Slide seminar gynecologic pathology, case no 2

Case history

A 48 year old, postmenopausal woman with a large solid and cystic mass in the left ovary was treated with laparoscopic adnexectomy. Subsequent surgical staging with peritoneal biopsies, hysterectomy, and systematic lymphonodectomy was performed after histological diagnosis. Adjuvant chemotherapy with 6 cycles of paclitaxel/carboplatin is ongoing.

Macroscopic features

Enlarged ovary (135 x 90 x 40 mm) with multiple cysts measuring up to 70 mm. Papillary fonds and solid areas within the cysts. Thick mucinous intracystic liquid. Adherent fallopian tube with normal gross appearance.

Microscopic features

Morphology: Papillary tumor with hierarchical branching of papillae. Stromal cores covered with stratified epithelium of heterogeneous differentiation: serous, mucinous endocervical-like, and indifferent cells alternate. Focally excessive mature squamous metaplasia originating from the tips of the papillae; focally squamous morules. Moderate atypia of nuclei with hyperchromasia and formation of nucleoli. Infrequent mitoses. Patchy necrosis. Focally heavy neutrophilic infiltration of epithelium and mucinous secretions. Multifocally complex growth pattern with confluent glands or cribriform architecture. Furthermore, several foci of frankly invasive glands within the cyst wall surrounded by desmoplastic stroma. Complex growth and invasive areas measuring from 5 to 20 mm in linear dimension. One 20 mm focus with invasive solid tumor nests of neuroendocrine appearance and oval nuclei with granular chromatim and focal eosinophilic inclusions. On two slides (constituting approximately 5% of the tumor), undifferentiated tumor component, intimately admixed with the papillary/glandular tumor: Diffuse growth of small to medium-sized dyscohesive cells with angulated atypical nuclei and nucleoli. Frequently rhabdoid appearance with eosinophilic cytoplasm. Many mitoses and apoptoses. Geographical necrosis. The only extra ovarian tumor manifestation was a metastasis of the undifferentiated component in the left-parametrial fat.

IHC: Papillary/glandular component positive for CK7, CA125, PTEN, focally for PAX8, heterogeneous for p16, focally for vimentin, ER (70%), PR (20%). Ki67 proliferative index heterogeneous, between 10 and 60%. No expression of beta-HCG, CD30, CDX2, CK20, AFP. Squamous metaplasia positive for CK5/6. Solid invasive component partially positive for synaptophysin, negative for chromogranin A. No unequivocal positivity for CD10 in the stroma. Undifferentiated component exclusively positive for vimentin. No expression of CK (MNF116, AE1/AE3), EMA, BerEP4, CK7, CK20, smooth muscle-specific actin, MyoD1, myogenin, caldesmon, CD34, S100, Melan A, HMB45, calretinin, ER, PR. Ki67 proliferative index 90%. 
Diagnosis

Low-grade seromucinous ovarian carcinoma with associated anaplastic carcinoma, metastatic to the parametrium.

Discussion

Seromucinous neoplasms of the ovary are rare. Synonyms are endocervical-like, Müllerian, or mixed-cell type tumors. The vast majority are borderline tumors (BLT). They are not infrequently bilateral and may reveal peritoneal implants, mostly of the non-invasive type. Microscopically they reveal a mixture of cell types, including mucinous, serous, and indifferent eosinophilic cells. There are no typical goblet cells or paneth cells. The architecture is quite similar to that of serous borderline tumors and the long, filigree papillae of intestinal-type borderline tumors are not seen. Typically, there is a strong infiltration with neutrophils. Microinvasion may be present and is defined similarly to serous BLT. Frequently, there is extensive epithelial stratification, but confluent growth of glands and cribriform patterns should be diagnosed as intraepithelial carcinoma.

The existence of invasive variants of seromucinous neoplasms (= carcinomas) is conflictive. They are not listed in the current WHO classification (2003); Jaime Prat¨s group, in a series of 31 seromucinous ovarian neoplasms, did not find any invasive tumor and concluded that invasive seromucinous neoplasms should be classified as endometrioid carcinomas. However, Robert Kurman¨s group, in analogy to serous tumors, defined destructive or expansive growth measuring more than 5 mm as invasion, a situation illustrated by the present case. In a series of 54 seromucinous tumors, they found 7 (invasive) carcinomas; 3 patients with stage III disease experienced recurrence or died of tumor, while none of the patients with stage I carcinoma, BLT with or without intraepithelial carcinoma or microinvasion died of tumor. Taking all available data together, it seems that seromucinous ovarian neoplasms have a favorable prognosis, which might be deteriorated if frank invasion occurs.

Seromucinous neoplasms of the ovary seem be strongly related to endometrioid tumors, as they gain endometrioid morphology in confluent/invasive areas, may exhibit squamous metaplasia, which is excessive in the present case, and reveal a similar immunohistochemical profile (so-called Müllerian profile, as opposed to intestinal-type tumors). Furthermore, they arise in endometriosis, similarly to ovarian endometrioid and clear cell tumors. Because of the rarity of seromucinous neoplasms, little is known about their molecular characteristics. k-ras mutations have been described. A recent study of Wu et al. showed that they may have mutations of the tumor suppressor gene ARID1A, along with loss of its gene product BAF250 protein, which is detectable by IHC. These data support the relationship between seromucinous and other endometriosis-associated histological types, as ARID1A mutations occur in 30-40% of ovarian endometrioid and clear cell tumors, as well as in subsets of endometrioid endometrial carcinomas. Potentially, seromucinous neoplasms constitute a variant of endometrioid tumor with excessive extracellular mucin production.

The most interesting feature of the tumor presented here is the anaplastic component. Although we cannot completely rule out the possibility of a collision tumor, the intimate admixture of papillary/glandular and anaplastic components rather suggest that the anaplastic component developed from the differentiated component. This seems to occur quite rarely. Extensive literature
research has revealed one publication by Boyd & McCluggage that describes some rare examples of low-grade serous ovarian neoplasms associated with undifferentiated carcinoma.\textsuperscript{10} One of those cases was a seromucinous BLT with microinvasion that relapsed as a high-grade serous carcinoma in mediastinal lymph nodes. Two low-grade serous neoplasms were associated with an anaplastic component with rhabdoid features, morphologically identical with our case; both patients ultimately died of tumor progression. This study shows that the association of low-grade serous and seromucinous tumors with undifferentiated carcinoma is rare, however, if present, a worsening of the prognosis should be expected. In line with these findings is that in our case, the only extra ovarian manifestation of the tumor was a metastasis of the anaplastic component. A de-differentiation of low-grade endometrioid carcinoma of the endometrium has also been described as a rare phenomenon and, similarly to ovarian tumors, frequently reveals rhabdoid features.\textsuperscript{11} Those tumors not infrequently show reduced of even missing immunoreactivity with epithelial markers, such as CKs, or EpCam, and are positive for vimentin. EMA expression may be expressed more consistently, however in our case, we might have missed reactive areas. It should be also be mentioned that our case reminds us of mural nodules of anaplastic carcinoma that are sometimes present in mucinous ovarian tumors, however, up to now they have exclusively been described in intestinal-type mucinous neoplasms.\textsuperscript{12}

In conclusion, seromucinous neoplasms of the ovary are low-grade tumors with a generally favorable prognosis, which however might be worse in the rare invasive variant. Morphological and molecular data strongly suggest that they are related to endometrioid tumors. An exceptionally rare complication might be the development of a de-differentiated component, in which case an aggressive behavior should be expected.

\textbf{References}


