Practical Issues in Endometrial Pathology

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Endometrial bleeding

The most common causes of endometrial bleeding are, “breakdown, disordered proliferative endometrium, endometrial polyps, and hyperplasia and carcinoma.

Breakdown

Breakdown is a very common cause of endometrial bleeding, it is explained by continuous estrogen effect which is the origin of fibrin thrombi and because of this there is stromal condensation and epithelial metaplasia finally resulting in significant fragmentation. Because of these changes the breakdown can be confused with a stromal or and epithelial proliferation and as a good rule I would say that we should never make diagnosis of a malignant lesion in a very fragmented endometrium.

Disordered proloferative endometrium

This is also a very common cause of uterine bleeding and is diagnosed when a proliferative endometrium has glands of different sizes and with significant variation in the amount glands from area to area. Therefore we can see an increase number of glands; however, the amount of glands does not represent more than 50% of the entire tissue.

Endometrial Polyps

When we are reviewing endometrial polyps it is very important to know the age of the patient. Endometrial polyps in premenopausal patients are usually benign and the most common lesion in polyps in this group is hyperplasia. However, endometrial polyps in peri or postmenopausal can have different lesions including hyperplasia, endometriod carcinoma, or small, focal carcinoma, which can be serous or clear cell, and different types of sarcoma.

Endometrial Hyperplasia

The most important component of endometrial hyperplasia for the clinician who is going to determine the treatment of the patient is whether there is or there is not cellulary atypia in the areas of hyperplasia. Most endometrial hyperplasias without atypia will be treated with progestins ; however, endometrial hyperplasias with atypia are treated with hysterectomy. Therefore the evaluation of the presence or absence of atypia is extremely important. Pathologists do not agree on how to disagnose atypia in the endometrium. Different authors have suggested to investigate the presence of nucleoli, or the size and the shape of the nuclei, but everybody agrees that the easiest way to determine whether there is atypia or not is to compare the area where we believe might have atypia with areas of normal endometrium.

Endometrial Intraepithelial Neoplasia

EIN has been defined as a precancerous clonal proliferation. There are three elements to diagnosis EIN:1. The area of glands should be larger than the area of stroma, 2. The cells in that area should have abnormal nuclei, and 3. The size of the lesion should be at least 1 mm. EIN has been recognized by some authors as a more strict criterium to identify endometrial carcinoma; however, since the most cases of low grade endometrial carcinoma survive I personally do not think that it would be necessary to have a more strict criteria to recognize endometrial cancer. The usual criterium to diagnose endometrial cancer is that the area where the glands are back to back should be larger than 2 mm instead of 1 mm. Otherwise the same criteria for EIN are the ones used for endometrial cancer including abnormal nuclei and the areas of glands which should be larger than the area of stroma. I personally continue using the terminology of endometrial hyperplasia and endometrial adenocarcinoma with the addition of the presence or absence of atypia in cases of endometrial hyperplasia.

The diagnosis of endometrial carcinoma requires that the glands back to back occupy an area of larger than 2 by 2 mm or that there is fibrosis of the stroma. There features mean that there is invasion of the stroma and, that most probably will be residual carcinoma in the hysterectomy specimen. When we evaluate fibrosis in the stroma before rendering diagnosis of endometrial carcinoma it is important to be certain that we are not evaluating an endometrial polyp or that it is not a previous biopsy site. A very simple rule is to look for areas of fibrosis not only on the surface of the lesion but in deep areas. The size of the area having glands back to

back has to be 2 by 2 mm but sometimes because of the biopsy technique or the preparation of the tissue the glands are back to back in an area of 3 by 1 mm rather than 2 X 2 because the biopsy is very fragmented. In this situation it is important to determine in the evaluation the age of the patient because peri/postmenopausal patients with either low grade carcinoma or atypical hyperplasia will be treated with a hysterectomy.

The diagnosis of endometrial carcinoma requires the presence of proliferative areas. Rendering the diagnosis of endometrial carcinoma in a background of secretory endometrium would mean that in addition to the secretory areas there are also some proliferative areas which justify the diagnosis of carcinoma.

Currently, cases of endometrial carcinoma undergo lymph node resection when the tumor is grade I but with invasion of more than 50% of the myometrium or with vascular invasion or Stage II disease. If the case is a grade 3 lesion a lymph node resection is done regardless of other features. Cases of grade 2 are controversial and usually they are managed as individual cases depending on other factors including pathology factors as well as clinical features that might be important in the prognosis of each case.

Vascular Invasion

The presence of vascular invasion in endometrial carcinoma is very important but with the current techniques of hysterectomy done by laparoscopic or robotic type of surgery we have found that frequently there is tumor inside vessels which most probably represent contamination. Features that suggest that the tumor in the vessels is a contaminant are the involvement of large vessels only, the absence of significant invasion, the absence of small vessels with tumor near the area of invasion, a polypoid endometriod tumor, and the presence of tumor within artificial clefts in the myometrium.

Endometrium Carcinoma Grading

According to the FIGO grading endometrial carcinomas are classified as grade 1, 2, and 3, based on the percentage of the solid component. A tumor with less than 5% of solid component is grade 1, if the tumor has 6-50% solid component it's a grade 2, and tumors with more than 50% of solid component are grade 3. An extremely important issue is whether there are glands in the foci of solid component. If no glands are seen in the areas of solid part, the tumor should be designated as undifferential carcinoma, and if in the solid areas glands are seen then it should be diagnosed as a grade 3 endometriod carcinoma. This is extremely important because

if we use the solid areas to grade the tumor without realizing that those areas were really undifferential parts, the survival of the patient is going to be much worse than that of a regular endometriod tumor. A component of undifferential carcinoma should be suspected in cases where a previous diagnosis of a grade 2 or grade 3 endometrial carcinoma is followed by rapid progression of the disease.

A very common issue is if in the areas of undifferentiated carcinoma there is neuroendocrine differentiation. This issue became very important in the cervix because frequently endocervical tumors are treated with radiotherapy and tumors with neuroendocrine differentiation might be resistant to radiotherapy; however, in the endometrium almost all tumors are treated with surgery and when investigating different stains including synaptophysin, chromogranin, and CD56, it's not unusual to find focal areas of neuroendocine differentiation. Up to 40% of cases of undifferentiated carcinoma have foci of neuroendocrine differentiation; however, the behavior is similar to that of carcinomas without neuroendocrine differentiation.

Endometrial adenocarcinoma, immunohistochemistry.

One very important issue when diagnosing endometrial carcinoma is whether the tumor arose in the endometrium or in the endocervix. The situation would be always solved if the clinicians would do a fractioned curettage, first from the endocervix, then from the endometrium; however, it is a very common practice to submit a specimen to pathology designated uterine curettage without specification of the site. There are four stains that are commonly used to determine if the tumor is from the endometrium or endocervix, vimentin, ER, CEA, and p16. It is important to use the four stains because no one of these stains is absolutely specific of either endometrium or endocervix. Positive vimentin in the tumor cells and positive ER in the nuclei favor an endometrial tumor. Positive CEA in the cytoplasm of the cells, and diffuse p16 in the nuclei and the cytoplasm favor primary tumor from the endocervix. A few comments regarding these results on these are the following: "vimentin can be very focal in positive cases. ER is normally negative in adenocarcinoma endocervix; except if the tumor is endometriod type. CEA should be evaluated only in the cytoplasm of the cells; normally CEA is positive in the luminal border of the cell, probably because of glycocalix. P16 is an indirect marker of HPV but it has to be diffuse and it has to be positive in both the cytoplasm and the nuclei.

Endometrial Carcinoma Staging

Stage 2 endometrial cancers is a tumor arising in the endometrium with metastases to the cervix. Metastatic tumors are usually similar to the primary lesion and the primary tumor is usually the dominant mass. There are cases in uterine endometrial cancer where both tumors in the endometrium and the endocervix are both different, or the carcinoma in the endometrium may not be invasive, or the carcinoma in the cervix might be larger than the one in the endometrium, and it is also interesting that all the cases in the endometrium and the cervix involve only the endocervix, never the exocervix. We reviewed this issue and found out that most cases that have different histology showed different clonality in the endometrium and the cervix. Therefore we believe that some of these cases of stage 2 involving the cervix are two independent lesions. In this type of situation it is important to remember that immunohistochemistry is not going to help solve the problem because frequently cases that are independent in the endometrium and endocervix are of endometriod type and most probably related to hormones and not to HPV. Therefore, both, the tumor in the endometrium and the endocervix, even when they are histologically different, and have different clonality will have the immunoreation of endometriod tumors.

Endometrial Tissue within Vessels

As we mentioned before the presence endometrial tissue within vessels is very common in hysterectomies done by laparoscopic or robotic type of surgery. The reason why endometrial tissue is seen within vessels is because in order to be able to remove the uterus it is important to move the uterus forward, backward, and laterally using an interuterine device called the uterine manipulator. During the movement of the uterus the manipulator breaks the tumor in different small parts and during the grossing of the specimen the pathologist contaminate the vessels with fragments of tumor that are floating in the endometrial cavity. It is very important to be aware of this situation so different methods of grossing the specimens including cleaning first the endometrial cavity or cutting the uterus from the serosa to the mucosa rather than from the mucosa to the serosa will assure us that if the tumor is invasive it represents real invasion and not fragments of tumors that were carried over during grossing.

Papilary Lesions in the endometrium

Uterine Serous Carcinoma

This is an entity that has been described by Dr. Hendrickson and is probably the most common of the highly malignant types of uterine carcinoma. The diagnosis of papillary serous carcinoma is based on the presence of irregular papillae having a very irregular border, with cell attachments floating between papillary areas. The cells on the surface of the papillary projections have significant atypia and mitoses. Most papillary serous carcinomas are mixed with endometriod carcinoma. I believe there are three types of serous papillary carcinomas, 25% are pure serous carcinomas, 50% are mixed papillary serous carcinomas and endometriod carcinoma, and 25% of the cases are papillary serous carcinoma in endometrial polyps are usually not associated with endometroid carcinoma and they can be a very superficial lesion without infiltration of the stroma. In these cases it is very important to submit the entire fallopian tubes and ovaries for microscopic examination because these patients might have associated serous carcinoma in the epithelium of the fallopian tube or on the ovarian surface and therefore they are frequently seen in cases of surface papillary serous carcinoma of the peritoneum. The serous carcinoma in polyps', even without invasion of the stroma have a peritoneal recurrence rate of 10-40 or 50%.

Sometimes it is difficult to see foci of serous carcinoma in endometrial carcinoma endometroid type. It is important to look for areas of papillary serous carcinoma when an endometrial carcinoma endometriod type has areas with significant cytologic atypia. One of the variants of papillary serous carcinoma in, the endometrium which can be difficult to recognize is the glandular form of serous carcinoma characterized by glands lined by only one cell layer and the epithelial cells are composed of almost only nuclei. The treatment of papillary serous carcinoma of the endometrium with platinum has improved significantly the survival of these patients from 30% to 60%.

Clear Cell Carcinoma

Clear cell carcinoma is tumor characterized by four different histologic patterns very well defined including: papillary, glandular, solid, and microcystic. The papillary pattern is characteristic because it only has a hyaline core and the papillae are lined by only one cell layer of atypical cells. The glandular pattern has significant hob nails, the solid pattern has significant atypia, and the microcystic pattern is characterized by spaces that are larger than a gland but

frequently lined by flat cells separated from each other. It is very important to recognize these different patterns because frequently clear cell carcinoma does not have clear cells but oxiphilic cells. Clear cell carcinoma is a tumor of high grade; however, it is not as malignant as papillary serous carcinoma in low stage disease.

Another unusual type of carcinoma in the endometriod with clear cells is an endometriod carcinoma with clear cell changes or clear cell metaplasia. In the spectrum of carcinoma with clear cells most pathologists are familiar with secretory carcinoma on one end and clear cell carcinoma on the other end. Secretory carcinoma is a tumor with subnuclear vacuoles, very uniform, low grade, and with an excellent prognosis. On the other hand clear cell carcinoma is a very aggressive tumor. There is another group between these two extremes which is endometriod carcinoma clear cell changes. The clear vacuoles do not have a uniform distribution like in the secretory carcinoma, and the cells in the clear cell changes are similar to the cells in the areas of endometriod carcinoma without clear cell changes. This is a feature that distinguishes endometriod carcinoma with clear cell changes from clear cell carcinoma. In addition we do not see the patterns of clear cell carcinoma. One of the most difficult situations to recognize is when the clear cell changes are characterized by a large single vacuole or when the nuclei are in the luminal border of the cell.

Papillary Metaplasia

Papillary metaplasia is frequently seen in areas of hyperplasia and carcinoma in endometrium and the tumor cells are frequently detached creating a similar appearance to that of papillary serous carcinoma. The main difference is that it is extremely rare to see in papillary metaplasia mitotic figures or very prominent nucleoli.

Adenocarcinoma in the Cervix

It is important to discuss adenocarcinoma in the cervix in papillary lesions because frequently adenocarcinomas in the cervix are papillary and they might be confused with an endometrial tumor. In this situation immuno stains can help separating the endocervical adenocarcinoma from endometrial adenocarcinoma. Frequently papillary carcinomas from the endocervix

resemble papillary serous carcinoma, but this is usually seen on the superficial part of the tumor not in the deep glandular portion.

Papillary Endometriod Carcinoma

There are different opinions regarding these lesion, some pathologists diagnose them as villous glandular and other pathologists prefer the term tumor papillary endometriod. In my opinion there is a papillary endometriod carcinoma which usually characterized by papillae having a core of connective tissue and the cells in the papillary area are identical to those in areas that do not have papillary changes. Papillary endometriod carcinoma is usually an invasive lesion and in the areas of invasion frequently there are foci of fibrosis with inflammatory response simulating granulation tissue. Papillary endometriod carcinomas should be considered a grade two tumors because they are aggressive lesions with frequent vascular invasion and with a recurrence rate higher than endometriod carcinoma without papillary architecture. It appears that papillary endometriod carcinoma is more aggressive than grade 2 endometriod carcinoma. This is the reason why in papillary endometriod carcinoma it is important to perform lymph node resection.

Malignant Mixed Mullerian Tumor

There is no agreement in the literature whether these tumors represent really mixed mullerian tumors or if they are sarcomatoid carcinomas. This is an important issue for the treatment of the patient because the treatment of sarcomas with chemotherapy is different from the treatment with carcinoma. Most sarcomas are treated with adriamycin and ifosfamide while carcinomas are treated with platinum and taxol. Because of these reasons it is important to determine the amount of the sarcoma component in the invasive areas in the primary, in the recurrence, and in the metastases. Another important issue is that most malignant mixed mullerian tumors arise de novo and approximately 15% of the malignant mixed mullerian tumors are from adenosarcomas. In this latter situation the tumor usually behaves as a sarcoma.

Microsatalite Instability

A very common issue today is to request studies to determine if there is microsatilite instability in some endometrial carcinomas. This study should be requested in any patient younger than 50 years, in poorly differentiated carcinomas with abundant lymphocytes, carcinomas involving the lower uterine segment, and in patients with family history of ovarian, colon and breast cancer. The studies are usually done with immunohistochemisty and the normal cases will have a positive reaction in the nuclei and those cases are considered microsatilite stable. When they are microsatalite unstable the reaction is negative in the tumor cells. Internal controls should be included in all cases which is given by normal tissue. Most cases that have microsatalite instability are seen in patients younger than 50, are high grade tumor that have vascular invasion, and have frequent tumor infiltrating lymphocytes.

Micosatalite instability is important mainly in endometrioid carcinomas and not in serous, clear cell, and malignant mullerian tumors. There are several forth coming issues, one of them is if every patient with adenometrial carcinoma should be screened because apparently between 5 and 7 % of the cases occurs in patients that are over 50 years and having tumors involving parts of the uterine corpus and not the lower uterine segment.

The New FIGO Staging

The new FIGO staging has significant changes regarding endometrial adenocarcinoma. Stage I is considered IA when the tumor involves less than 50% of the myometrium, and IB when it involves more than 50% of the myometrium.

Stage II is a tumor involving endocervical stroma, the involvement of endocervical glands is still within stage I. Positive peritoneal cytology has been eliminated from a stage III and the rest of the staging system remains the same.