CALIFORNIA TUMOR TISSUE REGISTRY
EIGHTY-FOURTH SEMI-ANNUAL SLIDE SEMINAR
ON
GYNECOLOGICAL PATHOLOGY

MODERATORS:
HENRY J. NORRIS, M. D.
CHAIRMAN OF GYNECOLOGICAL AND BREAST PATHOLOGY
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CHIEF SURGICAL PATHOLOGIST
WOMEN'S HOSPITAL
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LOS ANGELES, CALIFORNIA

SUNDAY - DECEMBER 6, 1987
9:00 A.M. - 5:00 P.M.
REGISTRATION: 7:30 A.M.
RENAISSANCE HOTEL
SAN FRANCISCO, CALIFORNIA

Please bring your protocol, but do not bring slides or microscopes to the meeting.
CONTRIBUTOR: Robert J. Kurman, M. D.  
Washington, D. C.  
DECEMBER 1987 - CASE NO. 1

TISSUE FROM: Vulva  
ACCESSION NO. 26078

CLINICAL ABSTRACT:

A 33-year-old white woman presented with multiple warty growths on the vulva. The lesions were present for one year and had been treated topically. Because of persistence, 3 lesions were excised. Two of the 3 were in excess of 1 cm. in greatest dimension.

CONTRIBUTOR: Robert L. Berggren, M. D.  
Orange, California  
DECEMBER 1987 - CASE NO. 2

TISSUE FROM: Uterus  
ACCESSION NO. 25472

CLINICAL ABSTRACT:

A 69-year-old white female presented with an episode of postmenopausal bleeding. A curettage was performed which was reported as showing no abnormality. Bleeding, however, persisted and a hysterectomy was performed. Examination of the uterus revealed a papillary lesion of the endometrium approximately 6 cm. from the external cervical os. There were no lesions involving either the ecto or the endocervix.
An 86-year-old female presented with a large vulvar exophytic mass measuring 12 x 10 cm. that replaced the entire vulva. The tumor was highly irregular and verrucous in appearance measuring 4 cm. in greatest dimension.

A 46-year-old woman had a large mass of edematous tissue excised from the vagina. The lesion was submucosal and measured 11 x 7 x 2.5 cm. It was soft, uniformly edematous, pinkish and located mostly extrinsic and lateral to the vagina, involving the ischiorectal space and extending almost to the bladder.
CLINICAL ABSTRACT:

A 30-year-old nulligravida female presented with an abnormal Pap smear interpreted as showing moderate to severe dysplasia. Colposcopic directed biopsy revealed mild dysplasia only. Because of the discrepancy between the Pap smear and the colposcopic directed biopsy, a cervical cone biopsy was performed.

A 48-year-old woman, gravida 2, para 2, had intermittent vaginal spotting and discharge for 3 months. Her cervix was slightly irregular, but otherwise appeared normal. A cervical biopsy was performed.
CONTRIBUTOR: Henry J. Norris, M. D.  
Washington, D. C.  

DECEMBER 1987 - CASE NO. 7

TISSUE FROM: Cervix  
ACCESSION NO. 26083

CLINICAL ABSTRACT:

A 65-year-old woman presented with vaginal spotting. A small erosion was noted in the lower endocervical canal. A Pap smear was negative.

CONTRIBUTOR: James C. Roberts, M. D.  
Torrance, California  

DECEMBER 1987 - CASE NO. 8

TISSUE FROM: Uterus  
ACCESSION NO. 25204

CLINICAL ABSTRACT:

An 80-year-old gravida 2 para 2 woman presented with a history of vaginal bleeding of 5 months duration. An endometrial biopsy was performed, however, only necrotic tissue was obtained. The patient was admitted to the hospital where a chest x-ray was reported as normal. An IVP showed a 9 x 13 cm. mass in the pelvis and tomography revealed that this was a lobulated uterine mass. A hysterectomy was performed.
CONTRIBUTOR: Henry J. Norris, M. D.  
Washington, D. C. 

DECEMBER 1987 - CASE NO. 9

TISSUE FROM: Endometrium 
ACCESSION NO. 26084

CLINICAL ABSTRACT:

A 46-year-old woman presented with vaginal bleeding after 2 years of amenorrhea. On pelvic examination, the uterus was enlarged. An endometrial curettage was performed.

CONTRIBUTOR: Henry J. Norris, M. D.  
Washington, D. C. 

DECEMBER 1987 - CASE NO. 10

TISSUE FROM: Endometrium 
ACCESSION NO. 26109

CLINICAL ABSTRACT:

A 33-year-old woman presented with menometorrhagia of 3 months duration. On pelvic examination, the uterus was slightly enlarged, but no other abnormalities were noted. A endometrial curettage was performed.
CONTRIBUTOR: Robert J. Kurman, M. D.  
Washington, D. C.  
DECEMBER 1987 - CASE NO. 11

TISSUE FROM: Uterus  
ACCESSION NO. 26086

CLINICAL ABSTRACT:

A 23-year-old woman (gravida 3, para 2) was admitted with heavy vaginal bleeding. Her last menstrual period was 10 weeks prior to admission. A urinary pregnancy test was negative. An endometrial curettage was performed at which time perforation of the uterus occurred.

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CONTRIBUTOR: Robert J. Kurman, M. D.  
Washington, D. C.  
DECEMBER 1987 - CASE NO. 12

TISSUE FROM: Uterus  
ACCESSION NO. 26079

CLINICAL ABSTRACT:

A 26-year-old woman (gravida 2, para 1) presented with heavy bleeding and cramping at 12 weeks gestation. Pelvic examination revealed that the cervix was open. An endometrial curettage was performed.
CONTRIBUTOR: Gary N. Pesselnick, M. D.
Canoga Park, California

DECEMBER 1987 - CASE NO. 13

TISSUE FROM: Uterus

ACCESSION NO. 24534

CLINICAL ABSTRACT:

A 56-year-old woman underwent a curettage for abnormal bleeding. It was thought that the curettings represented a malignant tumor and consequently a hysterectomy and bilateral salpingo-oophorectomy were performed. On gross examination the uterus demonstrated multiple myometrial nodules ranging up to 2.5 cm. in diameter.

CONTRIBUTOR: Henry J. Norris, M. D.
Washington, D. C.

DECEMBER 1987 - CASE NO. 14

TISSUE FROM: Ovary

ACCESSION NO. 26110

CLINICAL ABSTRACT:

A 50-year-old woman, postmenopausal 2 years, was found to have an enlarged left ovary on routine pelvic examination. A sonogram revealed a cystic mass in the region of the left ovary. Eventually, a total abdominal hysterectomy and bilateral salpingo-oophorectomy was done for a 10 cm. cystic ovarian tumor. The neoplasm was encapsulated, and the inner surfaces of the cysts were shaggy and yellow. The cyst contents were mucoid.
CONTRIBUTOR: Robert J. Kurman, M. D.  DECEMBER 1987 - CASE NO. 15
Washington, D. C.

TISSUE FROM: Ovary  ACCESSION NO. 26108

CLINICAL ABSTRACT:

A 46-year-old woman was found to have a unilateral adnexal mass. At operation, the ovary contained a firm, partly cystic neoplasm. No other abnormalities were evident at operation.

CONTRIBUTOR: Henry J. Norris, M. D.  DECEMBER 1987 - CASE NO. 16
Washington, D. C.

TISSUE FROM: Ovary  ACCESSION NO. 26085

CLINICAL ABSTRACT:

This 63-year-old woman with a large left adnexal mass was explored and found to have a 15 x 11 x 7 cm. partly ruptured ovarian tumor. The neoplasm was mainly solid and focally hemorrhagic. The cut surface was nodular and smooth except for a few small 1 cm. cysts and a 5 cm. cyst.
CLINICAL ABSTRACT:

An 8-year-old girl presented with lower abdominal pain and a flu-like syndrome. Examination revealed a left lower abdominal mass confirmed by ultrasound. At laparotomy, a large left ovarian mass was found. The remainder of the peritoneal surfaces were clear. Blood, drawn at the time of surgery, showed elevated AFP and beta hCG levels. The tumor was morselated during removal. The largest fragment of tumor was 10 cm. in diameter. Reconstruction of the tumor revealed a lobulated, focally hemorrhagic friable tumor admixed with slightly firmer, fleshy tissue and foci of yellowish infarction.

CLINICAL ABSTRACT:

A 28-year-old woman was found to have a pelvic mass on routine gynecologic examination. At exploration, the right ovary was replaced by an encapsulated 15 x 9 x 5 cm. tumor weighing 289 grams. Although mostly solid, it was partly cystic, friable, mucoid, and variable in color.
CONTRIBUTOR:  Henry J. Norris, M. D.  
Washington, D. C.  
DECEMBER 1987 - CASE NO. 19

TISSUE FROM: Ovary  
ACCESSION NO. 26089

CLINICAL ABSTRACT:

This case was received with the pathology report describing neoplasms in both ovaries measuring 9 cm. in greatest dimension, occurring in a 69-year-old woman. Both neoplasms were similar, being within the substance of the ovary. Both were brownish with areas of sclerotic tissue, focal hemorrhage small cysts and a few gelatinous areas on cut surface. Subsequently, we learned that the patient had seen a physician because of a sensation of abdominal fullness. A sonogram had revealed a mass in the region of the right ovary, and at operation only the ovaries were removed because they contained cystic enlargements. The uterus was small and a hysterectomy was not performed.

CONTRIBUTOR: Wafa Michael, M. D.  
Fontana, California  
DECEMBER 1987 - CASE NO. 20

TISSUE FROM: Ovary  
ACCESSION NO. 26020

CLINICAL ABSTRACT:

This 50-year-old G7P7 woman had complaints of lower abdominal discomfort, pain on defecation and dyspareunia. An adnexal mass approximately 10 cm. in diameter was palpated on pelvic examination. At surgery, and 11 x 10 x 7.5 cm., 365 grams mass was observed replacing the right ovary. A hysterectomy was performed.
A 59-year-old woman was seen with abdominal discomfort and distention. Pelvic examination revealed a mass in the region of the right ovary, confirmed by sonograms. A total abdominal hysterectomy and bilateral salpingo-oophorectomy was done. A 19 cm., partly cystic, gray-white, encapsulated tumor replaced the right ovary. The cyst lining was gray-yellow and shaggy.
ADDENDA

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WASHINGTON, D. C.

DEDICATED TO:

WELDON K. BULLOCK, M. D.
EXECUTIVE DIRECTOR
CALIFORNIA TUMOR TISSUE REGISTRY

CHAIRMAN:

GERRIT D'ABLAING, M. D.
CHIEF SURGICAL PATHOLOGIST
WOMEN'S HOSPITAL
LAC-USC MEDICAL CENTER
LOS ANGELES, CALIFORNIA

SUNDAY, DECEMBER 6, 1987
RAMADA RENAISSANCE
SAN FRANCISCO, CALIFORNIA
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Case #1 Vulvar Intraepithelial Neoplasia (Bowen's disease, Carcinoma in situ, Bowenoid dysplasia, Bowenoid papulosis) (Acc. #26078)

A wide variety of terms have been used to classify intraepithelial neoplasms of the vulva. The current terminology proposed by the International Society for the Study of Vulvar Disease and the International Society of Gynecological Pathologists in conjunction with the World Health Organization is either vulvar intraepithelial neoplasia (VIN) graded I, II or III or dysplasia (mild, moderate, and severe) and carcinoma in situ. When these lesions present clinically as papules the term "bowenoid papulosis" has been used but since they are histologically indistinguishable from other forms of intraepithelial neoplasia (1,2) this term is not recognized by these organizations.

VIN presents clinically as macular or papular lesions that can be single but typically are multiple. They can be gray, red or white but are frequently pigmented and in fact represent one of the most common pigmented lesions on the vulva. Patients range in age from 25-35 years and frequently have neoplasia elsewhere in the genital tract, typically the cervix (3)).

Microscopically, VIN is characterized by a thickened epithelium displaying abnormal maturation. Cellular atypia is usually marked as is mitotic activity. Abnormal mitoses abound and these lesions are frequently aneuploid. Koilocytosis may occur but is often not evident. VIN frequently is associated with and merges into typical condylomas. When the cellular abnormalities are confined for the most part to the lower one third of the epithelium the lesion is classified as VIN I whereas full or nearly full-thickness involvement is classified as VIN III. Intermediate degrees of involvement qualify as VIN II. Usually, lesions present as VIN III. The process may involve underlying sebaceous glands and frequently involved rete pegs extend deeply into the stroma simulating invasion. This, however, should not be confused with invasion since treatment is drastically different.

HPV 16 has been the most frequent HPV type associated with VIN (4) but in addition HPVs 1, 6, and 35 have also been identified (3). In the present case HPV 16 was identified within the lesion by in situ hybridization with RNA probes (Dr. Mark Stoler, University of Rochester). Nearly one half of patients have a history of previous condylomas. Progression is relatively rare occurring in approximately 6% of patients (3). This data is difficult to interpret, however, since most patients are treated by wide local excision and hence the "natural history" of this disease is unknown. Older women and those who are immunosuppressed
are at greatest risk of progression (5). Invasion is rarely associated with VIN and tends to occur more frequently in postmenopausal women (6). Spontaneous regression occurs in approximately 6% of women, mostly young women and pregnant patients (7).

The differential diagnosis includes malignant melanoma and Paget's disease. Immunohistochemistry can assist in the distinction. Paget's cells are positive for CEA whereas melanoma cells are reactive for S-100 and melanoma specific antigen. VIN is negative for all of these markers.

The vast majority of these lesions can be treated by wide local excision. For extensive lesions laser treatment or skinning vulvectomy may be necessary.
REFERENCES


Case #2 Verrucous Carcinoma of the Endometrium with underlying Squamous Carcinoma (Acc. #25472)

For a more detailed discussion of verrucous carcinoma of the female genital tract see below (Case #3). Twenty one cases of primary squamous carcinoma of the endometrium fulfilling the criteria of Fluhmann have been reported. The criteria are: (1) adenocarcinoma is not present in the endometrium; (2) the squamous carcinoma of the endometrium has no connection with the squamous epithelium of the cervix; (3) squamous carcinoma is not present in the cervix. One case of verrucous carcinoma of the endometrium has been reported (1) that fulfills these criteria. As in the present case atypical endometrial glands were present at the base of the tumor suggesting that the neoplasm arose by a process of metaplasia and malignant transformation from glandular epithelium or directly from reserve cells. Analysis for HPV was not performed. Unlike the patients with squamous carcinoma of the endometrium, the woman with verrucous carcinoma has survived for over 5 years without evidence of disease.

Typically, the pattern of invasion of verrucous carcinoma is characterized by large bulbous masses of squamous epithelium with minimal cytologic atypia that advance with a pushing margin. Although this type of invasion is present in this case, in addition, there are nests of neoplastic squamous epithelium invading the stroma in a fashion similar to well differentiated squamous carcinoma.

In the present case in situ hybridization utilizing RNA probes for HPV 6,11,31,16, and 18 failed to detect HPV in the tumor (Mark Stoler, M.D., University of Rochester). See Case #3 for further discussion of the role of HPV in verrucous carcinoma. Finally, HPV has now been identified by Southern blot hybridization in a wide variety of carcinomas outside of the lower genital tract (Table 1).
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<td>Anorectal</td>
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TABLE 1

HPV IN VARIOUS TYPES OF CANCER

de Villiers, E-M
Sixth International Papillomavirus Workshop
Most authorities regard the tumor termed "giant condyloma acuminatum" or "Buschke-Lowenstein tumor" as synonymous with verrucous carcinoma. The latter term was proposed by Ackerman (1) to describe a distinct variant of squamous carcinoma in the oral cavity that frequently recurred but rarely metastasized. Subsequently, this neoplasm was reported in a variety of locations including the female genital tract. In that location the vulva, vagina, cervix and endometrium (See Case #2) have been involved. The tumor is exophytic, solitary and on gross examination closely resembles a condyloma acuminatum except for its large size.

Microscopically, verrucous carcinoma consists of large rounded masses of neoplastic squamous epithelium with minimal cytologic atypia that characteristically invades in a "pushing" fashion, rarely displaying destructive infiltration. This feature distinguishes verrucous carcinoma from well-differentiated squamous carcinoma, a neoplasm that has greater metastatic potential. Verrucous carcinoma is distinguished from condyloma acuminatum by the absence of a central fibrovascular tissue support in the papillary processes.

Since the tumor rarely metastasizes it is usually amenable to wide local excision. Occasionally, verrucous carcinoma may behave in an aggressive fashion particularly if the tumor has been irradiated (2). In these instances verrucous carcinoma becomes converted to a poorly differentiated rapidly metastasizing squamous carcinoma. An example of a verrucous carcinoma with a "sarcomatoid" appearance has been reported (3) but I am not aware of a spindle cell carcinoma associated with a verrucous carcinoma.

The etiology of verrucous carcinoma is not known, however, there is evidence implicating human papillomaviruses. HPV 6 has been detected in the vast majority of condylomas and HPV 16 in invasive carcinoma of the vulva. HPV 6 has been reported in verrucous carcinoma (4) but was not identified in the present case using in situ HPV RNA probes for HPV 6,11,31,16,18 (Mark Stoler, M.D. University of Rochester). Recently a unique variant of HPV 6 termed HPV6c was reported in a highly aggressive locally invasive verrucous carcinoma (5). For a discussion of the methods by which HPVs are typed and subtyped see below (Case #5). Structural analysis of the HPV 6 DNA showed a high degree of sequence homology and genetic organization between HPV6c and the different HPV 6 types. Only one region of variation was observed and that was in the noncoding region of the viral
genome. This noncoding region contains the putative viral origin of replication and elements promoting expression of early viral proteins that may be associated with cell transformation. This variant HPV 6 subtype may therefore offer a possible explanation of why verrucous carcinoma, although it shares many histologic features with the typical condyloma, behaves in an intermediate fashion between a benign genital wart and a typical invasive squamous carcinoma of the vulva.
REFERENCES


Case 4. Aggressive angiomyxoma (Acc. #26081)

Since the initial series of 13 cases in 1983, another 13 cases have been reported. The patients range in age from 18 to 63 years, with a mean age of 34. Two men have developed the problem; all the others were women. The lesion characteristically involves the region of the Bartholin's gland, but vulva, vagina, perineum, pelvis and perianal regions tend to be involved and may be the site of origin. Characteristically a slowly growing polypoid mass, recurrences are common, attributed to incomplete excision. Recurrences usually have taken 2 years, but most take longer and some have not reappeared for 10 or more years.

The lesion is similar to an angiofibroma with more myxoid change in the stroma. The vessels characteristically appear in clusters or groups, and medial hypertrophy is common. Ultrastructural analysis confirms the fibroblastic or myofibroblastic nature of the cells.

The differential diagnosis involves myxoma, myxoid lipoma and liposarcoma, neurofibroma, neurilemmoma, and myxoid variants of fibrous histiocytoma and leiomyoma. Sarcoma botryoides is not a serious consideration because it occurs in younger women and has a cambium layer of cells. A vulvar or vaginal polyp is not a concern because those are mucosal or superficial lesions that protrude intraluminally, rather than infiltrate deeply like an angiomyxoma. Malignant fibrous histiocytoma has a myxoid variant, but the greater cellularity, nuclear atypia, and mitotic activity are unlike AA. Postoperative pseudosarcoma (spindle cell tumor) tends to have a history of recent operation, appear in the region of incisions, and be associated with pregnancy.

The most serious diagnostic considerations are myxoid neurofibroma and neurilemmoma, but they lack the prominent vessels of an angiomyxoma and are S-100 positive in most instances. A classic myxoma tends to occur in older women. These are intramuscular and lack the cellularity seen in angiomyxomas. Also, myxomas have fewer blood vessels. Myxomas seldom recur, whereas most angiomyxomas do recur. Myxoid lipoma is a diagnostic consideration, but will have transitional zones between myxoid areas and mature fat. The best discussion of the differential diagnosis is in the initial report by Steeper and Rosai, although Begin et al have a fine report in 1985.

References:

December 6, 1987

Case #5 Cervical Intraepithelial Neoplasia III (Carcinoma in situ) - (Acc. #26082)

In the last seven years mounting evidence has associated human papillomaviruses with cervical neoplasia. In this case HPV 31 was identified by in situ hybridization with RNA probes directly within the lesion (Mark Stoler, M.D., University of Rochester). It is therefore important to discuss the relationship of HPV to cervical intraepithelial and invasive neoplasia.

Papillomaviruses are classified as genus A in the family papovaviridae. HPV particles are about 55 mm in diameter according to electron microscopic measurements and HPV has a major capsid protein with a molecular weight of 54,000 to 63,000 daltons. The viral genome exists as a double-stranded superhelical DNA molecule enclosed within the capsid.

For classification of a virus as a new type of HPV, a maximum of 50 percent polynucleotide sequence homology with other classified viruses should exist, in conjunction with significant serologic deviations in reciprocal assays. Viruses with DNA homology of greater than 50 percent but less than 100 percent are subtypes. To date, over 50 HPV types have been identified and of these nearly a third involve the genital tract.

There are four methods by which HPV infection can be detected: 1) koilocytotic atypia (1), 2) immunoperoxidase localization of HPV capsid protein (2), 3) electron microscopy (3), and 4) molecular hybridization (4,5). It is not entirely clear as to whether koilocytosis is specific for HPV infection but nonetheless it is a very useful marker of HPV infection in microscopic sections and cytological smears. The antibody used to identify papillomavirus capsid protein recognizes a genus specific antigen that is present on the internal surface of the capsid. This protein is shared among all types of papillomaviruses both in humans and in a wide variety of animals (6). A positive reaction with the antibody indicates that permissive infection is present in the cell with assembly of infectious viral particles (1,2). Electron microscopy also identifies assembled virus but it is only half as sensitive as immunocytochemistry in identifying virions (3). It should be emphasized that viral DNA may be present in a lesion that does not express the structural protein and consequently the immunoperoxidase reaction and electron microscopy will be negative. Molecular hybridization for papillomavirus DNA sequences, however, is positive.

It has been shown that HPV infection begins in the basal layer of the epithelium, although no changes are evident by light
microscopy. Viral DNA replication occurs in proliferating basal cells, but structural capsid proteins are not detected. It has therefore been speculated that basal cell proliferation is due to early gene function, resulting from the synthesis of nonstructural viral proteins that may have a stimulatory or reverse repressive effect on the control of host cellular proliferation (4,7). Immediately above the proliferating basal layer the cells begin to mature and differentiate and the cytoplasm becomes more abundant and eosinophillic, indicative of keratin synthesis. Late gene expression, manifested by the production of viral structural proteins, is detected in these cells as nuclear staining for HPV capsid antigen by immunocytochemical techniques (2). As viral assembly ensues in the terminally differentiated squamous epithelial cells the latter degenerate and the classic cytopathic effect, koilocytotic atypia, is observed (1,2,8-11).

To appreciate the role of HPV in cervical neoplasia, it is important to understand the pathology, epidemiology and behavior of premalignant lesions of the cervix in the light of recent developments in our understanding of HPV infection. Dysplasia is defined as a disturbance of differentiation of the squamous epithelium, differing from carcinoma in situ (CIS) in that CIS is a full thickness proliferation of atypical cells showing no differentiation. The concept of cervical intraepithelial neoplasia (CIN) was introduced to emphasize the continuum of the preinvasive process and to facilitate management. The more advanced lesions tend to persist or progress, whereas the milder lesions have a greater tendency to regress. Only half of CIN 3 is thought to progress if untreated. It is estimated that only about 10 to 15 percent of the mild lesions progress. DNA microspectrophotometry has indicated that diploid or polyploid lesions usually regress; aneuploid lesions tend to persist or progress. Aneuploidy is best correlated in routine microscopic sections by abnormal mitotic figures.

Molecular studies have revealed the presence of multiple HPV types in 80 to 90 percent of CIN invasive squamous carcinoma but the distribution differs (Table 2) (5,12). HPV 16 and 18 comprise nearly three-quarters of all HPV types found in invasive cancer but account for a much lower proportion of CIN (5). A large number of HPV types can be identified both in normal metaplastic squamous epithelium of the cervix and in low-grade CIN (5,13). In fact, 10 to 20 percent of women with normal Pap smears may have HPV-DNA demonstrated by molecular hybridization (14) indicating latent viral infection (15). As the grade of the CIN increases the distribution of HPV types becomes more homogeneous such that nearly all CIN 3 lesions containing HPV DNA sequences contain HPV 16. Although viral DNA is carried as an episome in CIN lesions, integration occurs in invasive neoplasms. Moreover, viral DNA sequences are typically integrated in the E1 and E2
### DISTRIBUTION OF HPV TYPES IN THE GENITAL TRACT

<table>
<thead>
<tr>
<th>Lesion</th>
<th>HPV Frequently Associated</th>
<th>HPV Rarely Associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condyloma</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>31</td>
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<tr>
<td>VIN</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>CIN</td>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td></td>
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<tr>
<td></td>
<td>11</td>
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<td>39</td>
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<tr>
<td></td>
<td>44</td>
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<tr>
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<td>16</td>
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<tr>
<td>Cancer</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>45</td>
</tr>
</tbody>
</table>

*de Villiers, E-M
Sixth International Papillomavirus Workshop*
opening reading frame but at random sites in the host cell DNA. Viral transcripts (mRNA) covering the E6 and E7 open reading frames are expressed in the cancers.

The terminology of cervical intraepithelial lesions until recently has undergone little modification as both the dysplasia-CIS and CIN classification have been adopted. The recognition of the cytologic similarity between benign exophytic condylomas and the milder degrees of CIN led to the introduction of the term flat condyloma and, subsequently, atypical condyloma, the latter corresponding to high grade dysplasia with morphologic evidence of HPV. Implicit in the use of the term flat condyloma is the view that it is a benign viral lesion that is fundamentally different and can be reliably distinguished from true dysplasia; i.e., a malignant lesion. This dichotomy creates an irreconcilable dilemma in classification, a taxonomic "Catch-22". First, it is clear that most CIN lesions are "viral" as evidenced by molecular hybridization studies identifying HPV DNA sequences in approximately 90 percent of all grades of CIN and invasive cancer. Second, high-risk HPV types (HPV 16 and 18), that are present in invasive cancer, have been identified in mild as well as in high grade CIN. Third, it is often difficult to distinguish neoplastic cellular alterations from the virus-induced proliferation and cytopathic effect. Fourth, it is not possible for the pathologist to confidently identify malignant transformation morphologically until invasion of the underlying tissue has occurred.

In summary, it is clear that the relation between HPV infection and cervical neoplasia is more complex than initially realized. Molecular virologic data indicate a preferential distribution of low and high risk HPV types in CIN that tends to correlate with the morphologic appearance. Thus, mild and moderate dysplasia (CIN 1 and 2) contain a diverse distribution of HPV types, including a minority that have a high risk of malignant potential. Since HPV is present in a nonintegrated form in CIN and is integrated in cervical cancer it appears that integration may play a role in malignant transformation. In addition, neoplastic transformation is probably determined by specific HPV types and requires other factors; e.g., HSV 2 infection, cigarette smoking, genetic predisposition, etc.

Despite numerous studies performed during the past 30 years, the long term behavior of dysplasia remains uncertain. The natural history of HPV associated lesions is unknown. Until this information is available, it is recommended that the conventional dysplasia-CIS or CIN nomenclature be used. The presence of associated viral changes can be added to the diagnosis; e.g., "moderate dysplasia (CIN 2) with evidence of papillomavirus infection." Treatment should be the same for all intraepithelial lesions regardless of the presence of HPV.
REFERENCES


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14. Lorincz, A; Temple, GF; Patterson, JA; Jenson, AB; Kurman, RJ; Lancaster, WD. Correlation of cellular atypia and HPV DNA sequences in exfoliated cells of the uterine cervix. Obstet Gynecol 68: 508-12, 1986.

Adenocarcinoma of the cervix is attracting more attention than formerly because it is assuming a more important proportion of invasive carcinomas of the cervix. Adenocarcinoma is untouched by cervical screening programs, whereas invasive squamous carcinoma is dramatically reduced by identification, treatment and elimination precursors. Thus, the proportion of invasive carcinomas of the cervix that are glandular has increased to the point that we must focus more attention to it. Adenocarcinoma is 13% of invasive carcinomas of the cervix at the Univ. California San Diego, 17% at the University of Michigan Hospital, Ann Arbor, and 25% at Walter Reed Army Medical Center. Whether there has been an absolute increase in incidence is not settled. In Mannheim, Germany, the increase in adenocarcinoma and in-situ adenocarcinoma has been found largely in oral contraceptive users taking the high dose progestin combinations. A few adenocarcinomas have contained HPV 16 and 18, but too few cases have been reported to form an association.

Patients with adenocarcinoma of the cervix do not have the same clinical profile as those with squamous carcinoma. The patients are usually older (55 versus 48), better off socio-economically, and lack the venereal associations of patients with squamous carcinoma. Nuns, virgins and patients in a higher socio-economic status are more likely to have the glandular form of carcinoma of the cervix. Bleeding and a profuse discharge are the two main symptoms.

Since an exocervical scrape is not effective in detecting adenocarcinoma of the cervix, a technique like the cytobrush should be a routine part of the pelvic examination. At present, the cost of the additional study is prohibitive, but when the cost of the brushes or other forms of sampling are reduced to about 15 cents per smear, mass screening programs can include it. An endocervical curettage as a routine is not practical.

The common types of adenocarcinoma of the cervix are endometrioid (40%), mucinous (23%), mixed (26%), adenosquamous (13%) and clear cell (8%). The other types of adenocarcinoma are more rare. (A mixed type is one in which 2 or more cell types are in equal proportion). The survival of patients with this disease is based on the interaction of prognostic factors such as stage, grade and size of tumor. About 15% have no visible lesion as the carcinoma is within the endocervical canal and infiltrative without ulceration or the usual polypoid mass. If the depth of invasion is less than 5 mm, at least 90% are cured. If the tumor is 3 cm in diameter, half of the patients have metastases. The survival is about 76% in stage 1b at 5 years and 49% in stage 11b. Therapy is unsuccessful for metastases, but otherwise adenocarcinoma is approached like squamous carcinoma in the same stage and has about the same prognosis.
Distinguishing a primary adenocarcinoma of the cervix from an endometrial primary carcinoma may not be possible, but about 80% of cervical adenocarcinomas are CEA positive, whereas only 15 to 20% of endometrial carcinomas are. Mucin stains may also help in the distinction. Since 43% of cervical adenocarcinomas also contain an overlying CIN, its presence also helps to detect some adenocarcinomas.

References


Case 6. Minimal deviation carcinoma of the cervix. (Acc. #25664)

Minimal deviation carcinoma of the cervix (MDC) is very rare, representing about 1% of adenocarcinomas of the cervix and less than one-fifth of well differentiated cervical carcinomas. The criteria for diagnosis are simple. The glands are uniform, but extend irregularly or too deeply for normal endocervical glands. If the extension is more than half-way through the thickness of the cervix, MDC is likely. Cytological atypia excludes the diagnosis. Claw-shapes, slit-shapes, a desmoplastic response, a single layer of cells and lack of orientation of the glands occur. Identification is based on (1) irregular gland shapes, (2) irregular deep margin, (3) variation in the size, shape and type of cells, (4) increased mitotic activity and (5) hyperplastic appearance of the glands at the surface. Michael, et al found that most benign endocervical proliferations lacked CEA, but that adenocarcinoma, including MDC contained it, suggesting that CEA helps to identify early malignancy and MDC. Hysterectomy is usually necessary to produce a sufficiently deep margin to permit identification of invasion.

MDC grows slowly. The two patients in our series of 13 cases who died of cervical adenocarcinoma did so 6 and 14 years after initial diagnosis and treatment. The 13 cases differed from those previously reported in that the cell types were more varied (most cases in the literature are of a mucinous cell type), the carcinomas were identified at earlier stages, and the survival of patients was much better than in earlier reports. An association with independent ovarian neoplasms was also found.

The name "minimal deviation carcinoma" was proposed by Silverberg and Hurt in 1975. Like others, they found that pap smears are sometimes helpful as cells may be arranged in a monolayer or in sheets, mitotic activity may be increased in the cells in smears, and at times a few rare clusters of malignant cells may be identified. This neoplasm is associated with ovarian neoplasms such as Sertoli (SCAT) tumor, mucinous cystadenoma, endometrioid carcinoma and the Peutz-Jeghers syndrome.
References:


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Case 7. Basaloid carcinoma (adenoid basal carcinoma) of cervix. (Acc. #26083)

Adenoid cystic carcinoma (ACC) is rare, representing about 1% of cervical adenocarcinomas. Reports have tended to include a carcinoma with a basaloid pattern (similar to this case) in which gland lumens are inconspicuous and basal cells surround squamous nests. Although only one report of pure basaloid carcinoma exists, the pattern overlaps with adenoid cystic carcinoma to the degree that they will be discussed together. Dinh and Woodruff refer to this pattern as an "adenoid basal carcinoma". Basaloid carcinoma should not be confused with carcinoid (endocrine carcinoma) or small cell carcinoma of the cervix and it should be separated from ACC whenever possible because ACC is more aggressive.

Occurring in old women, ACC of the cervix is usually found in Blacks or Asians. About 100 cases have been reported. The main age is usually in the 60's. As in most adenocarcinomas of the cervix, the main symptom is bleeding, and early stages are the rule. Papanicolaou smears usually are only suspicious or atypical. Grossly, the tumor is usually hard, polypoid and more deeply invasive than expected. An associated in situ component, often with squamous differentiation, is evident in half of patients. The prognosis for ACC is about the same or better than ordinary squamous or adenocarcinoma of the same stage, although the early literature of ACC tends to suggest a bad prognosis.

Basaloid carcinoma (adenoid basal carcinoma) also tends to occur in old women, cause no symptoms, and infiltrate relatively widely in the cervix even though it has a favorable prognosis with conservative surgery. The best description is by Daroca and Dhurandhar. If one accepts the 12 cases in the literature at face value, none of the 12 have died of tumor and none have been staged higher than Ia (a visible lesion apparently confined to the cervix but invading more than 3mm). Hysterectomy should be curative.

Reference


Mixed mesodermal tumors are the most common sarcoma arising in the uterus but constitute less than 2% of all uterine malignancies (1,2). Mixed mesodermal tumors are composed of carcinoma and sarcoma and are classified as homologous or heterologous depending on the histologic characteristics of the sarcomatous element. If the sarcomatous element is composed of cells normally found in the uterus the neoplasm is considered a homologous tumor and is termed "carcinosarcoma". If the sarcomatous component contains cells that are not normally present in the uterus such as bone, cartilage, or striated muscle, the tumor is considered a heterologous neoplasm and is classified as "malignant mixed mesodermal tumor" or simply "mixed mesodermal tumor" (MMT). Pure heterologous sarcomas such as osteosarcoma, chondrosarcoma, angiosarcoma and rhabdomyosarcoma are very rare in the uterus (3-8). MMTs typically display a heterogeneous composition of carcinomatous and sarcomatous elements. Either one of these components may represent an extremely small proportion of the tumor and may therefore be overlooked unless the entire neoplasm has been thoroughly sampled. Reports of "pure" heterologous tumors must therefore be viewed with this in mind.

Approximately 40 cases of pure rhabdomyosarcoma have been reported in the uterus (3-6). In the past, these have been regarded as variants of MMTs displaying monomorphic differentiation into rhabdomyoblasts. Review of published cases comparing their behavior to MMTs and analysis of recent immunohistochemical studies, however, reveals that these tumors are distinctly different. Rhabdomyosarcomas are highly aggressive tumors and even when confined to the uterus the vast majority of patients that have been reported died within one year of diagnosis and treatment. In contrast, although the survival of patients with MMTs confined to the uterus is only 20-40%, for tumors that are limited to the endometrium or invading into the inner third of the myometrium, the prognosis is excellent (9,10). Furthermore, the histologic appearance of the metastases of pure rhabdomyosarcoma and other pure heterologous sarcomas such as chondrosarcoma (7) is the same as that of the primary tumor. In contrast, it has been our experience that the metastases of MMTs are always carcinoma, suggesting that the tumor behaves as a poorly differentiated carcinoma (11). In fact, the survival of patients with MMTs when stratified according to the depth of myometrial invasion is similar to that of women with poorly differentiated carcinoma.
Immunohistochemical analysis of the present case revealed that almost all of the neoplastic cells showed a positive reaction for muscle specific actin (MSA). A small population of undifferentiated cells failed to react with MSA and three different broadly reactive monoclonal antibodies against cytokeratins suggesting that the rhabdomyoblasts differentiated from a primitive totipotential mesenchymal cell present in the endometrium and myometrium. On the other hand, the histogenesis of MMTs is more controversial. The major issue is whether these tumors are composed of true sarcoma and carcinoma or whether they represent a type of metaplastic carcinoma. Electron microscopic studies have traced the development of rhabdomyoblasts and chondroid cells from undifferentiated mesenchymal cells (12,13). In addition, we have completed an immunohistochemical analysis in which we used four monoclonal antibodies to detect epithelial lineage, three that recognize cytokeratins (AE1/AE3, Cam 5.2, MAK6) and one that recognizes epithelial membrane antigen (EMA). Keratin and EMA were identified in the epithelial component in all cases and in 92% of the cases in the mesenchymal component. In the latter, keratin and EMA reactivity occurred in scattered individual cells, clusters of cells, and small glands with barely discernable lumens. The latter had not been noted on earlier H&E examination. Vimentin was identified in 60% of the cases in the epithelial component and in 75% of the cases in the mesenchymal component. The findings suggest that epithelial differentiation as well as sarcomatous differentiation develops from proliferating primitive totipotential mesenchymal cells. Since the metastases were always carcinoma it appears that it is the epithelial component of these neoplasms that determines their behavior. These data support the view that MMTs are a form of metaplastic carcinoma.

Clinically, women with rhabdomyosarcomas, like MMTs, are usually postmenopausal (mean age; 65 years) and present with bleeding. The uterus is almost invariably enlarged and often the tumor prolapses through the cervical os (3,9).

On gross examination rhabdomyosarcomas, like MMTs, are large polypoid tumors that fill the endometrial cavity. On cut section they are soft and tan with areas of hemorrhage and necrosis.

Microscopically, rhabdomyosarcoma of the pleomorphic type is composed of spindle-shaped cells, rounded or racquet-shaped cells with abundant eosinophilic cytoplasm as well as strap cells. Cross striations are readily identified in most cases. The pleomorphic rhabdomyosarcoma should be distinguished from the embryonal rhabdomyosarcoma or sarcoma botryoides, a tumor that usually occurs in much younger women. The embryonal rhabdomyosarcoma has an edematous appearance and is composed of small primitive spindle cells that form a compact zone, the so-called cambium layer, beneath the surface epithelium. Rhabdomyoblasts are scattered throughout the edematous stroma.
The behavior of embryonal rhabdomyosarcoma appears to be better than the pleomorphic rhabdomyosarcoma. Unlike the latter, patients appear to benefit from combination chemotherapy. A few cases of long term survival and cure have been reported. Total abdominal hysterectomy and bilateral salpingo oophorectomy is the treatment for stage I pleomorphic rhabdomyosarcoma. It is clear that some form of adjuvant systemic chemotherapy is needed in view of the poor survival for patients with even localized disease, however, there are no active agents at the present time.
REFERENCES


Case 9. Atypical Endometrial Hyperplasia (Acc. #26084)

Atypical hyperplasia is characterized by an increase in the number of endometrial glands lined by cells displaying cytologic atypia. Enlarged cells that show loss of polarity and an increase in the nuclear cytoplasmic ratio are considered atypical. Nuclei are enlarged, irregular in size and shape, have a thickened nuclear membrane, coarse chromatin clumping and prominent nucleoli. They tend to be round as compared to the oval nuclei of proliferative endometrium and simple and complex hyperplasia. As a result, the nuclei often have a cleared or vesicular appearance despite peripherally clumped chromatin. The glands may be relatively simple and separated by fairly abundant stroma or have irregular outlines and demonstrate marked structural complexity and back-to-back crowding.

Atypical hyperplasia must be distinguished from well-differentiated carcinoma. A diagnosis of well-differentiated carcinoma is established easily when there is myometrial invasion or when the tumor is moderately or poorly differentiated, but well differentiated carcinomas and those lacking myometrial invasion in curettings may be difficult to identify because 60% of endometrial carcinomas are diploid and lack hyperchromatism. Atypical hyperplasia, however, can be separated from well-differentiated adenocarcinoma if arbitrary criteria are used to reduce the subjectivity of the appraisal. The stroma interacts with invasive carcinoma and the morphologic changes it undergoes can serve as a means of identifying carcinoma. The stroma interacts with invasive carcinoma and the morphologic changes it undergoes can serve as a means of identifying carcinoma. The stromal and epithelial alterations associated with invasive carcinoma are referred to collectively as "endometrial stromal invasion". There are four criteria, any of which identifies stromal invasion: 1) an irregular infiltration of glands associated with an altered fibroblastic stroma (desmoplastic response); 2) a confluent glandular pattern in which individual glands, uninterrupted by stroma, merge and create a cribriform pattern; 3) an extensive papillary pattern; and 4) replacement of the stroma by masses of squamous epithelium. A process manifesting the features of invasion must be sufficiently extensive to involve half (2.1mm) of a low-power field 4.2mm in diameter or it will not have value in predicting the presence of a biologically significant carcinoma in the uterus.

Increasing degrees of nuclear atypia, mitotic activity, necrosis and stratification of cells in curettings are associated with a higher frequency of carcinoma in the uterus, but are of limited value because even a mild degree of these changes is associated with carcinoma in nearly one-third of cases. Even with mild atypia, low mitotic activity and lesser degrees of stratification in curettings, when the uterus is removed, 20% of residual carcinomas are moderately or poorly differentiated and 10% deeply invade the myometrium. In contrast, when stromal invasion is absent in curettings, carcinoma is found in the uterus in only 17% of cases, and all the carcinomas are well-differentiated and either confined to the endometrium or only superficially invasive (Table 1).
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If stromal invasion is present in curettings, residual carcinoma is found in the uterus in half; more than one-third of the carcinomas are moderately or poorly differentiated, and a fourth of them invade deeply into the myometrium (Table 2). A small proportion (7%) of these patients will have extraterine metastases at hysterectomy and half with metastasis will die of tumor. Thus, the absence of stromal invasion provides the basis for distinguishing atypical hyperplasia from a biologically significant well-differentiated carcinoma.

Endometrial proliferations without evidence of invasion constitute a group of heterogeneous lesions of differing biologic potential displaying a continuum of cytologic and architectural alterations. Recently, 170 patients with all grades of endometrial hyperplasia in curettings were followed (mean 13.4 years) without a hysterectomy being performed for at least one year.6 Various histologic features were evaluated, and cytologic and architectural abnormalities analyzed independently in an effort to delineate the histologic features associated with an increased risk of progression to carcinoma. Those lesions without cytologic atypia were designated "hyperplasia" and those with cytologic atypia were designated "atypical hyperplasia". A third of the patients with either type of hyperplasia (nonatypical and atypical) were asymptomatic after the diagnosis and required no further treatment. Only two (2%) of 122 patients with hyperplasia lacking cytological atypia progressed to carcinoma whereas 11 (23%) of the 48 women with atypical hyperplasia progressed to carcinoma (p=0.001). The two cases of hyperplasia that progressed underwent an alteration to atypical hyperplasia before developing into carcinoma. Thus cytological atypia appears to be the most useful feature in identifying a lesion that might progress to carcinoma.

Morphometry can be used to assess nuclear ploidy, area, perimeter, longest diameter, shape, cells per unit area, and degree of gland formation. These features and a number of parameters derived from them can be used to compare various degrees in the proliferative continuum. A probability classification using the principle of a linear discriminant function can be used to compare the groups. Morphometry is very reproducible and it can be applied to archival material. In one study using descriptors of nuclear measurements and degree of gland formation, 80% of atypical hyperplasias were correctly classified.7 In another study, using nuclear measurements and DNA values, only 70% were correctly classified.8 While the predictive value of a morphometry classification is unclear, it is more reproducible than microscopic examination by a pathologist where only about 85% of atypical hyperplasia is reproducibly classified. In two studies, 83% of the atypical hyperplasias that progressed were identified correctly.9,10 Aggressive carcinomas can also be identified cytophotometrically.9 It is the lack of reproducibility and uncertainty over the predictibility of the pathologist's diagnosis that has driven morphometric studies with the hope of enhancing reproducibility and improving the significance of the diagnosis. It's possible that new measurement techniques and programs will eliminate the need for microscopic diagnosis of the endometrium by a pathologist. Pathologists must agree on reproducible criteria for hyperplasia and carcinoma or watch the technical revolution push them aside.
TABLE 1

Hysterectomy Findings when Stromal Invasion is Absent in Curettings
(89 Patients)

<table>
<thead>
<tr>
<th>Residual Carcinoma</th>
<th>15(17%)</th>
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</thead>
<tbody>
<tr>
<td>Grade</td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>15(100%)*</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>0</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>0</td>
</tr>
<tr>
<td>Myometrial Invasion</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>8(53%)*</td>
</tr>
<tr>
<td>Inner 1/3</td>
<td>7(47%)*</td>
</tr>
<tr>
<td>1 mm or less</td>
<td>5</td>
</tr>
<tr>
<td>2-4 mm</td>
<td>2</td>
</tr>
</tbody>
</table>

*The percentages refer to the proportion of carcinomas in the hysterectomy specimen.
TABLE 2

Hysterectomy Findings When Stromal Invasion is Present in Curettings (115 Patients)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual Carcinoma</td>
<td>58 (50%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>38 (66%)*</td>
</tr>
<tr>
<td>Grade 2</td>
<td>14 (24%)*</td>
</tr>
<tr>
<td>Grade 3</td>
<td>6 (10%)*</td>
</tr>
<tr>
<td>Myometrial Invasion</td>
<td>42 (72%)</td>
</tr>
<tr>
<td>Depth of invasion</td>
<td></td>
</tr>
<tr>
<td>Inner third</td>
<td>28 (48%)*</td>
</tr>
<tr>
<td>Middle and outer thirds</td>
<td>14 (24%)*</td>
</tr>
</tbody>
</table>

*The percentages refer to the proportion of carcinomas in the hysterectomy specimen.
References:


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Case 10. Atypical polypoid adenoma of Mazur (Acc. #26109)

Through the wonders of light microscopy, you were face to face with the dreaded and oft misdiagnosed atypical polypoid adenomyoma of Mazur (APAM)\(^1\). If you failed to consider APAM in the differential diagnosis, then you missed one of the most difficult diagnostic problems in curettings. It is better to guess wrong in a slide seminar than to proceed unknowingly through a pathology career. Note the irregular glands with squamous metaplasia embedded within muscle. The pattern resembles carcinoma invading fragments of myometrium. In fact, it may be impossible to rule out carcinoma because carcinomas incite a desmoplastic response and may intermingle with muscle in curettings. Atypical hyperplasia is excluded by the presence of smooth muscle around the glands and the focal nature of the APAM. The problem is to exclude invasive carcinoma when APAM is encountered in curettings.

The small size is helpful as few APAM exceed 1 cm and most are confined to the endometrium \(^1\text{-}^4\). For that reason, hysterectomy usually clarifies the nature of the lesion. In curettings, the muscle fibers may appear bland, parallel and rather circumferential, suggesting a leiomyoma containing the glands of adenomyosis. Adenomyosis differs from APAM in that the glands are not atypical, squamous metaplasia is infrequent, and endometrial stroma is often a minor component of adenomyosis and adenomyomatous endometrial polyps. The "adenomyomatosis" that Silverberg thought might be a hamartoma probably is the same as APAM \(^5\). Adenosarcoma differs from APAM in that smooth muscle is usually not evident. The epithelium is less hyperplastic in adenosarcoma and squamous metaplasia is unusual in it. Also, adenosarcoma contains 4 or more mitotic figures per 10 HPF in the stroma, whereas APAM does not have mitotic figures in the stroma\(^6\).

APAM occur in premenopausal women with menometrorrhagia. Half of reported patients have been multiparous\(^1\text{-}^4\). An association with estrogenic states as in Turner's syndrome or with exogenous stilbestrol or estrogen has been reported \(^2\). An associated endometrium showing stimulation or hyperplasia occurs in about 75\% of patients, suggesting that unopposed estrogen predisposes to it.

Most writers think the lesion can be reliably diagnosed in curettings, but they are probably reporting adenomyomas and not the real APAM characterized by squamous metaplasia. Easily removed by curettage and often small, solitary and polypoid, usually nothing is found in the hysterectomy. APAM may represent 1 or 2\% of polyps \(^7\). Since one cannot always rule out carcinoma in the curettings, a hysterectomy may have to be recommended to find out if it is APAM or carcinoma. In this case, there was nothing in the endometrium when the uterus was removed.
References:
The placental site trophoblastic tumor (PSTT) is the rarest form of gestational trophoblastic disease (1). The tumor was originally termed atypical chorionepithelioma by Marchand (2), but because of its rarity it never became established as a separate entity distinct from choriocarcinoma. In recent years it was periodically rediscovered and renamed. Terms such as atypical choriocarcinoma, syncytioma, and trophoblastic pseudotumor have been used (3,4).

Patients are in the reproductive age group and can present with either amenorrhea or abnormal bleeding accompanied by uterine enlargement. Most patients have been parous; at least three have had a preceding hydatidiform mole. Patients typically appear to be pregnant but unless sensitive assays for hCG are employed, pregnancy tests may be negative (1,5).

Tumors can vary from microscopic size to mass lesions that diffusely enlarge the uterus. The mass may be either well-circumscribed or ill-defined. The sectioned surfaces are soft and tan and contain focal areas of hemorrhage. Invasion frequently extends to the uterine serosa and rarely to the adnexa.

The predominant cell in PSTT is intermediate trophoblast (IT)(6,7). The majority of the cellular population is monomorphic in contrast to the mixture of cytotrophoblast (CT), IT, and syncytiotrophoblast (ST) in choriocarcinoma. The IT cells invade singly in cords and sheets, typically separating individual muscle fibers or groups of fibers without producing extensive necrosis of the muscle. Many of the IT cells assume a spindle shape and are closely apposed to myometrial cells. The tumor displays a characteristic pattern of invasion in which blood vessel walls become completely replaced by trophoblastic cells and fibrin while the lumen remains patent. A decidual reaction or Arias Stella reaction may be found in the adjacent uninvolved myometrium.

Most cases of PSTT are benign. The tumor often invades through the myometrium to the serosa and therefore curettage may easily result in perforation. There have been several reports of malignant behavior (8,9). Among a group of nearly eighty reported and unreported cases 10% have resulted in the death of the patient (10). The malignant tumors have disseminated widely like choriocarcinoma, but the histologic appearance of the metastasis resembles that of PSTT. Unlike choriocarcinoma, these tumors do not respond to multiagent chemotherapy and, because the
PSTT is composed of IT, it contains only small amounts of hCG. The serum levels of hCG are therefore much lower than those in choriocarcinoma.

Comparison of benign with malignant tumors indicates that the malignant lesions generally are composed of larger masses and sheets of cells. In addition, the cytoplasm is clear instead of amphophilic, and the tumor displays more extensive necrosis and higher mitotic activity. In benign lesions, the mean rate is 2 mitotic figures/10 HPF, with the highest reported being 5/10 HPF. In contrast, most of the malignant lesions have displayed greater than five mitoses/10 HPF. In one fatal case, however, the mean mitotic rate was only 2/10 HPF (9).

An apparently unique form of renal disease has been described in a few patients with PSTT (11). Patients present with severe proteinuria and renal biopsy shows glomerular lesions with prominent intracapillary deposits that stain for fibrinogen and IgM. The pathogenesis is unknown, however, the nephrotic syndrome that occurs with this lesion is not seen in other forms of gestational trophoblastic disease.

The PSTT must be distinguished from choriocarcinoma. In contrast to choriocarcinoma the PSTT is composed of a relatively monotonous cell population and the alternating arrangement of CT and ST is not found. Immunoperoxidase reactions are intensely positive for hPL and only focally positive for hCG in PSTT. This is a reversal of the pattern found in choriocarcinoma. Other neoplasms to be considered in the differential diagnosis include leiomyosarcomas, especially epithelioid leiomyosarcoma, poorly differentiated carcinoma or even metastatic melanoma. The patterns of infiltration into smooth muscle and blood vessel invasion as well as the extensive deposition of fibrinoid material are helpful in the diagnosis of PSTT. Leiomyosarcomas, poorly differentiated carcinomas and melanomas are almost invariably negative for hPL and hCG although there are rare instances of poorly differentiated carcinomas that have been associated with production of these hormones.

PSTT must also be differentiated from a normal but exaggerated placental site. Distinction may be difficult in curettings. Generally, in the placental site the IT cells do not form confluent masses, and there is no mitotic activity. In addition, other chorionic elements, including villi and spiral arteries are present in normal gestations but not in PSTT.
REFERENCES


Partial hydatidiform mole (PM) represents a placenta in which only a portion of the villi undergo the hydropic change that is characteristic of molar gestation (1). Clinical, pathologic and chromosomal studies of the PM indicate that this is a distinct entity that can be separated from complete mole (CM) and from non-molar abortions (2-11). The PM, in addition to only focal villous hydrops, typically shows the presence of an embryo or fetus and has an extra complement of paternal chromosomes (triploidy). Morphologic features of PM include: 1) focal villous edema with cistern formation, 2) mild and focal hyperplasia of trophoblast, 3) an irregular or scalloped villous outline, 4) trophoblastic infoldings that yield apparent inclusions in villous stroma, 5) evidence of development of an embryo or fetus.

The evidence of embryo/fetal development can include identification of a fetus or fetal parts, fetal circulation and villi containing nucleated red cells or the presence of an amnion. The non-molar villi in PM often are fibrotic.

The PM with these histologic features constitutes a clinicopathologic subset of hydatidiform mole that should be distinguished from CM. The PM often is not diagnosed before curettage since these patients typically have "small for dates" uteri and relatively low serum levels of hCG (11). Uterine bleeding often is limited, and many patients present as spontaneous or missed abortions in which molar pregnancy is not anticipated preoperatively. PM also may be found in elective abortions if searched for. The CM, in contrast, typically presents with uterine enlargement greater than that expected for the date, heavy vaginal bleeding, and high hCG levels. Ovarian enlargement due to theca lutein cysts and toxemia are other associations with CM that are rarely seen in PM. Often, hydatidiform mole is suspected clinically before curettage when CM is present.

The pathologic distinction of PM from CM appears to be important since PM is less prone to develop persistent gestational trophoblastic disease (GTD) that will require therapy. Between 4-11% of PM have had persistent GTD requiring therapy in comparison to between 10-30% of CM (13-16). Most cases of persistent GTD with PM appear to represent disease limited to the uterus, and there are few cases of well documented invasive mole following PM. Importantly, however, no case of well documented choriocarcinoma has followed a PM, while 2 to 3% of CM will be followed by choriocarcinoma (17,18).
Cytogenetically, PM is usually triploid, composed of a haploid maternal set of chromosomes and two sets of haploid paternal chromosomes. The CM, in contrast, is diploid, usually XX, although both sets of chromosomes come from the biologic father. Thus, the ratio of paternal to maternal chromosomes is 2:1 in PM but 2:0 in CM (19).

Although the clinical data suggests a lessened chance of sequela following PM as compared to CM, follow-up remains important. When a diagnosis of PM is made, serum beta-hCG titers should be followed until the levels fall to normal and remain at that normal level. Pregnancy must be avoided until complete resolution is assured. Cases of PM with persistent disease usually are successfully treated with single agent chemotherapy.

### Comparison of Partial and Complete Hydatidiform Mole

<table>
<thead>
<tr>
<th>Pre-operative Diagnosis</th>
<th>PM</th>
<th>CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mole</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Missed abortion</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Heavy bleeding</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>Toxemia</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Uterus enlarged</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Uterus small</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Amount of tissue</td>
<td>Partial</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Villous hydrops</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Fetus</td>
<td>+/++</td>
<td>++</td>
</tr>
<tr>
<td>hCG</td>
<td>XXY or XXX</td>
<td>XX</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>(2:1, paternal:maternal)</td>
<td>(all paternal)</td>
</tr>
<tr>
<td>Behavior</td>
<td>4-11% persistent GTD</td>
<td>10-30% persistent GTD</td>
</tr>
</tbody>
</table>

The PM must be distinguished from CM and from non-molar gestation. Molar pregnancy, PM or CM, often is suspected grossly when the enlarged, grape-like, swollen villi are seen. In PM a mixture of edematous and normal size villi is present, and a fetus or embryo may be visualized. Often gross deformities are present in the fetus. The CM, in contrast, shows universal
villous edema, and the amount of tissue is usually large with no fetal parts present.

Histologically, the distinction of PM from CM rests on the relative proportion of villi that show the marked edema. In PM there is a mixture of small and large hydropic villi while in CM most villi show the marked edema. A few small villi may be present in CM, but these should represent less than 10% of all villi, and they, too, have an edematous stroma. Ancillary features often seen in PM such as scalloped villous outlines, trophoblastic inclusions, or fetal parts or amnion are helpful clues to the diagnosis. Conversely, trophoblastic hyperplasia and atypia generally is more pronounced in CM while it is focal in PM. The amount of trophoblastic proliferation can be highly variable in CM, however, so this feature is less reliable than the amount of villous involvement in separating these two entities.

Immunohistochemistry for hCG and placental alkaline phosphatase (PLAP) can aid in distinguishing complete from partial moles. In complete moles there is a much greater distribution of hCG compared to PLAP, while in partial moles the reverse is found.

Non molar abortins may mimic molar pregnancy because of the presence of actively proliferating trophoblast or because villi in abortions may become edematous, especially in the so-called "blighted ovum" in which fetal development ceases early in gestation. Changes in abortions can be especially difficult to separate from features of PM since the trophoblastic and villous changes tend to not be prominent in PM. The most important feature is the identification of central villous cisterns in moles, PM or CM. The "cistern" is a large, acellular central space composed only of edema fluid. The central cistern typically has a sharp border with the remaining peripheral rim of stroma that contains mesenchymal cells. Lesser degrees of edema can be found in some villi in both moles and in non-molar abortions, so identification of cisterns becomes critical for separating these entities.

Trophoblastic proliferation in moles also is distinguishable from the trophoblastic growth in non-molar placentas. In mole, PM or CM, abnormal trophoblastic hyperplasia is identified by circumferential growth around the villous. This is in sharp contrast to polar growth on one end of villi that occurs normally in anchoring villi where implantation is occurring.
REFERENCES


The mean age of patients with adenosarcoma is approximately 50-70 years, the most common presenting symptom is abnormal vaginal bleeding usually accompanied by a pelvic mass.

Endometrial adenosarcoma typically forms a sessile, polypoid mass that fills the endometrial cavity. In most cases there is little evidence of myometrial invasion on gross examination. Hemorrhage and necrosis occur in approximately one quarter of cases (1).

The tumor is characterized by papillary fronds covered by benign appearing epithelium that resembles glands of proliferative or hyperplastic endometrium. Atypia may be present in glands but carcinomatous changes such as cribriform bridging are not found. The epithelium also lines glands deep within the tumor itself. Glands are large and cystic or cleft-like. Metaplastic mucinous or squamous epithelium often lines a portion of the epithelium. The mesenchymal component of the neoplasm is a sarcoma. It is often hypercellular around glandular epithelium, forming a characteristic cuff. All grades of cytological atypia may be seen and mitotic activity tends to be low, with a mean of 4 mitotic figures/10 HPF. Heterologous elements including cartilage, striated muscle and fat have been reported in approximately one quarter of cases. Smooth muscle is rarely present (1,7).

Forty percent of adenosarcomas recur and metastases most commonly involve the pelvis although metastases develop outside the pelvis in a small proportion of patients (1). The histologic appearance of the recurrent tumor is similar to the sarcomatous component of the primary tumor and epithelium is rarely evident (1,2). Approximately one quarter of women die of tumor. The interval from diagnosis to death is 7 years. Similar tumors may occur in the cervix, ovary and adnexal region (8,9).

Treatment is total hysterectomy and bilateral salpingo-oophorectomy. Tumors invading greater than halfway through the myometrium have a high likelihood of recurrence, and consequently, postoperative pelvic radiation has been recommended.

The adenosarcoma must be distinguished from hyperplastic polyps, papillary adenofibroma, and carcinosarcoma. The hyperplastic polyp may have glands and stroma similar to that found in adenosarcoma, but these lesions are smaller and are usually mixed with benign endometrium in curettings. The stroma
in polyps is less cellular than in adenosarcoma. The papillary adenofibroma is composed of both benign epithelium and mesenchymal tissue that forms large, frond-like projections into the uterine cavity. The stroma of the adenofibroma appears fibrous and has only rare mitosis. Carcinosarcomas and mixed mesodermal tumors are composed of malignant epithelial as well as stromal components. Adenosarcoma, in contrast, contains benign epithelium while the stroma appears malignant.

In contrast to the usual adenosarcoma the lesion in this case, rather than being exophytic, is composed of multiple intramural nodules. Also although the epithelium is bland and the stroma hypercellular with cytologic atypia the leaf-like papillary fronds, characteristic of adenosarcoma, are not present. Immunoperoxidase studies reveal that the predominant cellular population within the neoplastic nodules reacts with the antibody against muscle specific actin indicating that these are smooth muscle cells. In some areas the mesenchymal cells that are closely applied to the epithelium are negative suggesting that these are endometrial stromal cells. Multiple foci of adenomyosis are present throughout the uterus. Typical adenosarcomas may show focal differentiation into leiomyosarcoma so this case may be interpreted as a variant of a mullerian adenosarcoma in which the predominant population of neoplastic mesenchymal cells have differentiated into smooth muscle. The multifocal, intramural distribution of the neoplasm and the close association with adenomyosis suggests that the tumor arose in adenomyosis.
REFERENCES


De cem ber 6, 1987

Case 14. Seromucinous tumor of low malignant potential. (Acc. #25110)

Mucinous cystadenomas are formed by epithelium resembling that of the endocervix. The cells are columnar with basally oriented nuclei. Intracytoplasmic mucin is present. As the mucinous tumor progresses in the continuum toward malignancy, the cells tend to lose the capacity for mucin production and resemble benign or adenomatous intestinal epithelium. Goblet cells and vacuoles of intracytoplasmic mucin are formed. In mucinous tumors of low malignant potential (LMP), mixtures of endocervical and intestinal epithelial cell types occur, with the latter predominating.

Serous tumors are composed of epithelium which resembles that of the fallopian tube. They arise directly from the ovarian surface epithelium (a modified peritoneal mesothelium) or from epithelial inclusions trapped within the substance of the ovary. Serous tumors are characteristically cystic and papillary, forming buds by cells that lack a supporting fibrovascular stalk. The cells are round, pleomorphic, and are usually atypical, and form detached clusters.

Our seminar case differs from the usual mucinous tumor of LMP and its serous counterpart. The basal layer of cells is mucinous throughout the tumor as in the cervix. Instead of converting to a pseudostratified intestinal type of epithelium as occurs in the usual mucinous tumor of low malignant potential, the epithelial cells are rounded, smaller, and held together by intercellular attachments. They form clusters of detached atypical cells, as in a serous tumor of LMP. Thus, the study case is a seromucinous tumor of low malignant potential.

Seromucinous tumors can be mixtures of two different cell types or, as in this case, can be derived from an underlying mucinous tumor that differentiates along serous lines as it progresses toward malignancy. Whereas mucinous differentiation reflects "intestinal metaplasia", serous differentiation may reflect "mullerian metaplasia". This view may annoy purists because the ovary is not a mullerian structure and serous differentiation should not be thought of as mullerian, just because it resembles tubal-type epithelium.

Purists may also question whether the complex classification of neoplasms of the reproductive tract currently in vogue is justified on a clinical basis. In this instance, we believe so. "Intestinal" differentiation in the typical mucinous tumor of LMP signifies a relatively innocuous neoplasm as only about one of 30 stage I mucinous tumors of LMP will metastasize. Stage I serous tumors of LMP, however, are more aggressive as about 1% per year metastasize or prove fatal and eventually about 15% will prove fatal. Thus, future studies are likely to show that seromucinous tumors of LMP are intermediate in aggressiveness between mucinous and serous tumors of LMP.

The survival of patients with ovarian tumors of LMP has been reviewed elsewhere. To summarize briefly, in all major series, the 5-year survival rate for patients with stage I serous tumor of LMP is 95% or better.2,3,5,7,8,10
Just how many patients with stage I neoplasms treated by unilateral oophorectomy will develop a recurrence or second primary tumor in the contralateral ovary is unknown, but it probably exceeds 10%. The 10-year survival rate for patients with stage I neoplasms appears to exceed 90%.2-10

Mucinous tumors of LMP are less aggressive. Evidence of extraovarian spread at the initial staging of mucinous tumor of LMP is found in 12 to 15% of patients.2,9,10 Survival rates ranging from 90% to 100% have been reported in stage I tumors, with a median follow-up of over 8 years.2-4,6,10 The best survival rate was reported by Bostwick et al. in 1985, who found no recurrences in 30 stage I mucinous neoplasms over a mean follow-up of 7 years.3 Hart and Norris,6 found 3 tumor deaths in 87 patients with stage I neoplasms over an 8 year mean follow-up, indicating that only about one of 29 or 30 stage I mucinous tumors of LMP will do badly.

References:
Clinicians have requested pathologists isolate "borderline" tumors because evaluation of the efficacy of therapy for patients with stage I "carcinoma" is difficult if tumors of low malignant potential (LMP) tumors are included in some reports and not in others. Serous and mucinous cell types make up 95% of LMP tumors. Stage I serous and mucinous LMPs are as common as stage I serous and mucinous carcinoma, but endometrioid LMP tumors are only 5-10% of all endometrioid tumors. Several patterns of benign and low malignant potential endometrioid tumors exist:

1. Proliferative endometrioid tumor (PET). This neoplasm is a partly solid, partly cystic neoplasm that is at least half solid. It usually arises in endometriosis. The epithelium is endometrioid in type with squamous metaplasia. It may have (1+) or moderate (2+) atypia. The epithelial component does not occupy more than 5 mm without intervening stroma. It resembles atypical hyperplasia of the endometrium in glandular complexity. Although benign, carcinoma may arise in PET. PET may evolve to endometrioid tumor of low malignant potential, also.

2. Endometrioid tumor of low malignant potential (ETLMP). This encompasses several patterns, none of which show clear-cut signs of stromal invasion: (a) An adenofibroma with glands and squamous metaplasia without intervening stroma occupying an area exceeding 5 mm in maximum dimension. The epithelium has mild (1+) to marked (3+) atypia. (b) Papillary neoplasms lined by epithelium exhibiting mild to moderate atypia with no contiguous supporting endometrial stroma, as in a PET. (c) Neoplasms with cribriform (back-to-back) glands occupying at least 5 mm without intervening stroma. Invasion is absent, but in-situ malignancy or extensive proliferation is evident.

3. Endometrioid tumor of low malignant potential with microscopic areas of invasion. In this, the neoplasm has the overall configuration of an ETLMP, but microscopic examination may show small areas of destructive infiltrative stromal invasion or intracyctic processes containing a solid undifferentiated glandular pattern with cytological evidence of malignancy. More than 1 or 2 low magnification (40x) fields probably conveys metastatic potential and should identify an endometrioid carcinoma.

The slides on Case 15 are from two different forms of ETLMP. Some slides show the papillary variety, others show the adenofibrous form in which epithelial proliferation akin to an extensive atypical hyperplasia of the endometrium exceeds 5 mm. In neither example is there infiltrative growth.

We believe ETLMP has very little potential, but has low malignant potential because of its tendency to give rise to infiltrating carcinoma (ETLMP withmicrocarcinoma) and to evolve into endometrioid carcinoma. Also, rare examples metastasize, as did of the 34 ETLMP in our study and one reported by Russell.
How frequent are "borderline" endometrioid tumors? In 1971 Aure and co-workers reported on 990 ovarian carcinomas which included 7 cases of endometrioid tumors of low malignant potential. They listed no criteria for the diagnosis, however. Russell subsequently reported on 144 "proliferating" epithelial tumors in 1979, of which 14 were classified as endometrioid based on histological similarity to endometrium. He was the first to discuss the pathological assessment of these tumors. In his schema, low grade and high grade proliferative tumors resemble atypical endometrial hyperplasia, with the exception that the ovarian tumors contain fibromatous stroma. One of the 14 in his series metastasized. The largest published series is that of Bell and Scully. They include only adenofibromatous lesions whereas we recognize a papillary variety. Bell and Scully categorize their adenofibromas as benign, atypical, borderline and malignant. Their atypical neoplasms correspond to proliferative lesions (above), but they provide no quantifiable criteria, only epithelial atypicality "similar" to atypical endometrial hyperplasia.

SUMMARY OF DIAGNOSTIC CRITERIA OF ENDOMETRIOID TUMORS

<table>
<thead>
<tr>
<th>ADENOFIBROMA</th>
<th>PROLIFERATIVE ADENOFIBROMA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-2+ ATYPIA</td>
</tr>
<tr>
<td></td>
<td>EPITHELIAL MASS DOES NOT EXCEED 5 MM</td>
</tr>
<tr>
<td></td>
<td>NO INVASION</td>
</tr>
<tr>
<td>LMP</td>
<td>0-3+ ATYPIA</td>
</tr>
<tr>
<td></td>
<td>EPITHELIAL MASS EXCEEDS 5 MM</td>
</tr>
<tr>
<td></td>
<td>NO DESTRUCTIVE INFILTRATIVE GROWTH</td>
</tr>
<tr>
<td>CARCINOMA</td>
<td>1-3+ ATYPIA</td>
</tr>
<tr>
<td></td>
<td>DESTRUCTIVE INFILTRATIVE GROWTH</td>
</tr>
<tr>
<td></td>
<td>PAPILLARY CARCINOMA (MORE THAN 1 OR 2 40X FIELDS)</td>
</tr>
</tbody>
</table>

Since one of 34 of our ETLMP had a metastatic implant, the designation as ETLMP is more appropriate than using the term "borderline" which is vague because it not only means "in between the classification", it also means "doubtful" and "indefinite". Microscopic areas of stromal invasion were found in 4 of 38 ETLMP. We believe those with invasion identify a higher risk group of neoplasms than ETLMP, but curiously, the only patient to present with a metastasis was in the group of 34 ETLMP without microinvasion.
References


Case 16. Clear cell adenofibroma containing a papillary tumor of low malignant potential. (Acc. #26085)

This neoplasm was mostly solid (a form of cystadenofibroma) and highly varied in its appearance. One area showed small tubules lined by hobnail cells as in a clear cell carcinoma, except that the tubules were not clearly invasive. Other areas showed spaces lined by a single or multilayered epithelium having mainly clear cell characteristics. In addition, about 100 slides were mailed out that included an atypical papillary hyperplasia or noninvasive papillary carcinoma that exceeded 5 mm. Since the tumor contains an in-situ malignancy, but lacks clear cut invasion, it qualifies as a tumor of low malignant potential. Using the classification above for endometrioid tumors (Case 15), this, by analogy, is a clear cell adenofibroma of low malignant potential. Clear cell adenofibromas are very rare. Russell estimates that only about 10% of clear cell tumors are benign or intermediate.

Clear cell tumors of low malignant potential have all been forms of adenofibroma with papillary areas. Stratified atypical cells with detachment of atypical cell clusters may also occur in papillary areas. The best description of intermediate clear cell tumors is Roth et al.

Although the slide seminar contains just one example, the discussion should convince you that clear cell tumors may contain atypical cells and tubules lined by cells that resemble noninvasive clear cell carcinoma, and that papillary carcinoma may arise in clear cell adenofibromas. We agree with Roth et al. that the histologic similarity of the epithelium in benign and LMP tumors to that seen in invasive carcinoma justifies the categorization. Also, some clear cell carcinomas have considerable stroma and benign-appearing areas to the degree that one suspects that some clear cell carcinomas arise in an adenofibroma. Unfortunately, the limitation in the number of cases in a seminar does not permit a complete demonstration of this spectrum.

References:


Case #17 Embryonal Carcinoma with Focal Endodermal Sinus Tumor (Acc. #26087)

The embryonal carcinoma was included in the 1973 WHO classification but was characterized as a separate clinicopathologic entity in 1976 (1). It is analogous morphologically and immunohistochemically with embryonal carcinoma of the adult testis but in the past was included with endodermal sinus tumor in the ovary, both terms being used interchangeably. Pure embryonal carcinoma in the ovary is rare, accounting for only 5% of ovarian malignant germ cell tumors in contrast to the testis where it represents 35% of all germ cell neoplasms.

The histogenesis of embryonal carcinoma is closely related to that of endodermal sinus tumor, teratoma and choriocarcinoma, embryonal carcinoma being the neoplastic progenitor of all three of the other neoplasms. This view is supported by light microscopic and electron microscopic observations, animal transplantation experiments and most recently by studies of oncofetal antigens associated with these tumors. Thus, the light microscopic resemblances of embryonal carcinoma to endodermal sinus tumor and choriocarcinoma have been confirmed by ultrastructural studies showing the common origin of all germ cell tumors (2, 3) and the similarity to embryonal carcinoma explants used in the experimental induction of murine teratomas (4, 5). Current research in embryonic and fetal antigens has also provided further confirmation of a common histogenesis for all these tumors (6). The demonstration that the human fetal yolk sac synthesizes AFP (7,8) supported Teilum's claim that the endodermal sinus tumor is of yolk sac origin and the localization of hCG in syncytiotrophoblast in choriocarcinoma and the immature placenta further corroborated the trophoblastic nature of choriocarcinoma.

In its most primitive form embryonal carcinoma appears to be incapable of synthesizing either AFP or hCG since neither marker is demonstrated in tissue sections of some ovarian embryonal carcinomas using immunocytochemical methods and 10% of patients with testicular embryonal carcinoma fail to show elevated serum marker levels (9,10). In most instances, however, embryonal carcinoma shows either biochemical or morphologic evidence of differentiation along yolk sac or trophoblastic pathways. Based on immunoperoxidase studies it appears that biochemical differentiation precedes the more complex histologic differentiation (6). This is manifested by localization of AFP in embryonal carcinoma cells showing no morphologic evidence of yolk sac differentiation. Early histologic differentiation into yolk sac is characterized by the formation of microcystic spaces lined by flattened embryonal carcinoma cells containing AFP (6,11,17).
As these microcystic spaces become the dominant pattern in contrast to the solid masses of cells, the microcystic areas merge with and in essence become the reticular pattern of endodermal sinus tumor characterized by micro- and macrocystic formation. These microcystic areas, reflecting yolk sac differentiation, appear to occur more commonly in embryonal carcinoma than was previously suspected (13,14). This is well illustrated in the present case where focal areas of obvious yolk sac differentiation are present in some sections and not in others.

Differentiation of embryonal carcinoma along trophoblastic lines is manifested by the localization of hCG but not AFP within isolated syncytiotrophoblastic giant cells and in the syncytiotrophoblast of bona fide choriocarcinoma (6). Immunoperoxidase studies have also shown that syncytiotrophoblast contains pregnancy specific beta globulin (12), further functional evidence of trophoblastic differentiation.

A tendency of embryonal carcinoma to differentiate towards teratomatous cell lines is manifested morphologically by the close association with cartilage and squamous epithelium (1). Functional evidence of teratomatous differentiation in embryonal carcinoma is based on the presence of markers such as AFP, alpha-1-antitrypsin and CEA in both embryonal carcinoma and components of teratoma (12). Embryonal carcinoma therefore appears to be comprised of a heterogeneous population of cells reflecting a dynamic process of differentiation along different pathways.

The age range is 4 to 28 years (median 15 years). Three-quarters of the patients have an abdominal or pelvic mass and half have abdominal pain. Symptoms tend to be of short duration (mean of 3 weeks). Signs of precocious puberty are present in almost half of the prepubertal girls (1). Amenorrhea or vaginal bleeding are found in one-third of the women in the reproductive age group. Pregnancy tests have proved positive in all the patients tested including the children with precocious puberty.

Typically the tumor is large (median size 17 cm.) encapsulated, and soft with an appearance that is not distinctive. The cut surface is solid, gray-yellow and variegated with extensive hemorrhage and necrosis. Cysts are common.

Pure embryonal carcinoma is composed of large primitive pleomorphic cells with amphophilic, vaculated cytoplasm and vesicular nuclei with one or more nucleoli arranged in solid sheets (embryonal carcinoma cells). These cells may form gland-like spaces and papillary processes but they lack the reticular, polyvesicular vitelline and festoon growth of endodermal sinus tumor. A second type of cell that is frequently found in
embryonal carcinoma is a large multinucleated giant cell present either at the periphery or among solid masses of embryonal carcinoma cells or scattered haphazardly in the stroma. These cells are syncytiotrophoblastic giant cells with eosinophilic or amphophilic cytoplasm and large vacuoles. The nuclei in these cells are large, hyperchromatic and flattened into bizarre shapes. The supporting stroma of the tumor is variable, either edematous and myxoid or cellular with primitive spindle-shaped mesenchymal cells.

Therapy is the same as in immature teratoma and endodermal sinus tumor consisting of complete excision of all resectable disease and adjuvant chemotherapy postoperatively. Since metastasis to the opposite ovary without visible disease elsewhere is rare or nonexistent, unilateral salpingo-oophorectomy for stage I tumors should be performed (Table 3). The number of cases is too small for firm conclusions to be made about prognosis. The five year actuarial survival before modern chemotherapy was 50% for stage 1 disease and 39% for all stages combined.

Recently, two other variants yolk sac tumors have been described, the hepatoid yolk sac tumor (15) and the endometrioid-like variant of yolk sac tumor (16). The former is a yolk sac tumor in which the predominant cellular population resembles hepatocellular carcinoma and the latter is composed of glandular structures resembling endometrioid carcinoma of the ovary. Focal areas within both types of tumor display typical endodermal sinus tumor and AFP can be localized in the tumor cells as well as being elevated in the serum. The importance of recognizing these variants lies in the fact they are highly virulent but since they are variants of endodermal sinus tumor probably respond to the same form of combination chemotherapy that is highly effective in the treatment of endodermal sinus tumor.
TABLE 3

Status of Contralateral Ovary in 191 Patients With Stage I Germ Cell Tumors of the Ovary

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Stage Ia Patients</th>
<th>Stage Ib Patients</th>
<th>Stage Ia Patients with Microscopic Spread to Opposite Grossly Normal Ovar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgerminoma</td>
<td>71</td>
<td>7 (10%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Endodermal sinus tumor</td>
<td>51</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Combination germ cell tumor</td>
<td>19</td>
<td>1 (5%)</td>
<td>1 (5%)*</td>
</tr>
</tbody>
</table>

* The primary neoplasm in the opposite ovary contained dysgerminoma and endodermal sinus tumor but the occult involvement in the grossly normal ovary was dysgerminoma only.
REFERENCES


Case #18 Immature Teratoma (Grade 3) With Focal Endodermal Sinus Tumor (Acc. #26088)

The vast majority (99%) of ovarian teratomas may be divided into two broad categories depending on the degree of immaturity of the component tissues. The remaining 1% of teratomas constitute a group of tumors that display monodermal or a highly specialized form of differentiation. Immaturity reflects the degree to which the neoplastic tissue resembles embryonic tissue and indicates a potential for recurrence that is directly related to the quantity and grade of immature tissue present (1, 2). Immaturity must not be confused with malignant transformation occurring in mature teratomas since such neoplasms, although they are malignant, develop from mature tissues.

These tumors are the third most common malignant germ cell tumor of the ovary after dysgerminoma and endodermal sinus tumor (3) and represent nearly one-quarter of all ovarian germ cell tumors in children under 15 years. The median age is 18 years, the oldest patients are about 40 years and 20% are prepubertal (1). The symptoms are nonspecific and are usually present for short duration. Three quarters of patients have a palpable abdominal or pelvic mass, frequently accompanied by pain.

Immature teratomas are usually large unilateral tumors with a median size of 18 cm. The external surface is smooth and the cut surface is soft, gray to pink, with visible hemorrhage and necrosis and large cysts in a third of the cases. Hair is present in two-fifths of the tumors. Teeth are rare, but bone, cartilage, or calcification are usually evident.

Microscopically, these neoplasms are comprised of varying proportions of immature tissue derived from the three germ layers. The degree of immaturity is graded; the immature neural tissue is the most common element and easiest to grade. In order to assess the degree of differentiation, adequate sampling is necessary. A block of tissue for each centimeter of the diameter of the tumor is required. The least differentiated area is then graded (1, 2).

Grade 0: Wholly mature tissue.

Grade 1: Abundant mature tissue but some immaturity, mainly glia in a primitive mesenchyme. Mitotic figures are rare and neural epithelium is absent or limited to one low power field (40X) per slide.
Grade 2: More than one lower power field of neural epithelium but not exceeding three power fields per slide.

Grade 3: Extensive areas of immaturity are present, neural epithelium is found in four or more low power fields per slide frequently merging with a highly primitive appearing "sarcomatous" stroma; mitotic activity is common.

Although neural epithelium, often forming tubules or rosettes and glial tissue are the most frequently encountered ectodermal derivatives, ganglion cells, nerve trunks, ocular structures, skin, sweat glands and hair may also be seen. Mesodermal derived tissue includes cartilage, bone, lymphoid tissue, and smooth muscle occasionally. Striated muscle is quite rare and is suggestive of a mixed mesodermal tumor. Endodermal elements include columnar tissue suggesting respiratory and gastrointestinal epithelium. The tissue elements in an immature teratoma may show varying degrees of immaturity but it is the most primitive areas that have a propensity to metastasize and consequently play the most important role in grading.

Approximately 70% of tumors are stage Ia. Bilateral involvement (stage Ib or Ic) does not occur in the absence of diffuse peritoneal spread (1,2) (Table 3). About 5% of contralateral ovaries contain a benign cystic teratoma. Early spread is by direct extension to the adjacent pelvic tissues and by peritoneal implantation. Lymphatic invasion and extra-abdominal spread are rare.

For stage I disease, prognosis is related to the histologic grade of the tumor. In view of the rarity or nonexistence of stage Ib (bilateral) disease (Table 3), stage I disease is best treated by unilateral salpingo-oophorectomy. Patients with grade 2 and 3, stage I neoplasms and all stage I tumors that have ruptured require adjuvant chemotherapy.

Once metastasis has occurred (stage II and stage III disease) the grade of the metastasis is the major prognostic determinant. Patients with stage II and III disease require maximal surgical reduction of all resectable disease for histologic grading and therapy. Those with grade 0 metastasis all survive after surgery and therefore need no further treatment. Prior to the use of modern chemotherapy, there was 40% to 50% survival for patients with grade 1 or 2 metastasis and no patient with grade 3 metastases survived. Recently there have been reports of patients with stage II and III disease and histologic grades 2 and 3 who were long-term (3-6 year) survivors following triple agent chemotherapy. Pathologic examination of residual disease at "second look" operation
following multiple courses of chemotherapy revealed grade 0 (mature teratoma) exclusively (4). These findings are thought to reflect selective destruction of the more primitive portion of the tumor leaving behind the more mature elements that do not proliferate and are therefore less likely to be affected by the chemotherapy.
REFERENCES


Case 19. Metastatic endometrial stromal sarcoma to ovaries. (Acc. #26089)

This distinctive neoplasm is identified by its resemblance to endometrial stroma and characterized by a uniformity throughout the tumor produced by small identical cells having little cytoplasm and a prominent capillary and arteriole pattern. The tumor cells appear to whorl around small vessels. A nonspecific gonadal stromal tumor may resemble this neoplasm, but our seminar case was bilateral and only two bilateral gonadal stromal tumors without extraovarian spread (stage Ib) exist in the AFIP files, so a primary gonadal stromal tumor is very unlikely on that basis. Because the tumor is bilateral and nowhere else (stage Ib), a metastasis to the ovary is likely. In our experience with endometrial stromal sarcoma involving the ovary, the primary site usually is in the uterus. A few cases are primary in the ovary, but those are not likely to be stage Ib. Endometriosis, which may give rise to endometrial stromal sarcoma, may also be a red herring. It was present in 19 of 32 reported cases involving the ovary, but not all of which were primary there. In a series of 23 cases of endometrial stromal sarcoma involving the ovary, Young et al. found only 9 were from the uterus.

In our seminar case, the bilaterality indicates the ovarian endometrial stromal sarcoma is metastatic to the ovary. We enquired whether the uterus had been removed as patients can develop metastatic endometrial stromal sarcoma 15 years after hysterectomy or, in rare instances, have the metastasis as the first manifestation 15 years before the primary site is discovered in the uterus. Our patient, a 69 year old woman, still had her asymptomatic uterus. At hysterectomy two months later, the uterus was symmetrical and weighed only 37 grams. The exterior appearance was normal. The endometrium was distorted by the presence of several nodules extending through the myometrium. Microscopic examination confirmed the presence of endometrial stromal sarcoma involving about half of the uterus.

This case illustrates that some uterine endometrial stromal sarcomas do not reveal their presence with bleeding and uterine enlargement until after metastasis has occurred. A survey of the 32 cases of endometrial stromal sarcoma involving the ovary reveals that the behavior parallels the mitotic activity and stage.

The division of endometrial stromal sarcomas into low and high grades is based on the number of mitotic figures. Less than 10 mitotic figures per 10 HPF generally is associated with an indolent course. For example, only 2 of 19 patients with low grade endometrial stromal sarcoma presenting in the ovary died of their disease, whereas 3 of 4 with high grade endometrial stromal sarcoma involving the ovary died within 4 years. This parallels our experience with low grade endometrial stromal sarcoma of the uterus wherein no one died within 12 years of discovery of their tumor, but half of patients with high grade endometrial stromal sarcoma of the uterus died within 5 years.
The therapy for metastatic endometrial stromal sarcoma is the same regardless of the primary site. Progesterone is useful for low-grade endometrial stromal sarcomas, but is of no proven value for high-grade ones. Endometrial stromal sarcoma of the uterus has higher estrogen and progesterone receptor values than all other primary uterine sarcomas. Radiation has been used for both low and high grade sarcomas with good results. Chemotherapy is of unproven benefit in the management of endometrial stromal sarcomas, although responses have been described.

Regarding terminology, some favor designating a primary extrauterine endometrial stromal sarcoma as "endometrioid stromal sarcoma", but this distinction is unnecessary since "endometrial" is adjectival enough, regardless of where the lesion is found.

TABLE 1. ENDOMETRIAL STROMAL SARCOMA INVOLVING OVARY

<table>
<thead>
<tr>
<th>IF PRIMARY IN OVARY</th>
<th>IF PRIMARY IN UTERUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. OLDER WOMEN; 13 OF 14 OVER 45</td>
<td>1. YOUNGER WOMEN; 4 OF 9 LESS THAN 45</td>
</tr>
<tr>
<td>2. SELDOM BILATERAL</td>
<td>2. USUALLY BILATERAL</td>
</tr>
<tr>
<td>3. ENDOMETRIOSIS USUALLY EVIDENT</td>
<td>3. ENDOMETRIOSIS USUALLY ABSENT</td>
</tr>
<tr>
<td>4. MOSTLY LOW GRADE</td>
<td>4. NEARLY ALL LOW GRADE</td>
</tr>
<tr>
<td>5. SURVIVAL RELATED TO GRADE</td>
<td>5. SAME</td>
</tr>
</tbody>
</table>

TABLE 2. BASIC FACTS OF ENDOMETRIAL STROMAL SARCOMA

1. OCCURS IN WOMEN OF ALL AGES.
2. MAY BE SILENT FOR YEARS.
3. MITOTIC ACTIVITY DETERMINES GRADE
4. HIGH ER AND PR LEVELS
5. PROGESTERONE AND RADIATION EFFECTIVE IN LOW GRADE STROMAL SARCOMA

References:


December 6, 1987

Case 20. Brenner tumor of low malignant potential. (Acc. #26020)

According to the classification of Roth et al. shown in Table 1, Brenner tumors are proliferative when undulating processes lined by bland transitional (urothelial) epithelium are present. A Brenner tumor of low malignant potential differs from a proliferative Brenner tumor in that the transitional-type of epithelium is cytologically malignant, but there is no stromal invasion. Stromal invasion and cytological malignancy are the two features needed to identify a malignant Brenner tumor. To qualify as a Brenner tumor of low malignant potential or a fully malignant Brenner tumor, a benign or bland proliferative Brenner component must be present to distinguish it from transitional cell carcinoma. In the case for discussion, a bland proliferative component merged with areas of malignant-appearing in-situ transitional cell epithelium. By definition, a malignant Brenner tumor has destructive infiltrative growth in addition to cytological malignancy.

TABLE 1. CLASSIFICATION OF BRENNER TUMORS AND CRITERIA FOR DIAGNOSIS

<table>
<thead>
<tr>
<th>BENIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>METAPLASTIC</td>
</tr>
<tr>
<td>-MULTILOCULAR CYSTS, NONPAPILLARY</td>
</tr>
<tr>
<td>-ORDINARY BT PRESENT</td>
</tr>
<tr>
<td>PROLIFIERATE</td>
</tr>
<tr>
<td>-MULTILOCULAR CYSTS WITH PAPILLARY FRONDS</td>
</tr>
<tr>
<td>-CYTOLOGICALLY ATYPICAL (PAPILLARY TCC GRADE 1 TO 2)</td>
</tr>
<tr>
<td>-ORDINARY BT PRESENT</td>
</tr>
<tr>
<td>LMP</td>
</tr>
<tr>
<td>-MULTILOCULAR CYSTS WITH PAPILLARY FRONDS</td>
</tr>
<tr>
<td>-CYTOLOGICALLY MALIGNANT (PAPILLARY TCC GRADE 3), BUT NO INVASION</td>
</tr>
<tr>
<td>-ORDINARY OR PROLIFERATIVE BT PRESENT</td>
</tr>
<tr>
<td>MALIGINAT</td>
</tr>
<tr>
<td>-CYTOLOGICALLY MALIGNANT</td>
</tr>
<tr>
<td>-DESTRUCTIVE INFILTRATIVE GROWTH</td>
</tr>
<tr>
<td>-ORDINARY OR PROLIFERATIVE BT PRESENT</td>
</tr>
</tbody>
</table>

The accumulated literature on malignant Brenner tumors includes proliferative and low malignant potential tumors, as well as primary ovarian transitional cell carcinoma (Case 21, below). Reports vary because some investigators required the presence of an admixed benign Brenner component while others did not. Also, the proliferative group, now thought to be entirely benign, was not delineated in old reports.

References:

Two types of ovarian carcinoma with urothelial differentiation occur. One type is a malignant Brenner tumor, a neoplasm that arises in association with a benign or proliferative Brenner tumor. The other type is a transitional cell carcinoma (TCC), which differs from MBT by lacking a benign Brenner component. TCC also lacks the calcification of a MBT and behaves more aggressively. Transitional cell carcinoma of the ovary, like benign and proliferative Brenner tumors, may arise directly from cells of the ovary with uroepithelial potential. Urothelial differentiation occurs in the mesothelium adjacent to the ovary in the form of Walthard rests and in the ovary with the formation of Brenner tumors and TCC. We reported the findings in 29 transitional cell carcinomas primary in the ovary and compared them with 16 malignant Brenner tumors in our files.¹

Patients with TCC presented with tumor in higher stages. Twenty (69%) of 29 TCCs were stage II-IV compared with 3 of 16 (19%) MBTs. As a consequence, only 7 of 29 (24%) patients who had transitional cell carcinoma were free of tumor on follow-up compared with 11 of 16 (69%) patients with malignant Brenner tumor. The difference in behavior is found even within the same stage. Only 3 of 7 patients with stage I A TCC were well at last contact, compared with 9 of 11 (88%) of women with stage I A MBT who were free of disease at last contact. Also, by turning to reports of MBT in stage I, a relatively favorable result is also evident. Of 19 MBT in the literature containing a benign Brenner component, cytological atypia and definite or probable invasion of the stroma, only 5 had progressive disease. ¹,²,⁴,⁵,⁶,⁷

In our study, histologic grade, age and tumor size did not differ significantly between TCC and MBT patients.¹ There may be an important distinction between gynecologic malignancies arising in the presence of benign precursor lesions compared with those that do not. For example, endometrial carcinomas arising de novo appear to represent more aggressive neoplasms than those arising out of a preexisting hyperplasia.⁸

You might argue that TCC could have arisen from a Brenner tumor and overgrown and obliterated the benign precursor areas. This probably occurs in some instances, but evidence suggests that at least some transitional cell carcinomas are independent. First, TCC is more aggressive than MBT, stage for stage. Second, distinct areas of stromal calcification are present in a majority of MBT and common in benign Brenner Tumors ⁹, but are absent in TCC of the ovary. Calcification was substantial in many MBTs, and it seems unlikely that overgrowth by TCC would be able to obscure large areas of calcification as well as a benign Brenner antecedent.

An explanation as to why benign and malignant neoplasms arising in the ovary and adjacent peritoneal mesothelium are similar to those of the bladder...
found in the proximity of the gonadal ridge to the mesonephros in the early coelom and the common mesothelial covering of the two. The gonadal ridge arises at the ventral border of the mesonephros and is covered by mesothelium that is continuous over the mesonephros. The mesonephros differentiates to form the mesonephric ducts, the ends of which become incorporated in a portion of the urogenital sinus that is destined to be the bladder. The coelomic mesothelium continuous with both the genital ridge and mesonephros thereby contributes the potential to form similar-appearing neoplasms in each location.

Classifications of epithelial neoplasms of the ovary should acknowledge TCC as a cell type. The distinction of MBT and TCC may have therapeutic as well as prognostic implications, as some patients with extraovarian spread of TCC appear to benefit from adjunctive therapy.

References:


