cystic carcinoma, salivary duct carcinoma, etc.).

The histopathological diagnosis of CEPA is difficult when the amounts of benign component or malignant component are extremely small. Antony et al, recommended to detect the PA component relies on previous biopsy, clinicopathologic correlation or additional sectioning of the specimen, in case of diagnosis of CEPA whose carcinoma

grows to occupy the entire neoplasm leaving no trace of the PA component [15]. In the present case, we could detect the small benign elements composed chondroid matrix embedding myoepithelial cells without atypia, which is one of histological features of PA.

The mechanism of the malignant transformation of PA has remained uncertain. The malignant transformation of PA is associated with longstanding or recurrent PA. A 1.6% incidence of malignant transformation in tumors of <5 years duration was reported compared with 9.4% in tumors present for >15 years [16]. Additionally, it was reported that laminin and collagen IV were involved in the process of malignant transformation of PA and biological progression [17]. Félix et al. reported that basement components such as laminin and collagen IV detected at interstitial matrix of mixed tumors can be associated with overproduction and/or secretion of abnormal macromolecules by the neoplastic cells, impairing their ability for normal assembly [17]. The partial loss of co-localization of these two components at the interstitial matrix may be associated with pathological conditions, such as neoplasias [17]. Moreover, they reported that the increased content in laminin of either malignant or benign areas of CEPA in comparison with that in benign mixed tumor may be related to the acquisition of metastatic properties [17]. Thus, longstanding PA has the possibility of the malignant transformation. Clinical awareness of such lesions should be stressed because regular screening and early treatment are very essential for good prognosis.

In conclusion, we report an extremely rare case of CEPA arising in the minor salivary glands of the anterior tongue. Sixteen months postoperatively, the patient is considered free of disease and is scheduled for careful follow-up control.

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Figure legends

Fig. 1 Photograph showing a 30×20×20 mm, relatively well-defined, elastic, hard, and tender mass of the left anterior surface of the tongue **(arrows)**.

Fig. 2 Axial enhanced magnetic resonance T1-weighted image revealing a relatively well-circumscribed rounded mass with heterogeneous hypointensity in the left tongue region (A). T2-weighted image showing the tumor to have hyperintensity (B). The mass was 20 x 20 x 18 mm in size (arrows).

Fig. 3 Biopsy specimen. (A) Submucosal infiltration of ductal, cribriform-like and solid nests was found. The continuity between tumor and mucosal epithelium was not identified. There was no tumor capsulation. (B) Pseudocysts of cribriform-like nests and ducts contained nerotic debris (arrows). The ducts showed single cell-layered. Tumor cells had large hyperchromatic nuclei. (C) Pseudocysts of cribriform-like nests and ducts included PAS-positive substance. (D) Most tumor cells were positive for EMA. (E) S-100 protein was mildly expressed in the cytoplasm and nuclei of the some tumor cells. (F) Although stromal cells expressed vimentin, most cells were negative.

Fig. 4 Cut surface of the tongue bearing tumor. The tumor showed a yellowish-white peripheral band-like zone (arrows) and inner fibrous or necrotic area (star).

Fig. 5 Surgical specimen. (A) Trabecular and ductal tumor infiltrated just below the surface epithelium. (B) Ductal structure (left) merged into trabeculae composed of clear cells (right). The ducts showed single cell-layered construction. (C) Ductal tumor invaded muscle(M). Massive nodular necrosis was included in the tumor (N). (D) Tumor invaded perineural area. Necrosis of the tumor cells were noticed (arrows). (NB:nerve bundle).(E) Cartilage-like area showing embedded cells without atypia (star). Nests of atypical cells with malignant trabecular transformation were at the periphery (arrows). (F) Immunohistochemistry for α-SMA in the transitional area from chondroid matrix to malignant region. The tumor cells embedded in the matrix were positive (arrows), but malignant clear cells nests (right side) were negative.

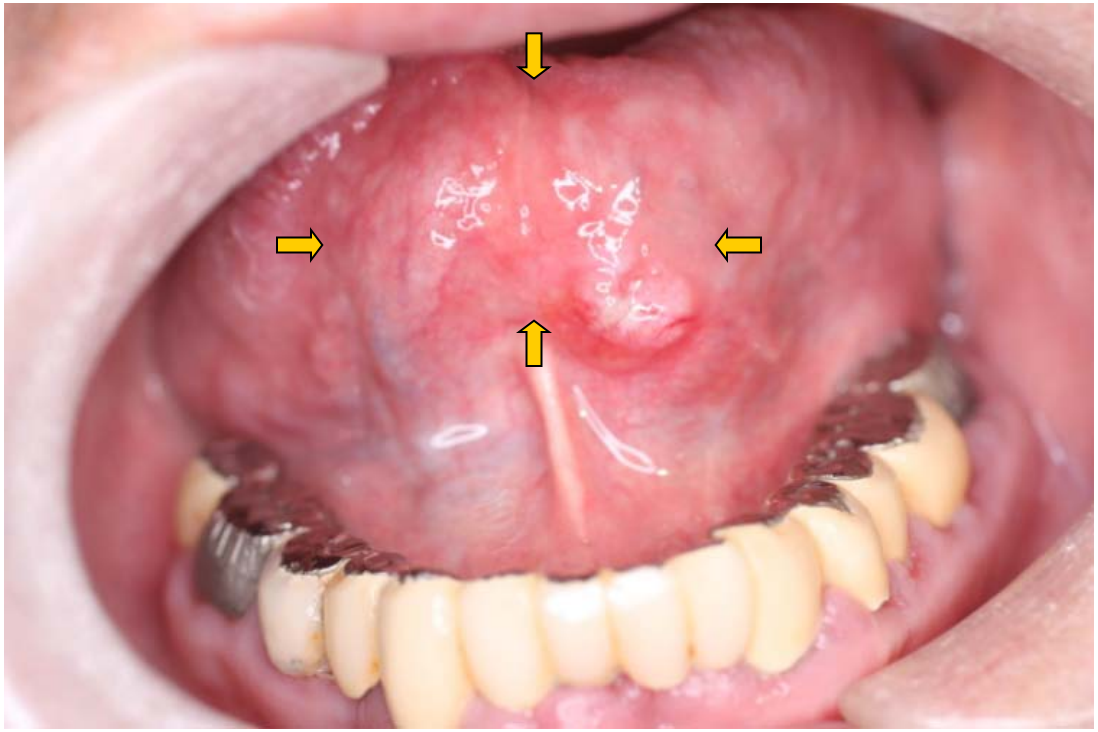

Fig.1

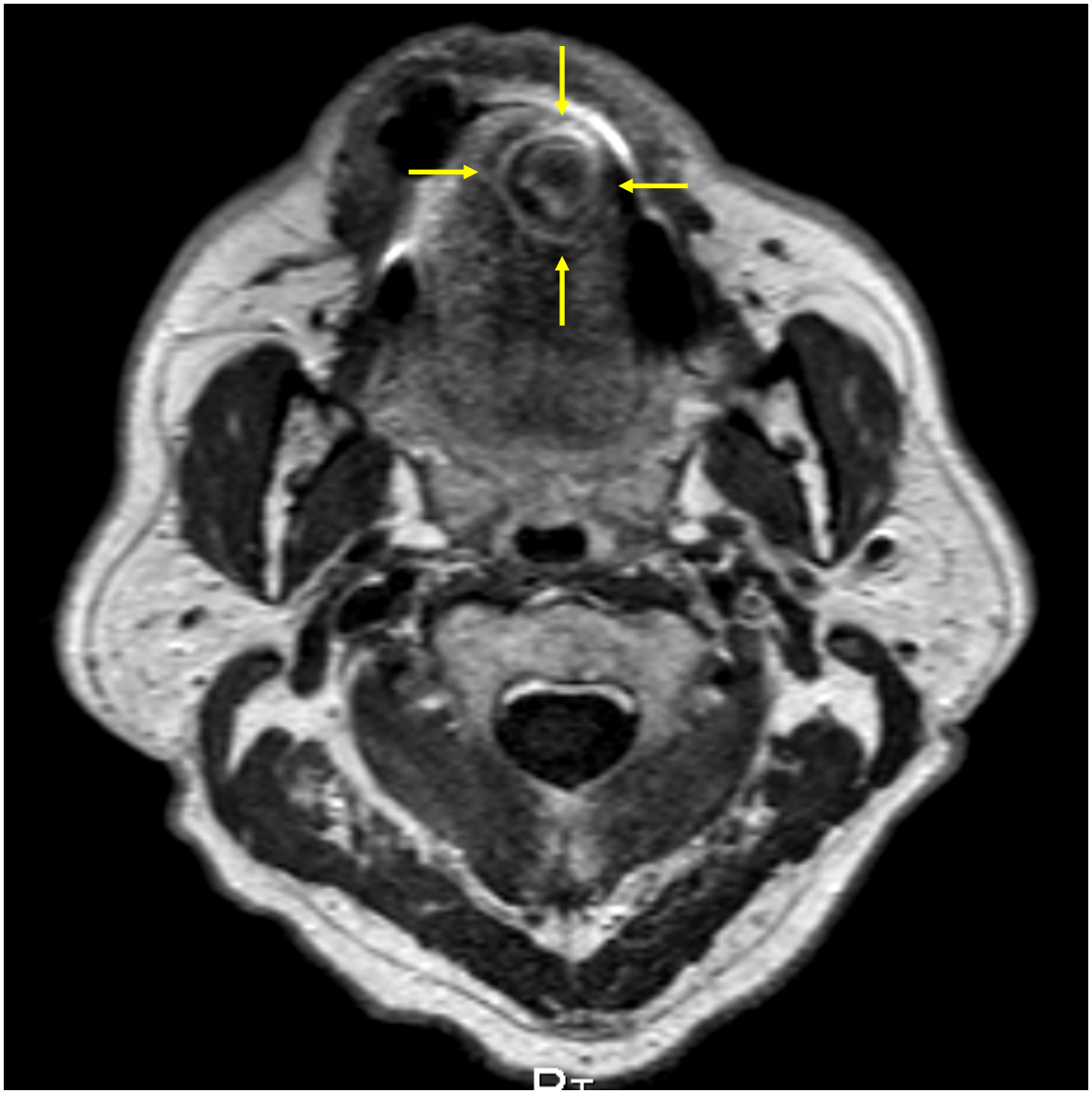

Fig. 2A

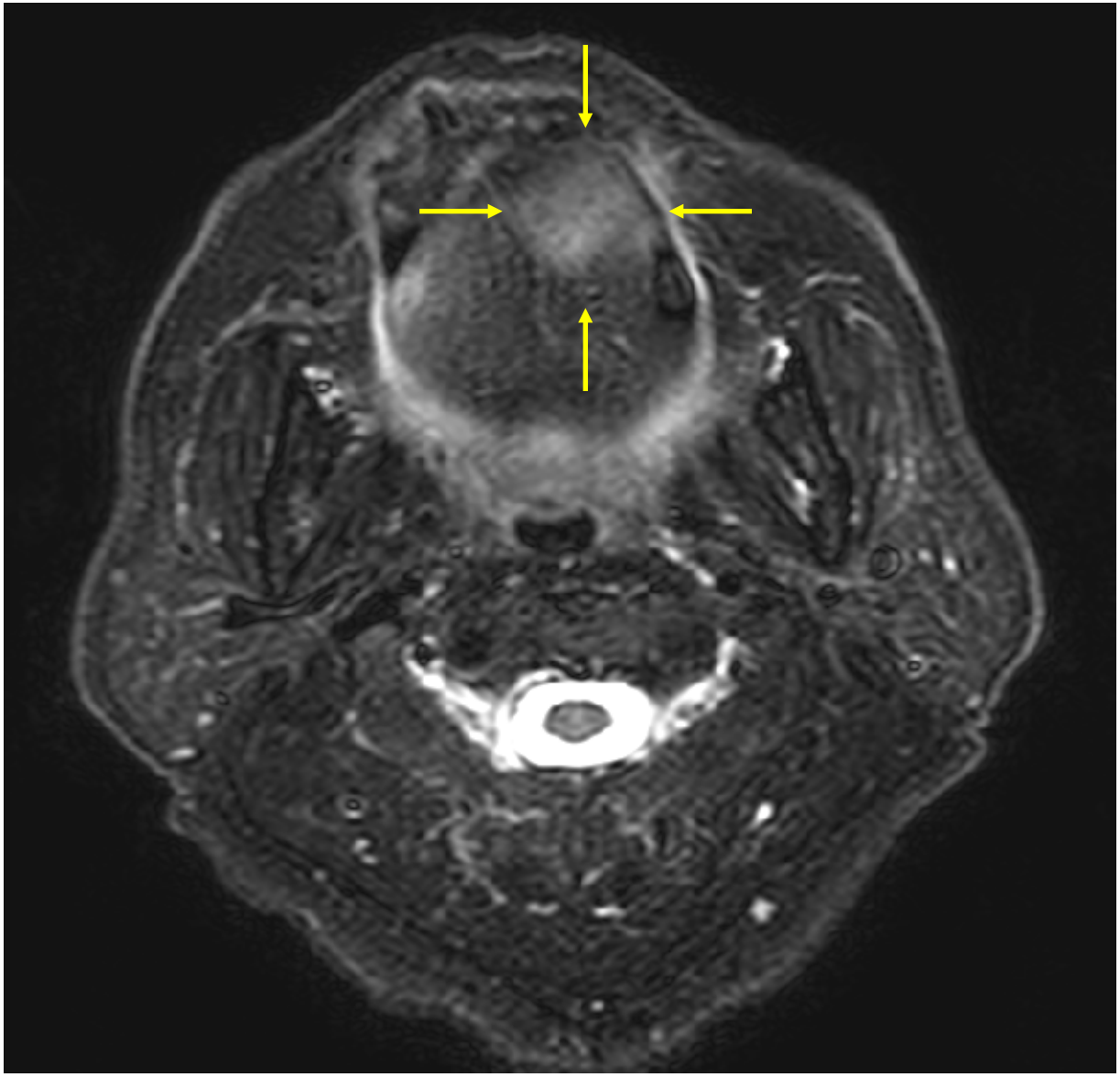

Fig. 2B

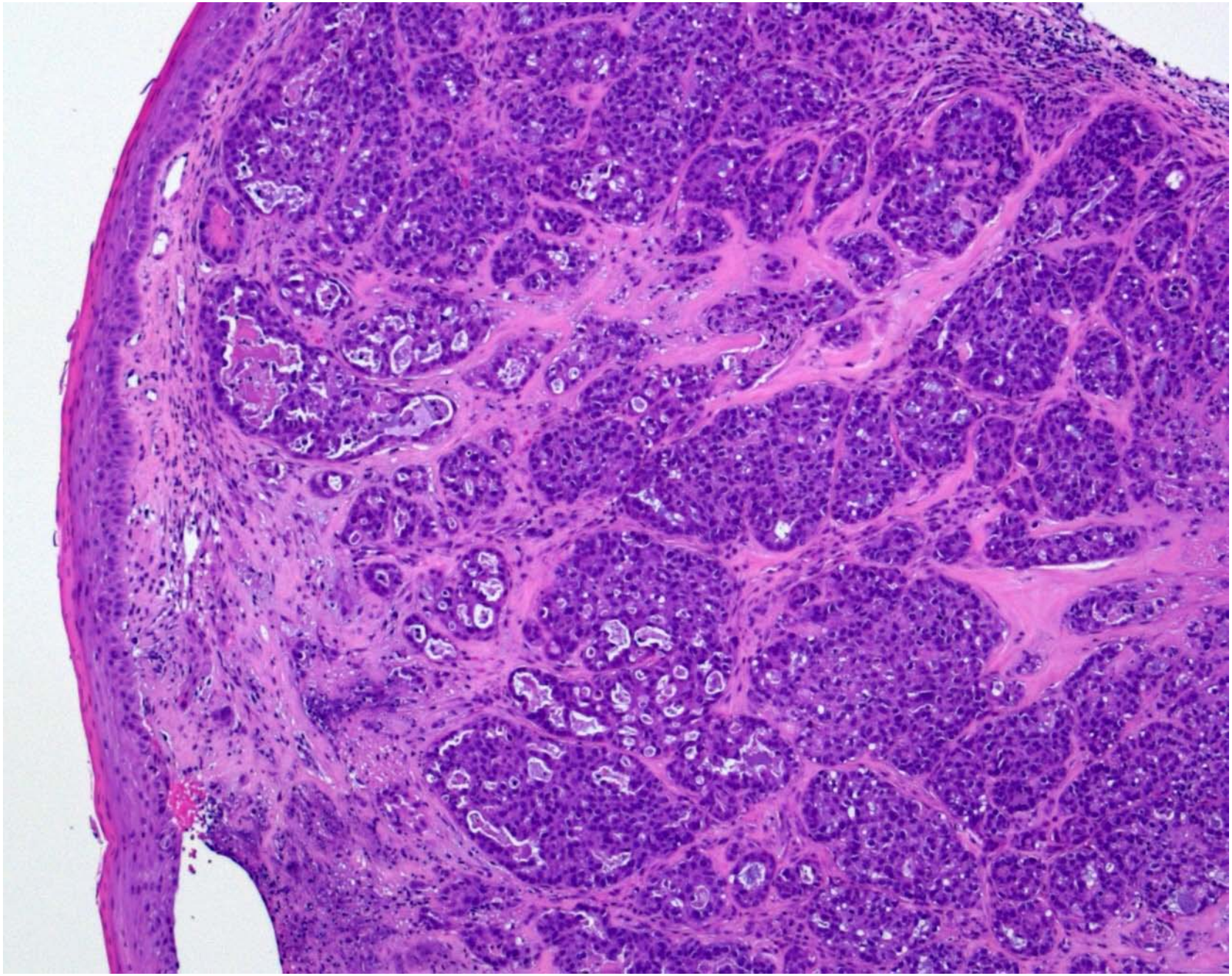

Fig.3A HE ×5

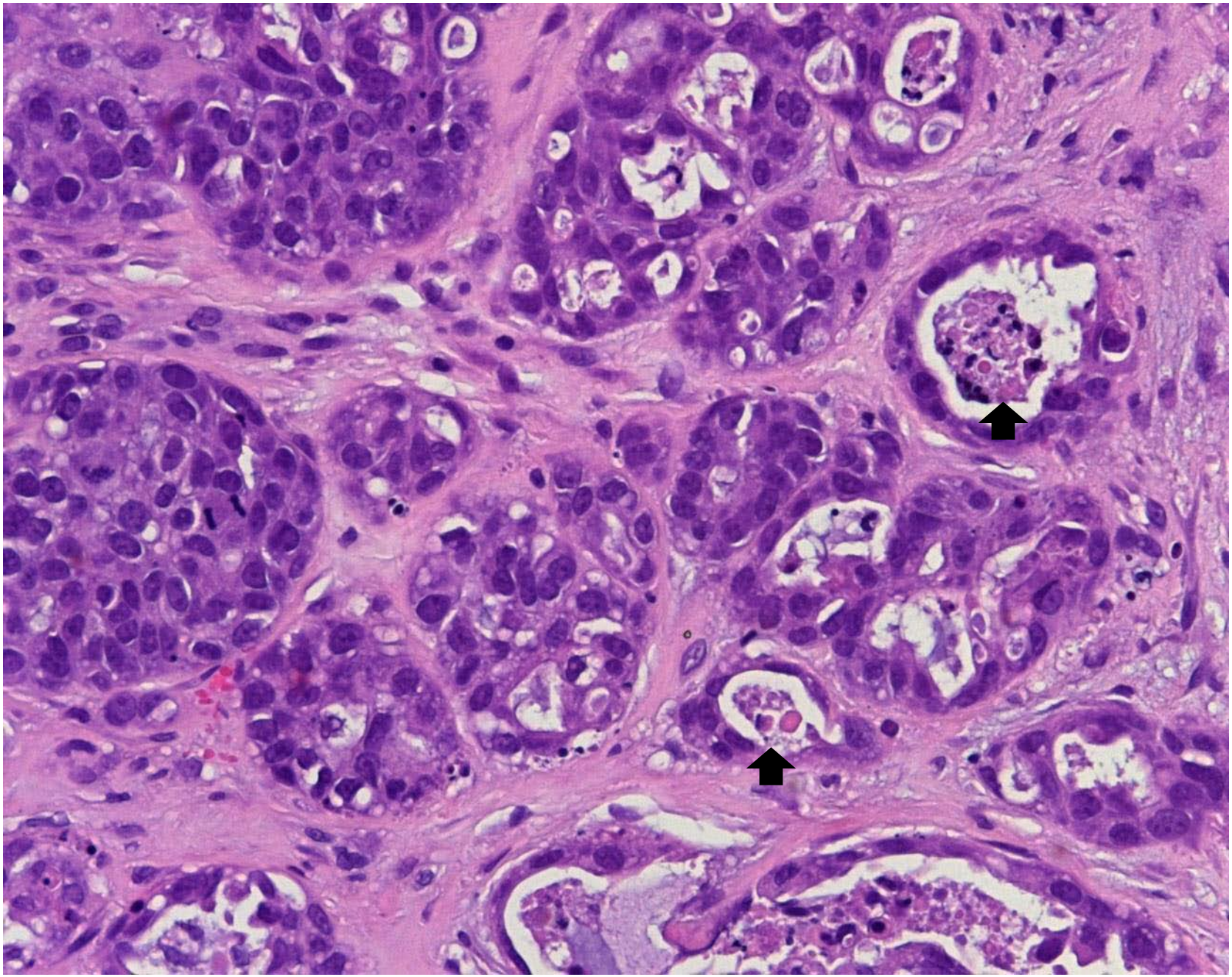

Fig.3B HE ×20

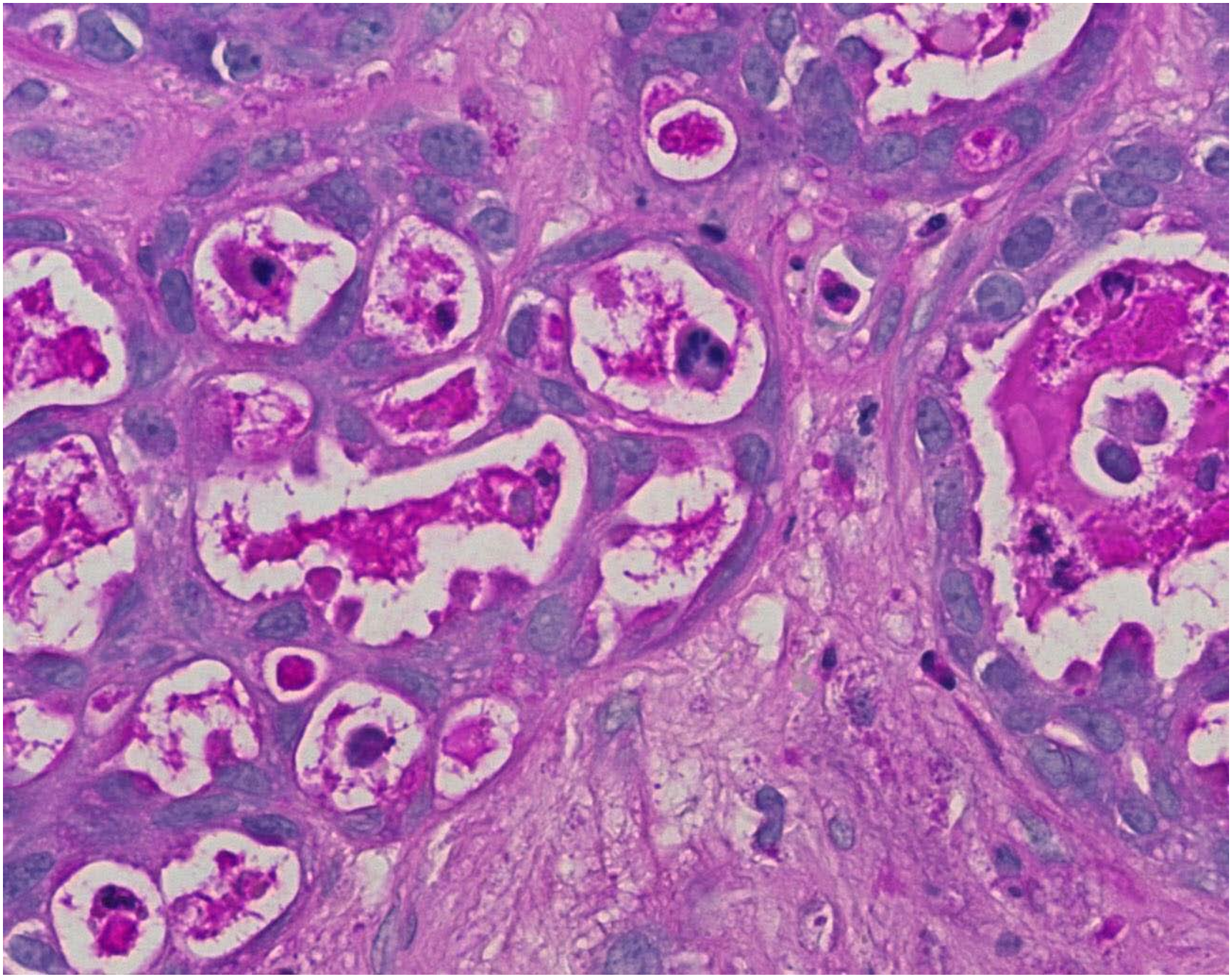

Fig.3C PAS ×40

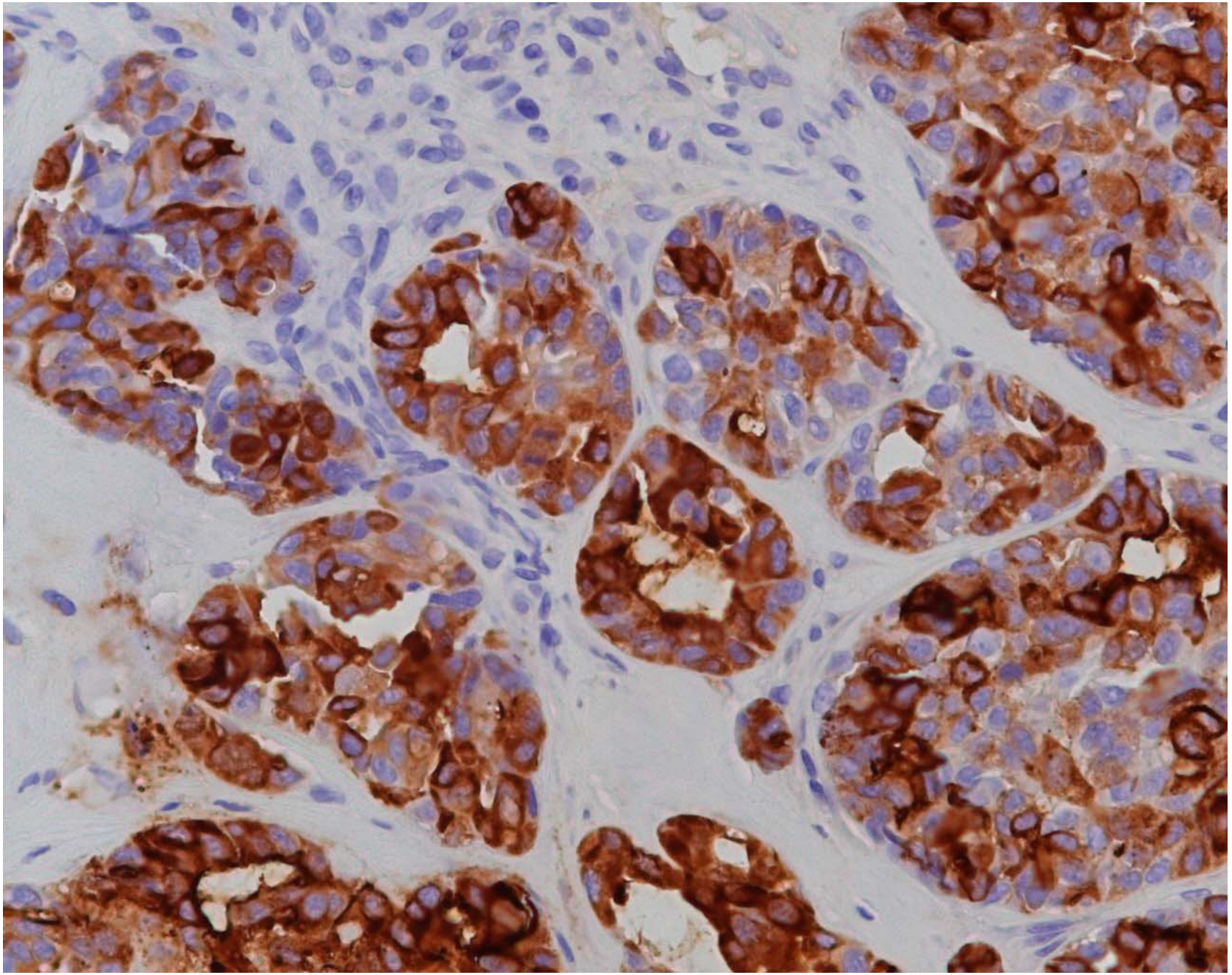

Fig.3D EMA ×40

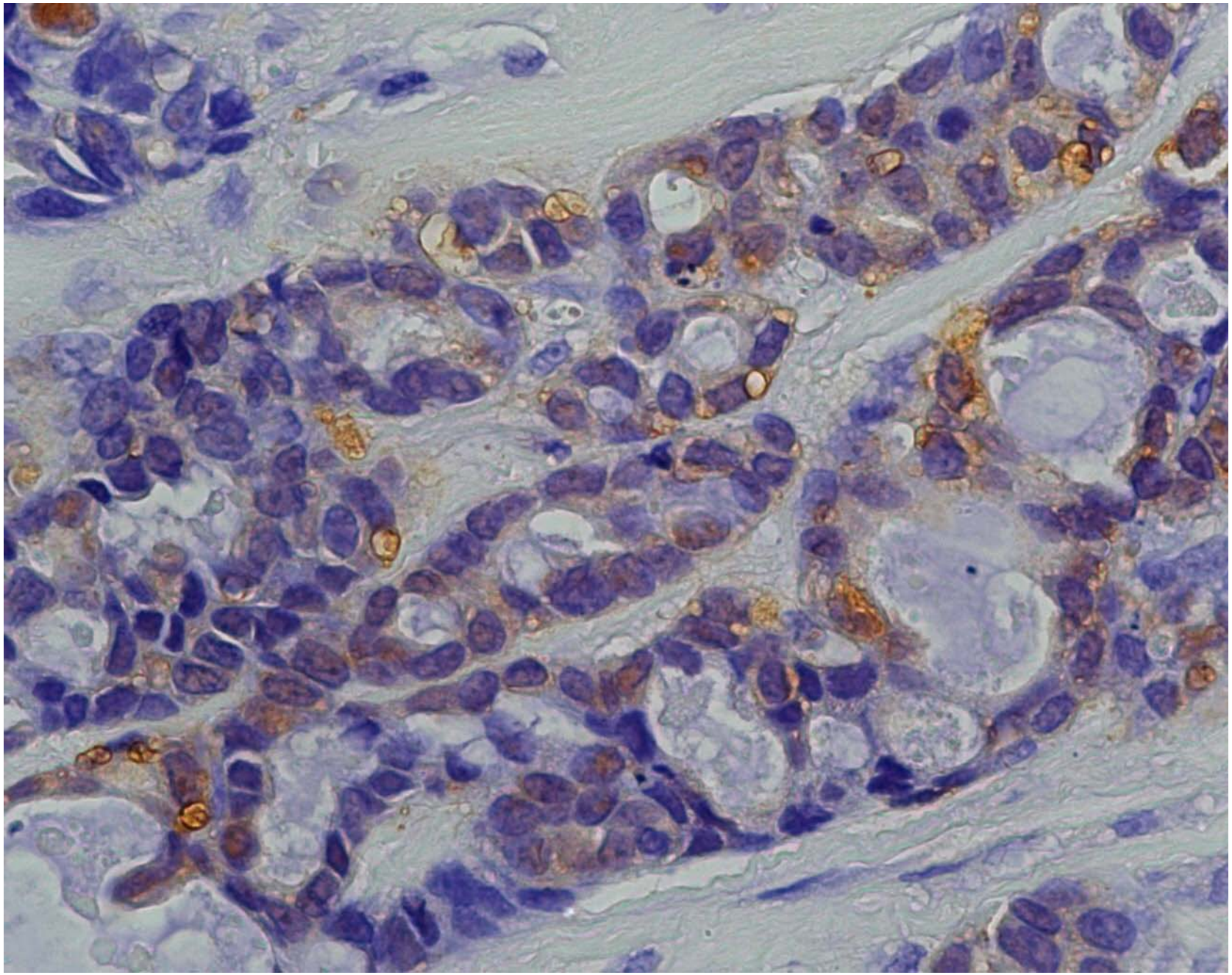

Fig.3E S-100 ×40

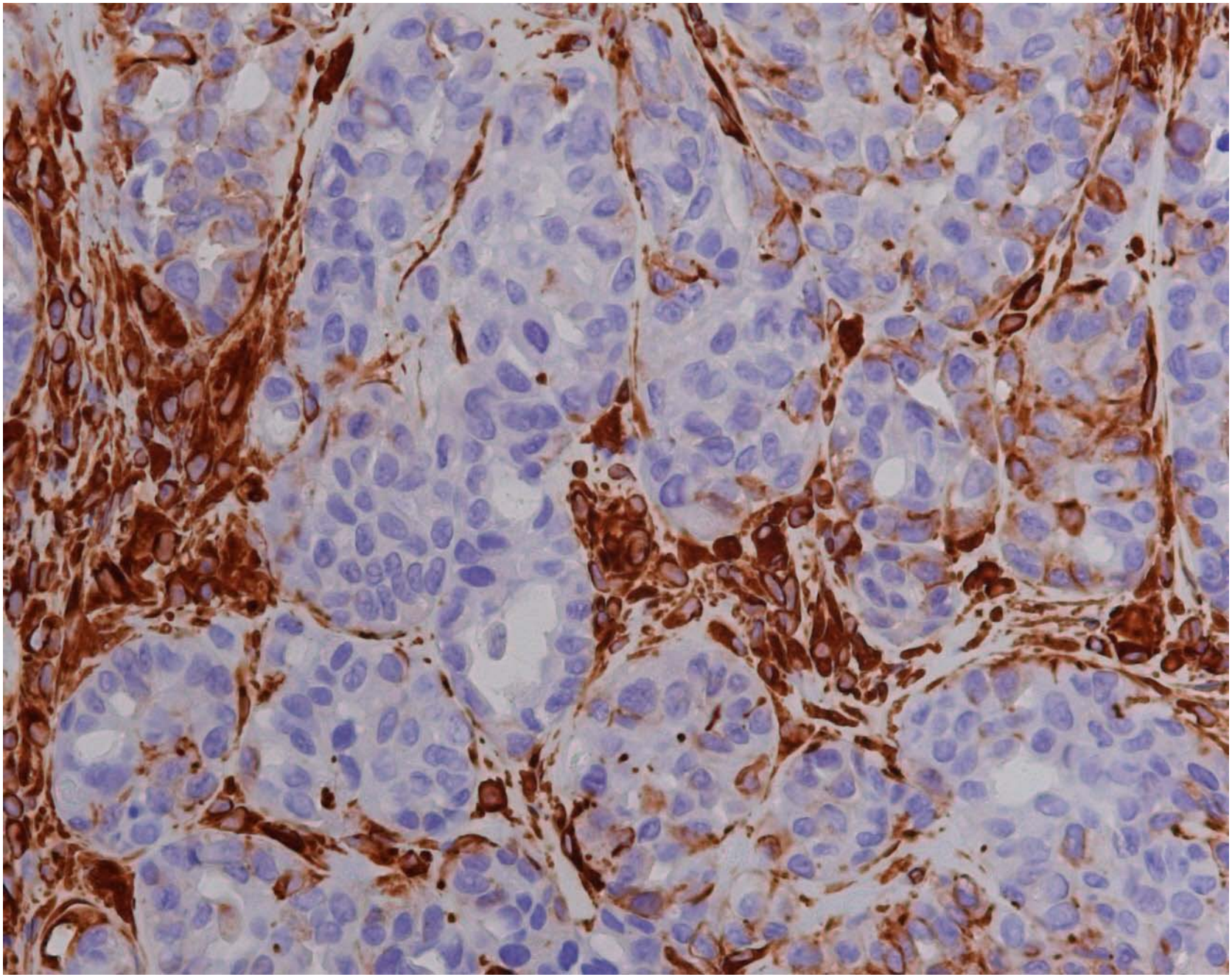

Fig.3F Vimentin ×40

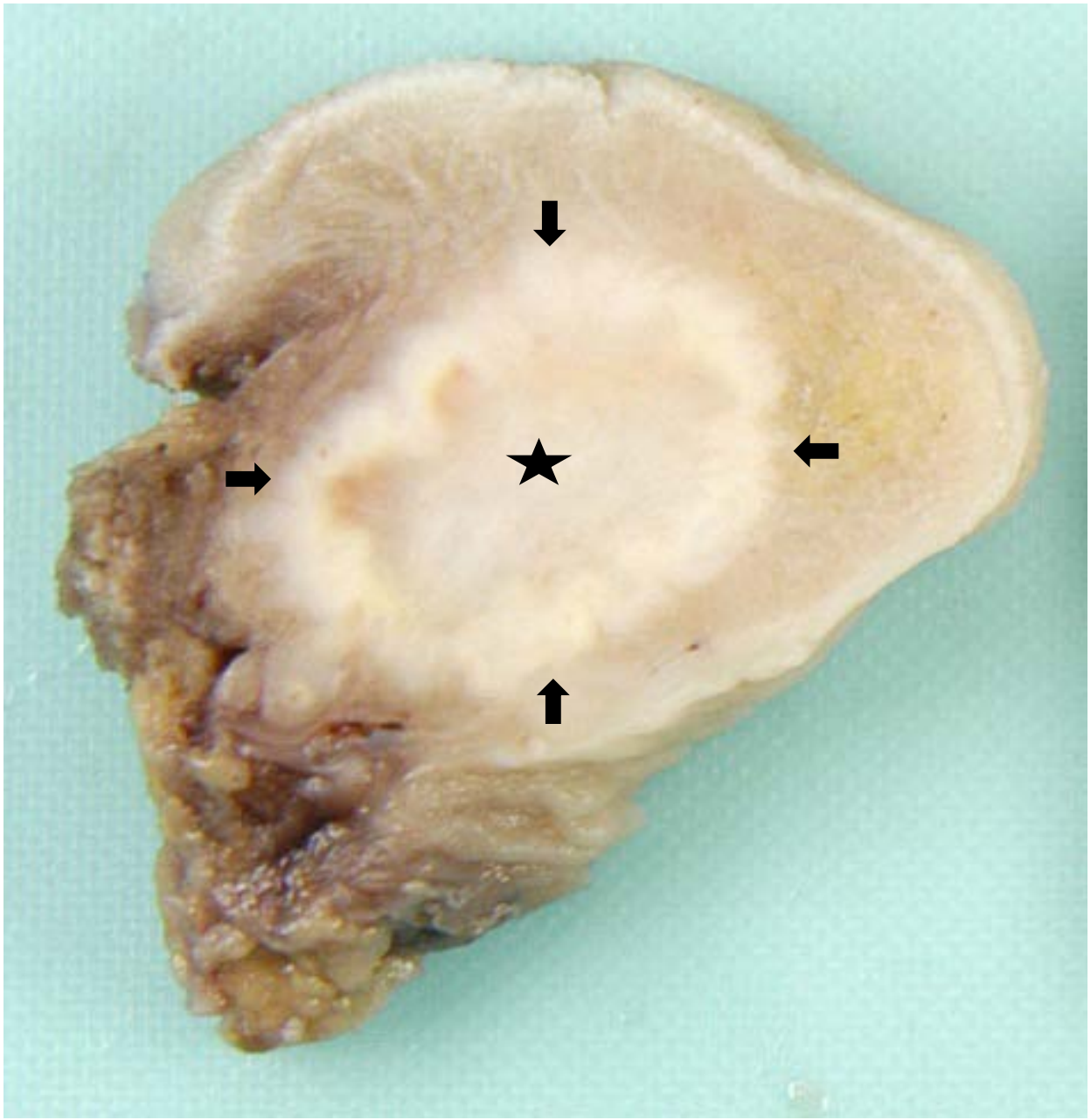

Fig.4

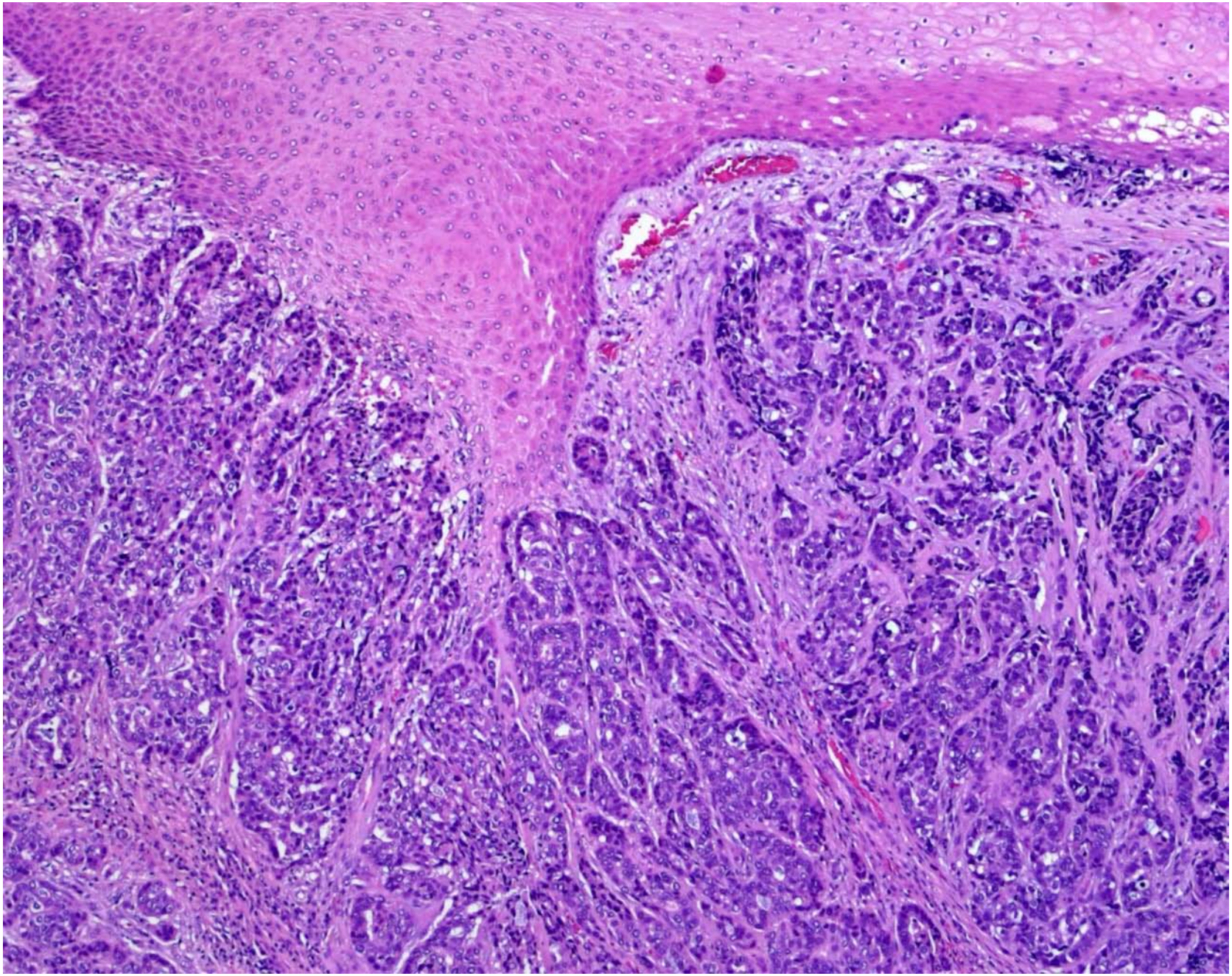

Fig.5A HE ×5

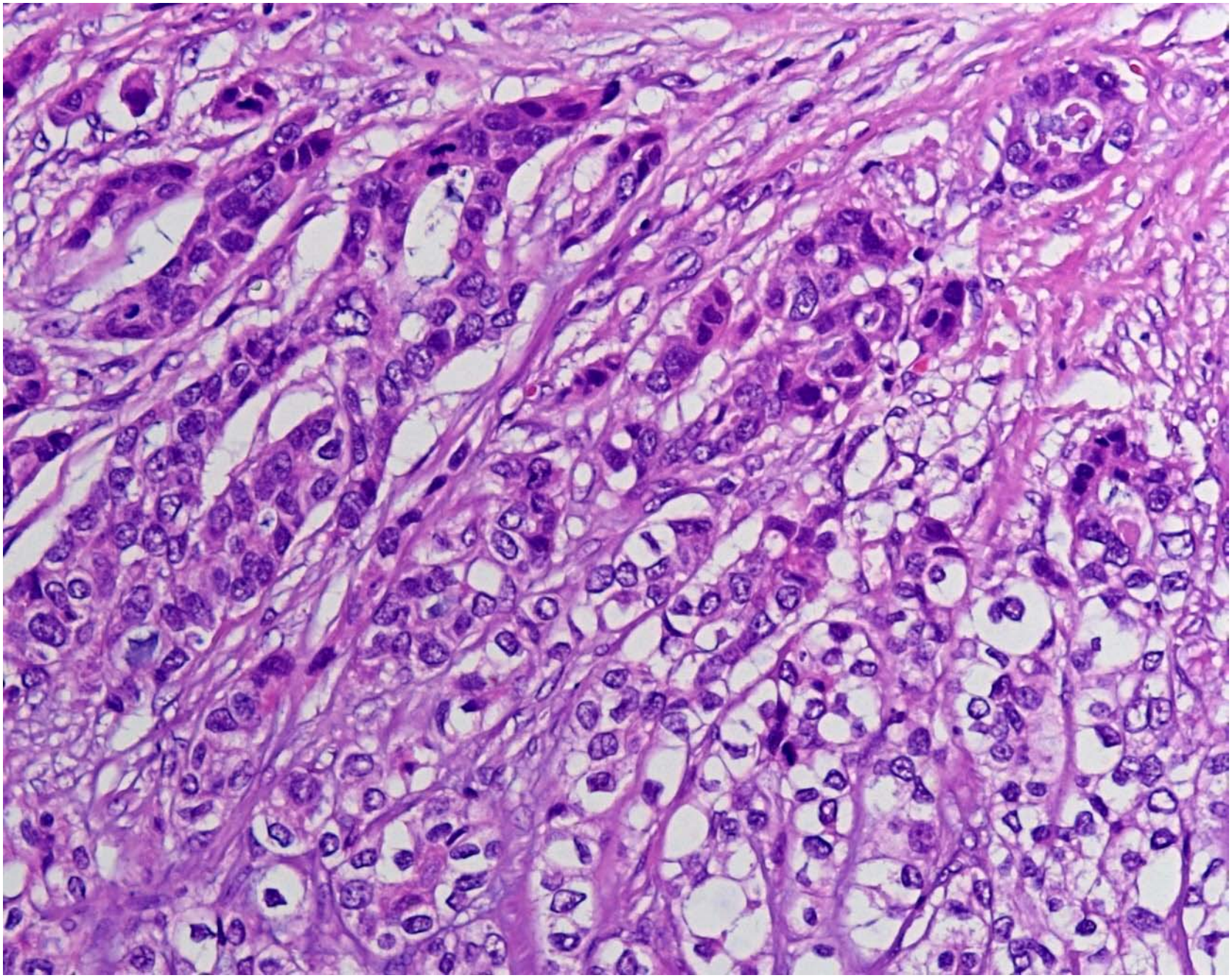

Fig.5B HE ×20

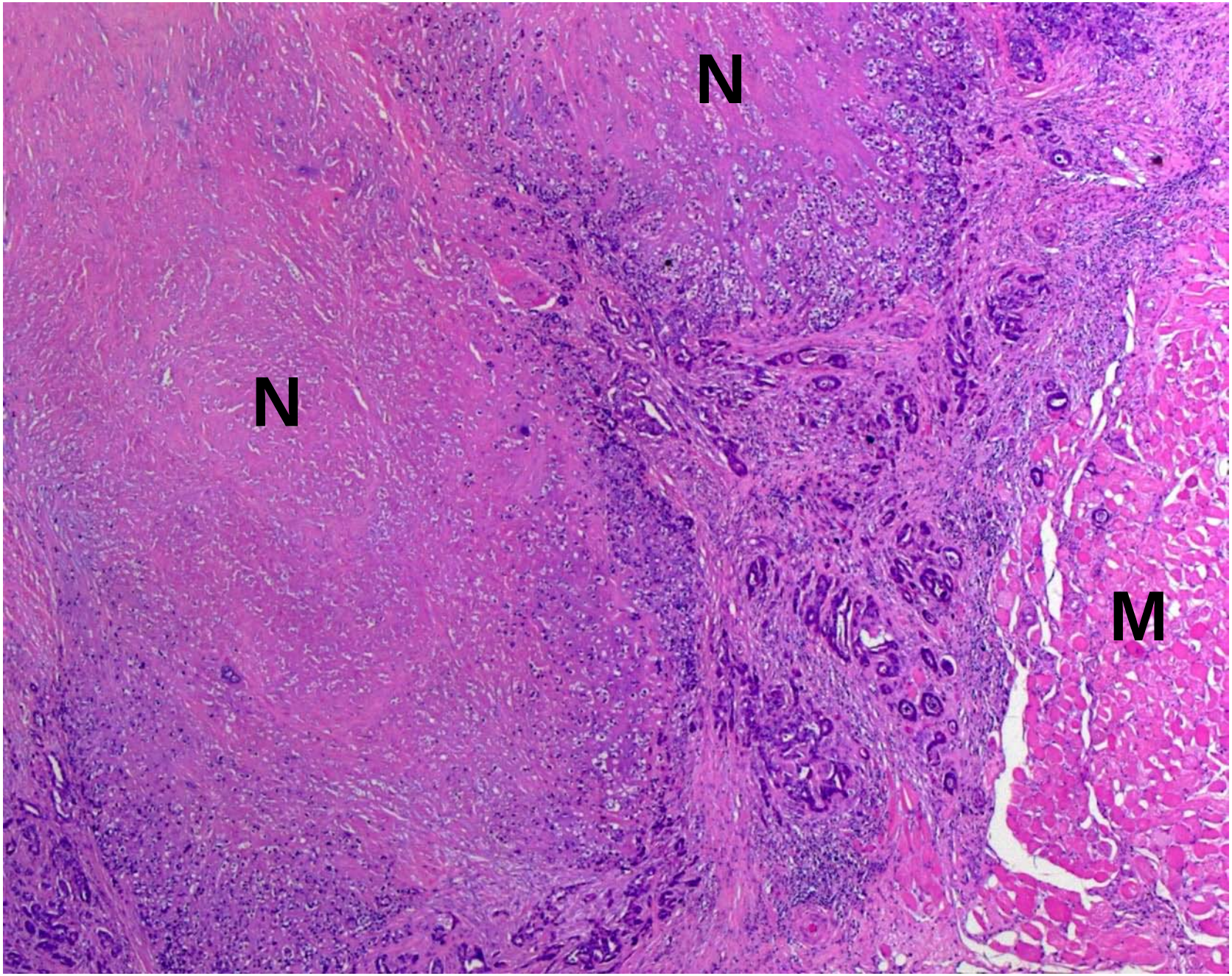

Fig.5C HE ×2.5

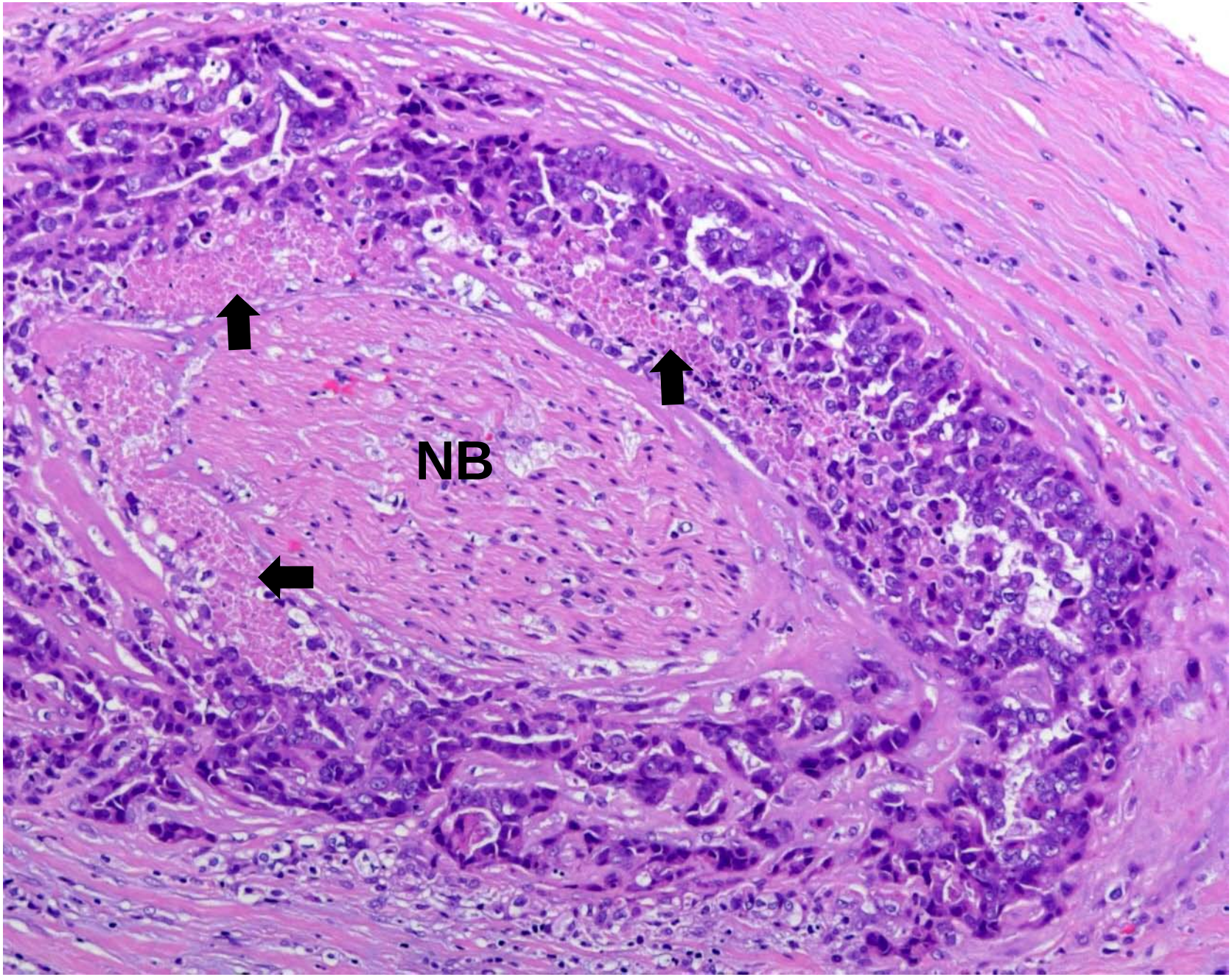

Fig.5D HE ×10

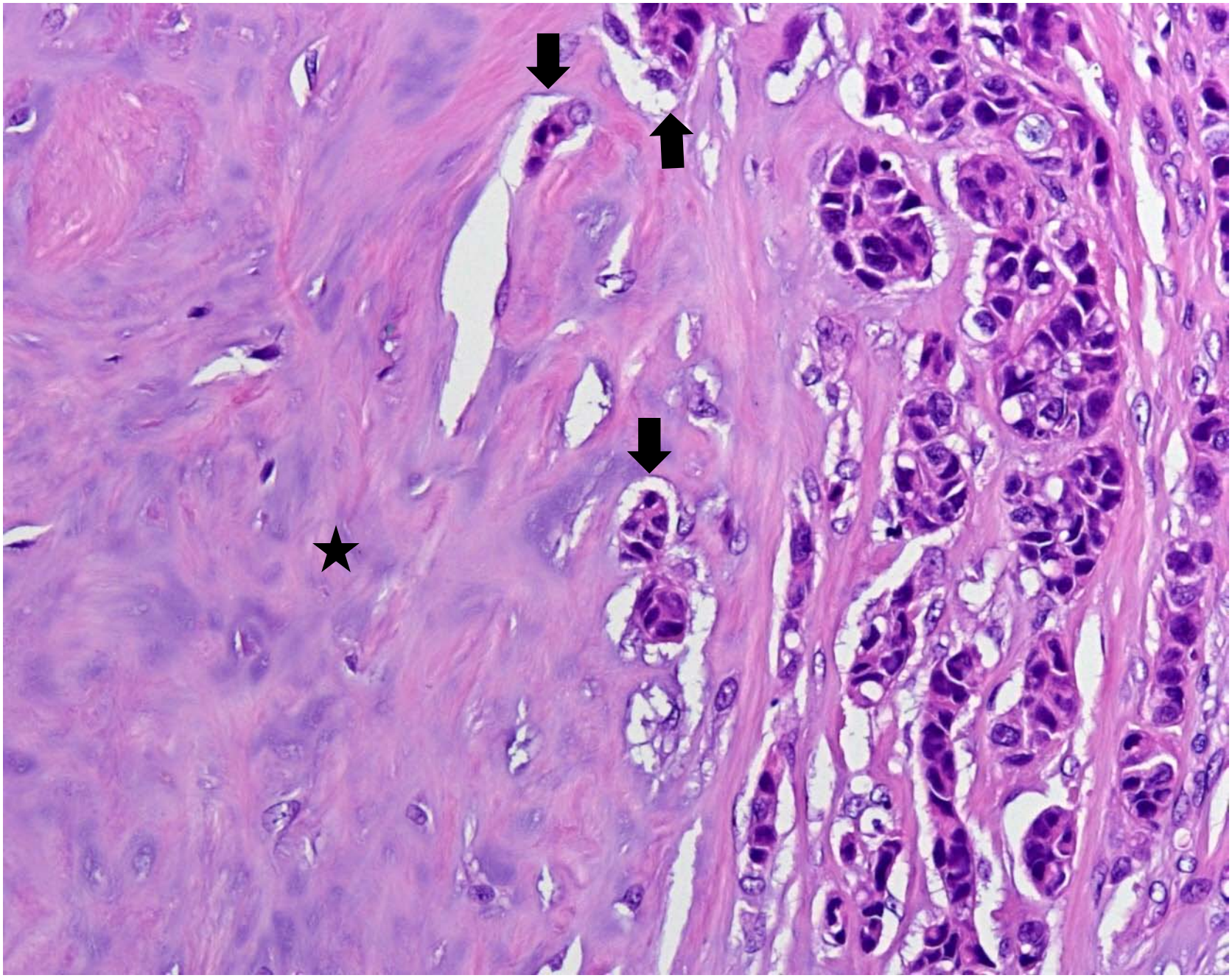

Fig.5E HE ×20

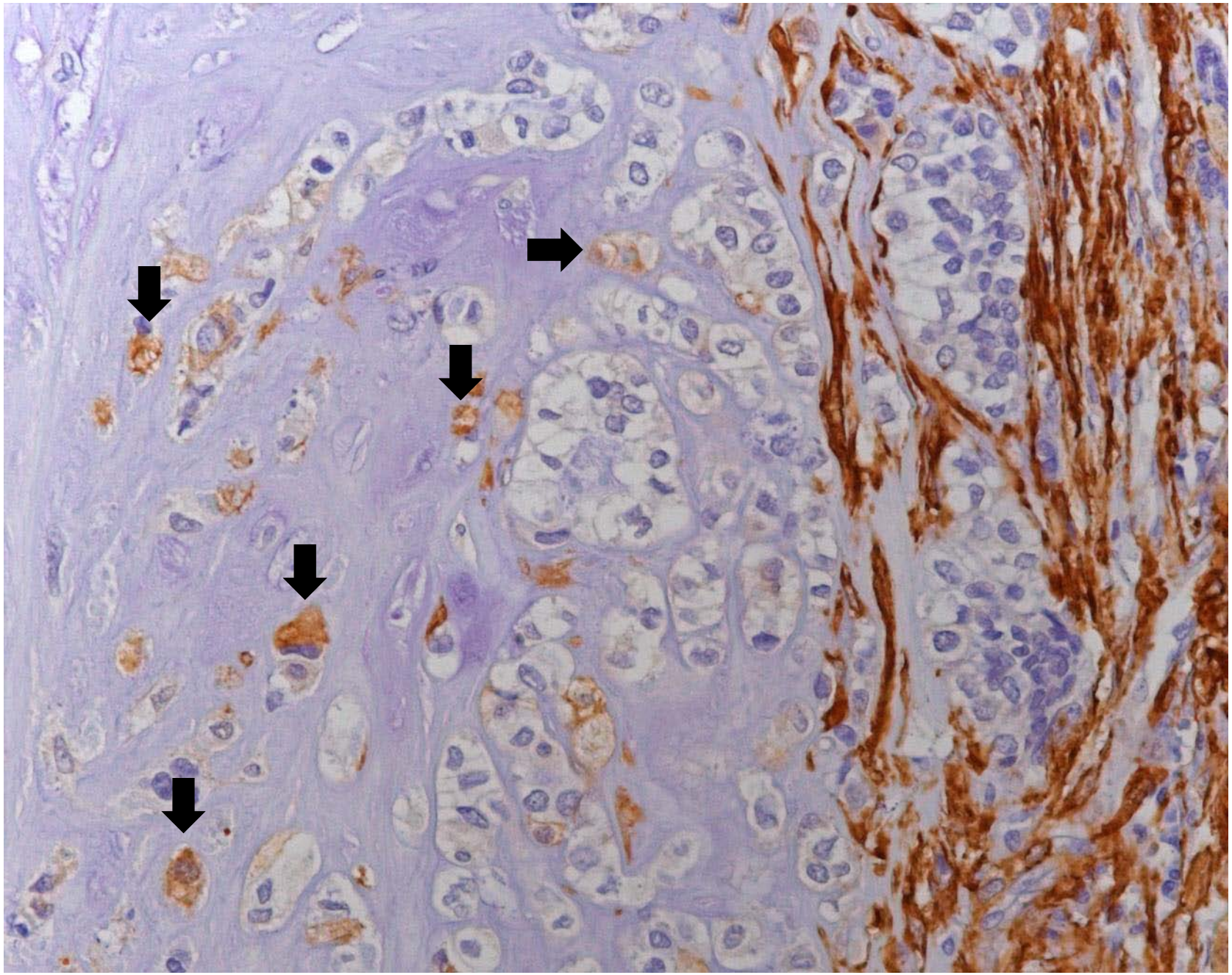

Fig.5F α-SMA ×20