Neuroendocrine Tumors of the Fallopian Tube: Report of a Case Series and Review of the Literature

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Running title

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ABSTRACT

Primary neuroendocrine tumors of the fallopian tube are extremely rare with a few reported cases of high-grade neuroendocrine carcinoma and a single report of a carcinoid tumor arising in a teratoma. We report four cases of probable primary neuroendocrine tumors of the fallopian tube (two carcinoid tumors/ low-grade neuroendocrine tumors and two high-grade neuroendocrine carcinomas) in patients aged 49-71. These represent the first reported cases of primary tubal carcinoid tumor unassociated with a teratoma. We review the published literature regarding primary neuroendocrine tumors of the fallopian tube and speculate on the possible histogenesis of these neoplasms.

Key words:- fallopian tube, carcinoid tumor, neuroendocrine carcinoma, immunohistochemistry.

INTRODUCTION

Neuroendocrine neoplasms occur at many sites in the body but primary neuroendocrine tumors of the fallopian tube are extremely rare with only a few case reports in the literature (1-6). There are occasional reports of high-grade neuroendocrine carcinoma of the fallopian tube and one reported case of a carcinoid tumor (also currently variously termed low-grade/ grade 1 neuroendocrine tumor) associated with a mature cystic teratoma (1-6). However, there have been no reports of isolated primary carcinoid tumor (not associated with a teratoma) at this location. We report a small series of probable primary neuroendocrine tumors involving the fallopian tube, including the first cases of carcinoid tumor unassociated with a teratoma. In reporting these cases, we discuss the possible histogenesis and review the literature on primary tubal neuroendocrine neoplasms.

MATERIALS AND METHODS

The cases derived from the pathology archives of the institutions to which the authors are affiliated. Clinical details and follow-up information were obtained from the pathology reports and liaison with the clinician or consulting pathologist. All available hematoxylin and

eosin-stained slides were examined as well as the immunohistochemistry performed as part of the work-up of the cases.

Immunohistochemical staining for chromogranin was performed on 16 normal fallopian tubes.

CASE REPORTS

Case 1

A 49-year-old woman with no significant past history underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy for an adnexal mass. Following the pathological diagnosis, the patient initially refused further investigations. A year later, she underwent an ultrasound of the abdomen and pelvis and a colonoscopy, both of which were normal. There was no clinical evidence of tumor elsewhere and the patient was asymptomatic.

Both ovaries and fallopian tubes were submitted in their entirety for histological examination. Both ovaries contained endometriosis and both tubes showed pseudoxanthomatous salpingitis secondary to endometriosis. Sections from the fimbrial ends of both fallopian tubes showed multiple (5 to 7 on each side) small microscopic nodules. These comprised small nests of cells with regular nuclei with a “salt and pepper” chromatin and abundant basophilic cytoplasm. There was no mitotic activity. These foci ranged in size from 0.17 mm to 0.96 mm, were confined to the fimbrial mucosa and submucosa with no connection to the epithelium and there was no lymphovascular space involvement. The cells were diffusely positive with synaptophysin, chromogranin, CD56 and CDX2. The Ki67 (MIB1) proliferation index was <1%. The morphological and immunohistochemical features were of multiple foci of carcinoid tumor/low-grade neuroendocrine tumor. No other tumor component was present.

There was a uterine corpus leiomyoma and the cervix was unremarkable.

Figure 1 shows representative images of the carcinoid foci and illustrates some of the immunohistochemistry.

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Case 2

A 61-year-old woman with hereditary breast and ovarian cancer (HBOC), but without a BRCA germline mutation, underwent risk reducing bilateral salpingo-oophorectomy and hysterectomy. One year earlier, she had surgery for a breast infiltrating ductal carcinoma, grade 3, with no neuroendocrine features. The patient had no prior history of a neuroendocrine tumor and a whole body Ga-PET-CT scan following the pathology diagnosis revealed no tumor elsewhere.

Both fallopian tubes and ovaries (which were grossly normal) were examined in their entirety. No tumor was identified macroscopically. However, histological examination showed a 1 mm tumor involving the fimbrial end of the right fallopian tube. This was located in the mucosa and ulcerated the surface epithelium. The lesion was well circumscribed, but not encapsulated, and composed of nests and trabeculae of cells with an organoid appearance. The cells had round to ovoid bland nuclei and a moderate amount of eosinophilic cytoplasm. There was no mitotic activity. Immunohistochemistry showed diffuse positivity for chromogranin, synaptophysin, CD56, WT1 and AE1/3. p16, estrogen receptor (ER), progesterone receptor (PR), PAX8, inhibin, calretinin, CK7, vimentin, GATA3, CDX2 and GCDFP-15 were negative. The Ki67 (MIB1) proliferation index was <1%. The morphology and immunophenotype were in keeping with a carcinoid tumor/ low-grade neuroendocrine tumor. No other tumor component was present.

The left fallopian tube, both ovaries, uterine corpus and cervix showed no gross or microscopic abnormality.

Figure 2 shows representative images of the carcinoid tumor and illustrates some of the immunohistochemistry.

Case 3

A 69-year-old woman presented with postmenopausal vaginal bleeding. A left adnexal mass was identified on PET-CT scan and the serum CA125 was mildly raised at 35 U/ml. Radiologically, there was no evidence of tumor outside the left adnexa. The patient

underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy and omentectomy. Following the histological diagnosis, she received vincristine, adriamycin and cisplatin chemotherapy. At three years follow-up, she is alive without disease.

Grossly, a 4 cm solid tumor involved the left fallopian tube. Histology showed a neoplasm involving the full thickness of the wall of the tube and composed of a diffuse arrangement of cells with ovoid hyperchromatic nuclei with nuclear moulding. The tumor cells had scant cytoplasm. There was high mitotic activity and areas of necrosis. CD56, chromogranin, and synaptophysin were diffusely positive. WT1 and p16 were negative and p53 showed a wild-type pattern of immunoreactivity. The morphology and immunophenotype were in keeping with a high-grade neuroendocrine carcinoma of small cell type (small cell neuroendocrine carcinoma). No other tumor component was present.

The right fallopian tube, both ovaries, uterine corpus and cervix were grossly and histologically normal. The pelvic lymph nodes and omentum were not involved by tumor.

Figure 3 shows representative images of the tumor and illustrates some of the immunohistochemistry.

Case 4

A 71-year-old woman presented with postmenopausal vaginal bleeding. An endometrial biopsy showed no tumor. MRI revealed a 5 cm left adnexal mass with no tumor elsewhere. She underwent hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection and omentectomy. The postoperative course was complicated by a wound infection and the patient died 22 days following the operation. An autopsy was performed and showed no evidence of tumor elsewhere.

On gross examination, the tumor involved the left fallopian tube, including the fimbria. Histology showed a neoplasm involving the full thickness of the wall of the tube and composed of a diffuse and nested arrangement of cells with large nuclei and abundant eosinophilic cytoplasm. There was high mitotic activity and areas of necrosis. Immunohistochemistry showed diffuse positivity for synaptophysin, chromogranin and

CD56. CK7, epithelial membrane antigen (EMA), HMB45, CD45, WT1 and ER were negative. The morphology and immunophenotype were in keeping with a high-grade neuroendocrine carcinoma of large cell type (large cell neuroendocrine carcinoma). No other tumor component was present.

Three of 8 left pelvic lymph nodes contained metastatic tumor; the 7 right pelvic lymph nodes were uninvolved. The right fallopian tube, both ovaries, uterine corpus and cervix were grossly and histologically normal. The omentum was not involved by tumor.

Figure 4 shows representative images of the tumor and illustrates some of the immunohistochemistry.

IMMUNOHISTOCHEMICAL STAINING OF NORMAL FALLOPIAN TUBES

Of the 16 normal fallopian tubes, 9 showed mucosal epithelial cells which exhibited positive cytoplasmic staining with chromogranin (figure 5). The number of positive cells varied greatly from occasional scattered cells to many cells.

DISCUSSION

We report four cases of probable primary neuroendocrine tumors of the fallopian tube (two carcinoid tumors/ low-grade neuroendocrine tumors and two high-grade neuroendocrine carcinomas), the first reported series in the literature. Primary neuroendocrine tumors of the fallopian tube are extremely rare and, in fact, the category of neuroendocrine tumor is not included in the 2014 World Health Organization (WHO) Classification of tumors of the female reproductive organs (7). There have been only occasional case reports in the literature of a primary neuroendocrine tumor at this location (1-6). In one case, a carcinoid tumor arose within a mature cystic teratoma of the fallopian tube. Although morphologically low-grade, the tumor had spread to involve both ovaries and the serosal surface of the uterus at the time of presentation (1). There are a few reports of primary tubal high-grade neuroendocrine carcinomas (2-6), including one admixed with a component of serous carcinoma, but we are not aware of any reports of isolated low-grade neuroendocrine tumor unassociated with a teratoma at this site.

The differential diagnosis of the carcinoid tumors (low-grade neuroendocrine tumors) is limited, given the characteristic morphology and positivity for neuroendocrine markers chromogranin and synaptophysin. Microscopic sex cord-like proliferations resembling adult granulosa cell tumor or sex cord tumor with annular tubules (SCTAT) have recently been reported involving the fallopian tube and might be considered in the differential diagnosis. However, the nuclear characteristics of these sex cord proliferations are morphologically distinct to carcinoid tumors and they have a different immunophenotype being positive with sex cord markers inhibin and calretinin (8). In the context of a patient with HBOC (case 2), including those with a *BRCA* germline mutation, the differential diagnosis might include serous tubal intraepithelial carcinoma (STIC) or high-grade serous carcinoma arising in the fallopian tube or metastatic breast carcinoma. Again, however, the morphologic features and immunophenotype are distinct and allow easy distinction from a low-grade neuroendocrine tumor.

High-grade neuroendocrine carcinomas may be of small cell or large cell type. The differential diagnosis of high-grade neuroendocrine carcinomas depends on whether this is predominantly of small cell or large cell type but in the fallopian tube potentially includes other high-grade epithelial neoplasms, such as high-grade serous or endometrioid carcinoma. Again the morphological features and a combination of immunohistochemical markers should allow ready distinction; high-grade serous and endometrioid carcinomas are usually PAX8 and ER positive while high-grade neuroendocrine carcinomas are generally negative. High-grade serous carcinomas are usually WT1 positive and high-grade neuroendocrine carcinomas generally negative.

A key issue in the cases we report is whether the neuroendocrine tumors represent primary tubal lesions or metastases from other anatomic sites. Immunohistohemistry is of limited value in this distinction since neuroendocrine neoplasms at various sites generally exhibit a broadly similar immunophenotype. For example, CDX2 is commonly positive in mid-gut carcinoid tumors but is also positive in ovarian carcinoids of insular type which commonly arise in teratomas and which are morphologically equivalent to mid-gut carcinoids (9). One of the carcinoids in our series was CDX2 positive. A metastasis was especially considered in case 1 since both fallopian tubes contained multiple small foci of carcinoid tumor. In all our cases, there was no clinical or radiological evidence of neuroendocrine tumor elsewhere at

presentation or on follow-up (one patient underwent an autopsy which revealed no evidence of tumor elsewhere); however, as stated, particularly in case 1 we cannot exclude metastasis. Nevertheless, the evidence available in each case supports the interpretation that these probably represent primary tubal lesions.

The histogenesis of primary carcinoid tumor (low-grade neuroendocrine tumor) of the fallopian tube is unclear. Possibilities include an origin from a teratoma (which are extremely rare in the fallopian tube) or as a neuroendocrine component of another tumor type. There was no evidence of any other tumor type in the two cases we report and total overgrowth of another neoplasm is highly unlikely given that the tumors were small and incidentally detected microscopic lesions. Another possibility is that they arise from dispersed neuroendocrine cells in the fallopian tube. To investigate whether neuroendocrine positive cells are present in the normal fallopian tube, we stained 16 tubes and chromogranin positive mucosal epithelial cells were present in 9 cases. It is possible that these are the origin of primary neuroendocrine tumors of the fallopian tube, especially low-grade neoplasms and we are not aware of neuroendocrine cells having been demonstrated in normal fallopian tubes previously. A similar histogenesis may apply to primary tubal high-grade neuroendocrine carcinomas. When these neoplasms arise at other sites within the female genital tract (cervix, endometrium, ovary), they often occur in association with another tumor type (10-18). While the two high-grade neuroendocrine carcinomas we report occurred in pure form (with no other tumor component), it is possible that another component was present and totally overgrown by the neuroendocrine neoplasm. One of the prior reported cases of primary tubal high-grade neuroendocrine carcinoma also contained a component of serous carcinoma (6).

In conclusion, we report four cases of probable primary neuroendocrine tumors of the fallopian tube, including the first reports of a primary carcinoid tumor/ low-grade neuroendocrine tumor not associated with a teratoma. Given the increased focus on the fallopian tube fimbria as the site of origin of extrauterine high-grade serous carcinoma, fallopian tubes are now more extensively examined and it is possible that additional cases, especially of microscopic carcinoid tumors, will be identified in the future.

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FIGURE LEGENDS

Figure 1. Case 1. Focus of carcinoid tumor in wall of fallopian tube (A). Higher power view showing carcinoid tumor just deep to surface epithelium of fallopian tube (B). Chromogranin stain highlighting several foci of carcinoid tumor (C and D).

Figure 2. Case 2. Low power view showing microscopic carcinoid tumor involving mucosa of fallopian tube (A and B). On higher power, the regular tumor cells grow in nests and trabeculae (C). The tumor cells are diffusely positive with chromogranin (D).

Figure 3. Case 3. High-grade neuroendocrine carcinoma (small cell neuroendocrine carcinoma) involving fimbria of fallopian tube (A). On higher power, the tumor cells exhibit a diffuse growth pattern and contain scant cytoplasm (B). The tumor cells are diffusely positive with synaptophysin (C).

Figure 4. Case 4. High-grade neuroendocrine carcinoma (large cell neuroendocrine carcinoma) involving fimbria of fallopian tube (A). On higher power, the tumor cells exhibit a diffuse growth pattern and contain abundant cytoplasm (B). The tumor cells are diffusely positive with synaptophysin (C).

Figure 5. Normal fallopian tube with chromogranin positive epithelial cells.

Figure 1

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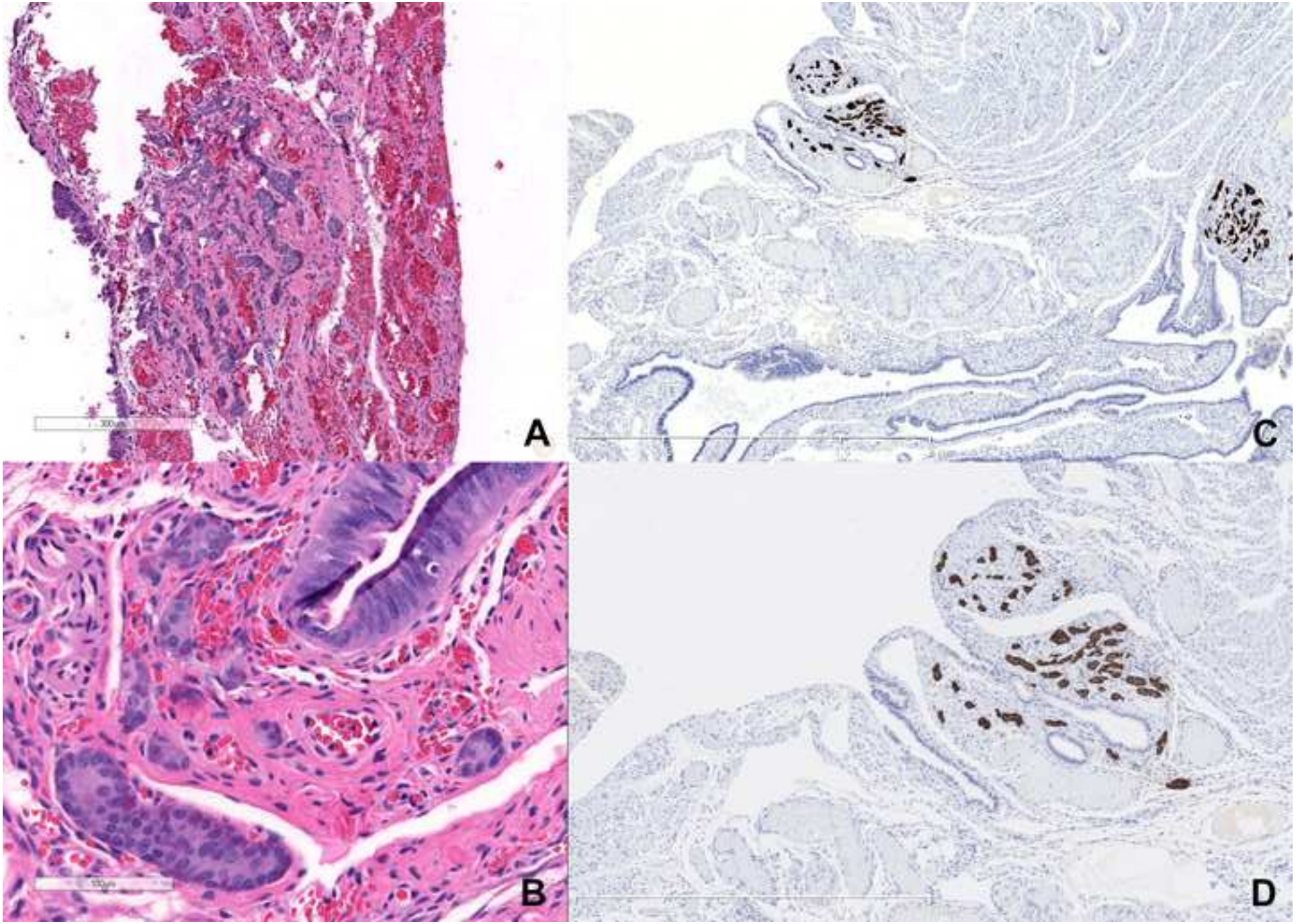

Figure 2

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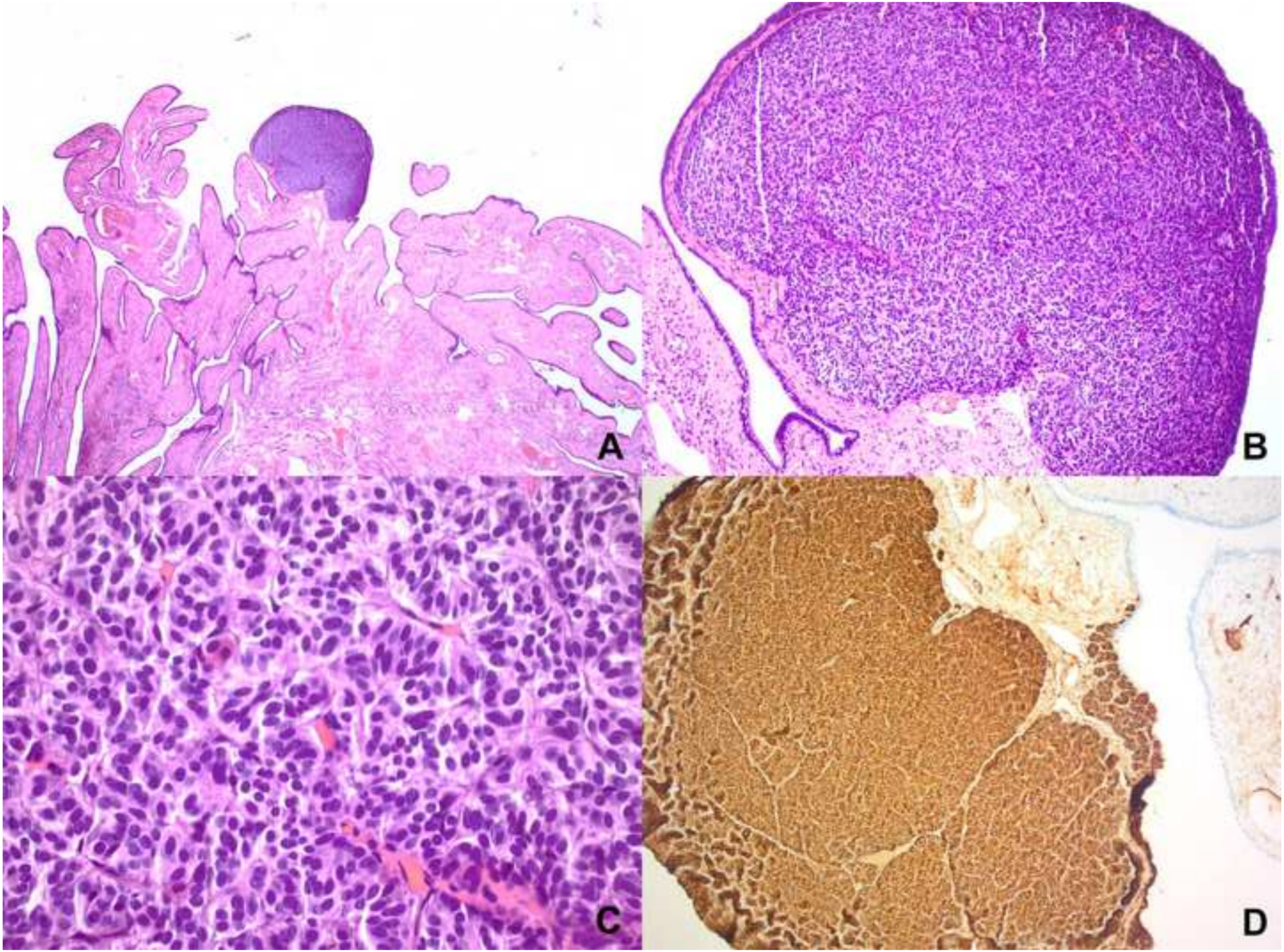

Figure 3

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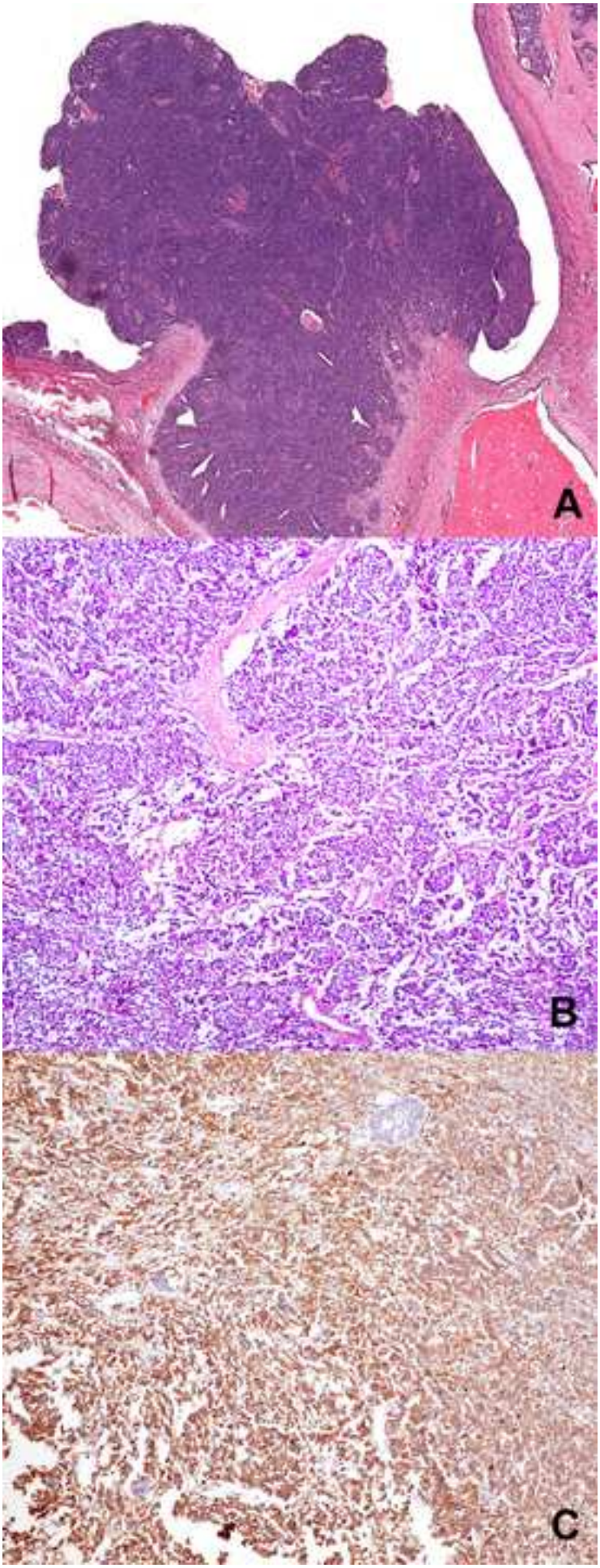

Figure 4

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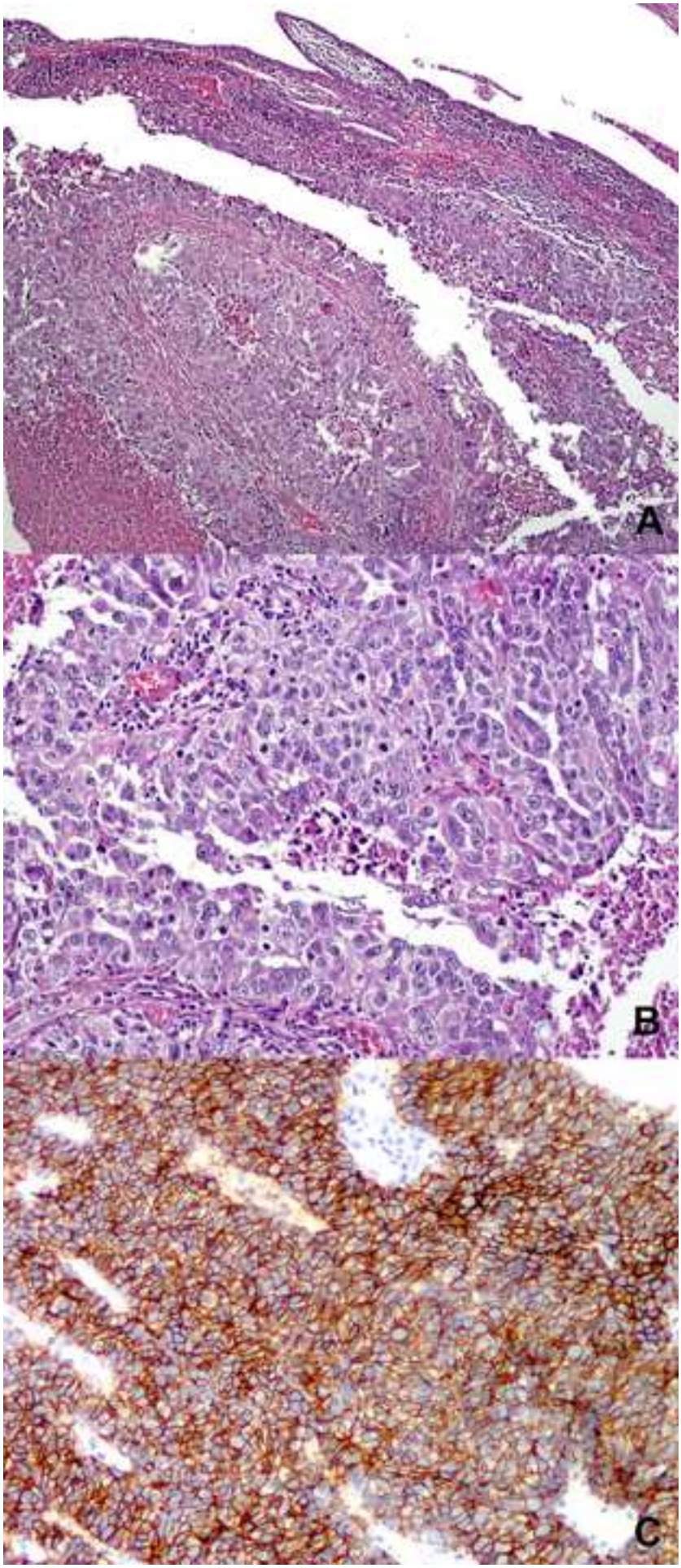

Figure 5

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