

ADENOCARCINOMA OF THE ENDOCERVIX

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There are different types of adenocarcinoma of the Endocervix. In this review we are going to see the following types - Villoglandular, Serous, Adenoid Cystic, Mesonephric, Clear Cell, Adenoid Basal, Endometrioid, and Mucinous.

Villoglandular – This adenocarcinoma is a papillary adenocarcinoma with absent or minimal invasion. The prognosis of all adenocarcinomas in the cervix depends on the invasion of the tumor. Therefore, since this tumor is predominantly non-invasive the prognosis is excellent. It is extremely important to make the diagnosis of this adenocarcinoma because many adenocarcinomas of the cervix have papillary pattern on the superficial portion but they are deeply invasive.

Serous Carcinoma – I believe that this is a highly unusual entity in the cervix because it is unlike the serous carcinoma in the endometrium. Over 70% of the patients reported with the tumor are younger than 45 years and most of them have low stage disease and excellent survival. Most probably these are not really serous carcinoma but they have serous appearance mainly on the superficial part of the tumor; however, when deeper sections are observed only a glandular involvement is seen without papillary serous configuration. In my opinion these are regular adenocarcinomas in the cervix that have a papillary serous like appearance on the surface of the tumor. Rarely papillary serous carcinoma of the endometrium, or the ovary might involve the cervix, focally, but this is a secondary type of involvement.

Adenoid Cystic Carcinoma – This tumor has been described in the cervix as similar to the adenoid cystic carcinoma seen in the head and neck area; however, in the cervix it does not have myoepithelial cells and this is the reason why some authors refer to the tumor as adenoid cystic-like. Most probably this is a regular adenocarcinoma in the cervix with some similar features to the usual adenoid cystic carcinoma.

Mesonephric Carcinoma – I always recommend that in any hysterectomy specimen, when random sections are going to be submitted they should be from the 3 and 9 o'clock positions, because these are the areas where the mesonephric rests are located, and it is a good practice to familiarize ourselves with the histology of the mesonephric rests and their histologic changes. The glands frequently contain eosinophilic material in the lumen, and this supports the diagnosis the presence of areas of hyperplastic mesonephric rests near the carcinoma. In case of doubt immuno stains are important and the best immuno stains to confirm the diagnosis of mesonephric carcinoma are: CD10, EMA, PAX-8, and Calretinin. It is important to remember that P16, is only focally positive and WT1, ER and CEA are negative.

Clear Cell Carcinoma – Clear cell carcinoma is a tumor with different patterns including papillary, with special typical hyaline material in the stroma glands with hob-nail cells, solid, and a pattern that can be a real problem in the cervix is microcystic in a small biopsy the microcystic pattern can show only cysts lined by flat cells and can be diagnosed a benign cyst. In this type of situation it is important to perform immuno-stains for keratin, to prove there are epithelial cells, Ki67 to show the proliferative activity of the cells lining the cysts, and ER which should be negative in clear cell carcinoma and positive in the regular, cervical cystic lesions. One of the main differential diagnosis of clear cell carcinoma is Arias Stella reaction. In the cervix Arias Stella reaction might involve isolated glands and frequently the cells in Arias Stella reaction are more atypical than the cells in clear cell carcinoma. Immuno stains might help, in Arias Stella reaction ER and PR are positive, and Ki67 is negative, while in clear cell carcinoma the opposite is seen.

Adenoid Basal Carcinoma – This type of neoplasm is well recognized but there is one situation where it can be a problem to diagnose adenoid basal carcinoma and this is when above the adenoid basal carcinoma there is an area of squamous carcinoma in situ. In this situation the adenoid basal carcinoma might be confused with an area of invasion. The presence of small glands and the basaloid appearance of cells without atypia or mitosis are all features indicating that the diagnosis is adenoid basal carcinoma. This is a benign lesion because no recurrences or metastasis have been reported. Based on this some authors have proposed to change the name to adenoid basal epithelioma.

Endometrioid Carcinoma – Is it possible to see endometrioid carcinomas in the cervix? Some people question the presence of an endometrioid carcinoma because when mucinous glands become malignant frequently there is no mucin in the cytoplasm and they appear to be endometrioid. I believe there is an obvious endometrioid tumor in the cervix, the cells in this type are positive for ER, and P16 is only focal.

In addition, we know that patients having only a supra cervical hysterectomy, and receiving only estrogens, frequently developed an endometrioid carcinoma in their residual cervix. The second problem when we have an endometrioid carcinoma is whether the tumor is from the cervix or the endometrium. Important features to distinguish this are the age of the patient, patients younger than 40 most probably have endocervical carcinoma, the amount of tissue, abundant tissue favors endometrium rather than cervix, and when there is involvement the lower uterine segment most probably the tumor is primary in the endometrium with secondary involvement of the cervix. If the endometrial and the cervical curettages are both positive for adenocarcinoma, then it is necessary to perform immunohistochemistry. Vimentin and ER are markers for endometrioid tumors, and P16 and CEA are markers for endocervical lesions. However, endometrioid types of adenocarcinomas involving the cervix have similar reaction to endometrioid carcinoma of the endometrium because most probably all of these 4 markers are not indication of cell of origin. They are markers of differentiation and most endometrial carcinomas are endometrioid and most endocervical carcinomas are mucinous. Vimentin can be very focal in few cells; ER is normally positive in endocervical glands and becomes negative when the glands are malignant. P16 is positive in both endometrial and endocervical tumors; however, in endometrioid carcinomas P16 is focal, and in the endocervical tumor, due to HPV, P16 is diffusely positive in the cytoplasm and nuclei. CEA has to be positive in the cytoplasm of the cells, not on the surface, because the positive CEA in the surface indicates glycocalyx and this can be seen in endocervical and endometrial carcinoma. The histologic appearance of the endometrioid carcinoma of the cervix is identical to that of the endometrioid carcinoma of the endometrium.

Mucinous Adenocarcinoma of the Endocervix – In this type of adenocarcinoma frequently the tumor has a classical appearance with abundant mucin; however, there are also intestinal and ciliated types of adenocarcinomas. There is an entity designated as SMILE which in reality represents a CIN with mucin and some people believe that it is like an in situ counterpart of adenosquamous carcinoma. In this situation it is important to see if the mucinous cells are mainly on the surface of the lesion, indicating metaplasia, or mixed with the lesion which would favor SMILE. In addition, in the SMILE, or CIN, obvious features of malignancy are seen. One important conclusion of this CIN with mucin, or SMILE, is that it has been accepted today that squamous carcinomas containing mucin are more aggressive than squamous carcinoma without mucin. The diagnosis of adenocarcinoma in the cervix is based on histologic features including nuclear stratification, atypia, and mitosis. If the features are not diagnostic we could use immunohistochemistry which shows that the malignant cells are positive for Ki67, positive for CEA, and negative for ER. Also, P16 is diffusely positive in the cytoplasm and the nuclei of the malignant cells. One of the main issues in the carcinoma in the cervix is to determine if the tumor is invasive or not. It has been extremely difficult to demonstrate invasion and today we know that immuno stains for laminin demonstrating the presences of the basement membrane is not important to separate

in-situ from invasive lesions because basement membrane can be seen in metastatic tumors. For the last few years we have been reviewing different methods of evaluating invasion in adenocarcinoma in the cervix because 95% of the lymph nodes resected in these patients are negative and the resection of the lymph nodes create multiple complications, including transient bladder or sexual dysfunction, lymphedema, and neuropathy. We have developed a new system to review these cases. All cases included were diagnosed as invasive adenocarcinomas and had lymph node resection. We compared the depth of the neoplasms, the tumor size, the status of the lymph nodes, invasion, and the pattern of tumor invasion. Based on these features we develop a new method with 3 different patterns. Pattern A characterized by well demarcated glands, frequently forming groups, regardless of the depth of the glands, or the complexity in the epithelium. In this pattern there is no unequivocal invasion or vascular invasion. Pattern B is similar to Pattern A but with superficial minimal invasion or vascular invasion. For Patterns A & B high power is needed because it is important to identify a small focus of invasion. Pattern C can be diagnosed on low power and it shows diffuse destructive tissue invasion. Using these patterns it is not important if the tumor is superficial or deep, it could be a deep tumor without unequivocal invasion. Using the classic evaluation 15% of the patients in these 359 adenocarcinomas have positive lymph nodes and of 8,151 lymph nodes resected only 83, which represents just 1% of the total number lymph nodes, were positive. Using our method, the cases with Pattern A represented 78 patients, or 22% of the entire group, and not one patient had either lymph node metastases or recurrences. We believe that by using this pattern system these 78 patients would have been spared of a lymph node resection. There were 91 patients in Pattern B, or 25% of the entire group, and only 7 of the 91 had positive lymph nodes. In Pattern C there were 190 patients, or 53% of the total number of patients and 24% of these had positive lymph nodes. All patients with Pattern A had Stage I disease. Patients with Stage II, III & IV had Patterns B or C. It is also important to remark that the depth of the tumor was not important because there were invasive tumors with less than 3mm of depth and positive lymph nodes, although most of the invasive tumors with metastasis were deeper than 5mm. A very important feature is that all cases with positive lymph nodes had areas of lymphovascular invasion. This pattern system is easy to evaluate and clinically significant. We believe that using this pattern system we will be able to spare resection of lymph nodes in 50% of adenocarcinomas of the endocervix.

Minimal Deviation Adenocarcinoma – The use of criteria for the regular endocervical adenocarcinomas including stratification, atypia, and mitosis, are not important in the evaluation of minimal deviation of adenocarcinoma. In this type of tumor the number of glands, the lack of organization, and the presence of focal atypia are very important. In most studies of minimal deviation adenocarcinoma only images with very well differentiated glands were included; however, in most studies the text refer to the presence of

focal atypical areas or atypical cells at least in some areas of the tumor. If these areas are not identified but there is suspicion for the diagnosis of minimal deviation carcinoma immuno stains might help including a focal positive Ki67 and a negative ER. P16 can be very focal because minimal deviation adenocarcinoma is not a tumor related to HPV. Probably one of the most important aspects of the minimal deviation adenocarcinoma is that the patients have enlarged cervix, therefore the first step is from the clinician when the information included is that the patient has an enlarged cervix. An antibody used mainly in Japan for minimal deviation endocarcinoma is HIK1083. This type of carcinoma can be associated with lobular endocervical hyperplasia. A carcinoma usually showing areas of minimal deviation adenocarcinoma is the gastric type of endocervical adenocarcinoma. Minimal deviation adenocarcinoma and gastric type of adenocarcinoma can be associated with Peutz-Jeghers disease and with sex cord tumors with annular tubules in the ovary. Most minimal deviation adenocarcinomas and gastric type are aggressive tumors.