SEMINARIO DE PATOLOGIA GINECOLOGICA CON ENFASIS EN ASPECTOS PROBLEMATICOS E INUSUALES EN LA PRACTICA DIARIA

Esther Oliva, Massachusetts General Hospital

Caso N 1

Mujer de 66 años que acude al ginecólogo para su visita anual, se le descubre un nódulo homogéneo de aproximadamente 4 cm que se origina en la pared de la vagina. La paciente es intervenida y se le extirpa la lesión. El examen macroscópico muestra un nódulo de 3.4 x 2.5 x 2 cms con una superficie de corte homogénea, elástica y blanquecina.

Diagnóstico: Angiofibroma celular.

This is a relatively recently described tumor that occurs in females and males. In women the vulvovaginal area is the most commonly involved. In men the lesion was initially reported as "angiomyofibroblastoma-like" tumor in the inguinoscrotal region. Cellular angiofibromas can also occur in other locations including the paratesticular region, urethra, anal region, retroperitoneum and others.

Clinical features: They usually present as a painless slowly enlarging mass in women with a mean age of 53 years. They are superficially located and only rarely they may ulcerate and bleed.

Gross features: They are well-circumscribed masses that shell-off from the surrounding tissues with a mean size of 3.5 cm. They have a firm to rubbery consistency and a white to tan to grayish cut surface. Sometimes a multilobulated appearance may be grossly appreciated. Rarely small foci of hemorrhage can be noted.

Microscopic features: The tumors have two components, the spindle cells and the vessels. The spindle cells are relatively small and homogeneous with no cytologic atypia and low or absent mitotic activity. This spindle component is typically cellular and although focally may form short fascicles, more often is arranged in no particular pattern. The background stroma contains thin, palely eosinophilic collagen fibers and may be associated with edema or hyalinization. The vascular component is composed of small to medium-sized, thick-walled vessels. Larger vessels are frequently present at the periphery of the lesion. Not infrequently fat may be seen at the periphery of the tumor and represents less than 5% of the tumor. Finally, inflammatory cells including mast cells are frequently seen.

Immunohistochemical profile: The tumors are frequently positive for CD34 and they may be positive for smooth muscle actin or desmin suggesting fibroblastic/myofibroblastic differentiation. They are consistently negative for S-100. Not infrequently they are also positive for estrogen and progesterone receptors, more often in female than male tumors.

Differential diagnosis:

- ***Aggressive angiomyxoma***. Although the superficial portions of these tumors may protrude into the vagina or form a vulvar swelling, pelvic examination will usually reveal a mass. On microscopic examination, aggressive angiomyxomas, in contrast to cellular angiofibroma is hypocellular with a myxoid background, contain an admixture of thin and thick blood vessels and more importantly show infiltrative borders. Another characteristic feature of aggressive angiomyxoma is the finding of small clusters of smooth muscle cells surrounding or "spinning off from" blood vessels. The spindle cells are typically positive for desmin but negative for CD34.

- ***Angiomyofibroblastoma*** is another mesenchymal lesion that occurs in the lower female genital tract, but in contrast to cellular angiofibroma the tumor has alternating hypocellular and hypercellular areas, the cells are spindle to epithelioid and in the hypercellular areas, the cells tend to swirl around the vessels, this being the most prominent characteristic of these tumors. The cells are desmin positive but CD34 negative.

- ***Solitary fibrous tumor*** has been reported in the vulva and perineum. This is a well-circumscribed tumor that characteristically shows a patternless spindle cell proliferation of alternating hypocellular and hypercellular areas often associated with dense hyaline collagen bundles, stromal hyalinization and hemangiopericytoma-like vessels, features that are only focally seen in a cellular angiofibroma. Immunohistochemistry is not helpful in this differential diagnosis as both tumors are CD34 positive.

- ***Cellular fibroepithelial polyp*** usually involves the vagina but may also be encountered in the vulva and the cervix. They have a sessile to pedunculated to villiform gross appearance in contrast to cellular angiofibroma. The stromal cells although banal they may have multiple nuclei that are frequently disposed in a wreath-like arrangement, giving a heterogenous appearance of the stromal cells. The lesion has large and thick blood vessels The stromal cells are typically immunoreactive for vimentin, and less commonly desmin and muscle-specific actin but are CD34 negative.

Behavior: These tumors are benign and no recurrences or metastases have been reported. The treatment should be local excision.

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Caso N 2

Mujer de 45 años que acude al ginecólogo por notar expulsión de moco por vagina. El examen colposcópico muestra abundante moco que parece originarse en el cervix donde se palpa una masa relativamente bien circunscrita y móvil. La paciente es sometida a histerectomia radical y anexectomia

bilateral. El utero muestra un tumor polipoide de 4 x 3 x 3 cm que se origina en el cuello uterino; al corte, el tumor contiene múltiples quistes de distinto tamaño rodeados de áreas blanquecinas de consistencia firme.

DIAGNOSTICO:
Cervix: Adenomioma.

MULLERIAN ADENOMYOMA

- Endocervical type
- Endometrioid type
- Atypical polypoid adenomyoma

Endocervical Adenomyoma

These tumors are frequently an incidental finding in reproductive age or postmenopausal women.

Gross Features: They are polypoid masses growing into the endocervical canal and sometimes protruding into the external os. The tumors are well circumscribed and gray-white or tan and frequently contain multiple mucin-filled cysts.

Microscopic Features: The *glandular component* is composed by glands and cysts lined by a single layer of endocervical-type mucinous epithelium. The glands have frequently a lobular architecture with a large irregular gland surrounded by smaller glands. Tubal or endometrioid-type epithelium can also be seen. The *smooth muscle* represents the mesenchymal component forming unoriented fascicles. Both epithelial and mesenchymal components are uniformly bland.

Differential diagnosis

- ***Adenoma malignum*** is the main differential diagnosis because of the finding of bland appearing endocervical glands admixed with muscle. The gross circumscription of the adenomyomas, their polypoid appearance, the frequent lobular arrangement of the glands, the absence of invasive glands with a desmoplastic stromal reaction, and lack of even focal atypia are helpful in this differential diagnosis. Adenoma malignum is rarely an incidental finding and well differentiated areas are admixed neoplastic glands associated with cytologic atypia, desmoplastic reaction or perineural invasion.

Behavior: These are benign tumors but if excision is incomplete they may recur.

Mullerian Adenomyoma of Endometrioid Type

Women range from 26 to 64 years of age and frequently present with abnormal vaginal bleeding. In some cases the tumor may be an incidental finding.

Gross Features: The tumors are more frequently located in the uterine corpus but they may be seen in the cervix. In the corpus they have a submucosal location. They may reach 17 cm in largest dimension. On sectioning they are firm and often show small cysts sometimes filled with blood. The firm areas have a similar appearance of that seen in leiomyomas. The tumors are well circumscribed from the surrounding tissues.

Microscopic Features: On low-power examination these tumors are well circumscribed.
The ***glands*** are usually well spaced and range from small simple glands to more irregularly shaped glands and large cysts. They are predominantly lined by proliferative endometrioid-type epithelium, but ciliated, endocervical-type mucinous and squamous epithelium may be found. Cytologic atypia is absent and scattered mitotic figures may be seen. The ***stromal component*** consists of endometrial-type stroma and smooth muscle, and the latter typically predominates. The endometrial-type stroma always has a periglandular distribution and the smooth muscle component is present surrounding the stromal-type component. The endometrial stromal component is characterized by small oval to spindle cells with scant cytoplasm and benign nuclear features. It may show sex cord-like differentiation. The smooth muscle component may be hyper or hypocellular with areas of edema and/or hyalinization. It may contain cells with bizarre nuclei, but there is no cytologic atypia of the background smooth muscle cells. Thick-walled blood vessels are typically found. Mitotic activity if present is more often seen in the endometrial stromal component than in the smooth muscle component.

Differential Diagnosis

- ***Leiomyoma with entrapped endometrial glands***. The glands are usually present at the periphery of the tumor and there are not surrounded by endometrial-type stroma.

- ***Atypical polypoid adenomyoma***. In contrast to the typical endometrioid adenomyoma, atypical polypoid adenomyoma is characterized by irregular crowded endometrioid glands with cytologic atypia and, in 90% of cases, squamous morules, embedded in a cellular, sometimes mitotically active stroma composed, in large part, of smooth muscle.

- ***Typical endometrial polyp***. These lack a prominent smooth muscle component, having instead fibrous and endometrial stromal components and the latter does not uniformly surround the glands as in adenomyomas.

- ***Endometrioid adenocarcinoma, diffusely infiltrating***. These are not well circumscribed and show cytologic atypia of the glandular component.

- ***Adenosarcoma with smooth muscle differentiation.*** They show the characteristic low-power appearance of dilated or leaf-like glands with periglandular condensation of the stroma.

- ***Mixed endometrial stromal-smooth muscle tumors***. No glandular differentiation has been described in those tumors yet and there is a different distribution of the stromal and smooth muscle components than that described in adenomyomas.

Behavior: These are benign tumors with no recurrence or spread reported to date.

Atypical Polypoid Adenomyoma (APA)

Most of these tumors occur in women of reproductive age (mean, 39 years of age), but occasional tumors occur in postmenopausal women. Rare cases are associated with long-term estrogen therapy. The patients typically present with abnormal vaginal bleeding, pelvic examination is usually negative, but in some cases a polypoid mass protrudes from the external

Gross Features: These tumors frequently involve the lower uterine segment, but they may arise in the corpus or cervix. They are typically solitary, well circumscribed, pedunculated or sessile, and <2 cm in

greatest dimension. The sectioned surfaces are yellow-tan to gray and white, solid and firm or rubbery.

Microscopic Features: The ***epithelial component*** has endometrioid glands with varying degrees of architectural and cytologic atypia and mitotic activity are separated by myofibromatous stroma. Squamous morules, present in 90% of cases may fill glandular lumens and occasionally have areas of central necrosis. Keratin liberated from these morules rarely may implant on the peritoneum and result in keratin granulomas. Rare findings include a cribriform pattern, severe cytologic atypia, or both. Foci resembling well-differentiated adenocarcinoma may be seen in APAs. Some APAs are contiguous to and appear to be the origin of a well-differentiated adenocarcinoma. The ***stromal component*** contains interlacing bundles of cellular smooth muscle, proliferating myofibroblasts, or both. The stromal cells exhibit mild to moderate atypicality in a minority of cases. Occasional mitotic figures are usually seen.

APAs usually are non-invasive, with a well-circumscribed border in hysterectomy specimens, although some involve the superficial myometrium. In one study no typical APAs invade the myometrium, but rare APAs associated with foci resembling well-differentiated adenocarcinoma superficially invaded the myometrium.

Differential Diagnosis

- ***Endometrial Adenocarcinoma.*** In a curetting specimen features favoring adenocarcinoma include a postmenopausal age and the presence of glands with overt malignant features.

- ***MMMT***. These usually lack a prominent smooth muscle component and overtly malignant appearance of the epithelial and stromal components.

- ***Adenosarcoma.*** They usually lack a prominent smooth muscle component and periglandular condensation of the stromal component around the glands.

- ***Typical Adenomyoma of the Endometrioid Type*** shows absence of architectural and cytologic atypia.

Genetics: These lesions share some of the molecular alterations seen in endometrial hyperplasia as some of them exhibit MLH-1 promoter hypermethylation with focal lack of MLH-1 immunostaining, a molecular abnormality involved in the transition from complex atypical hyperplasia to endometrioid adenocarcinoma.

Behavior: There is a recurrence index of 45% in patients treated conservatively and those treated in this manner rarely may progress to adenocarcinoma. Those APAs with foci resembling well-differentiated carcinomas have a higher recurrence rate (60% versus 33%).

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Caso N 3:

Mujer de 87 años que acude al ginecólogo por sangrado vaginal de un mes de duración. El examen ginecólogico y una ecografia pélvica muestran un tumor polipoide ocupando toda la cavidad endometrial que aflora por el orificio cervical. La paciente es sometida a histerectomia y anexectomia bilateral. Al abrir el utero se observa un engrosamiento difuso del endometrio (1.5 cm) de color amarillento y consistencia semifirme. El proceso parece infiltrar profundamente la pared miometrial.

DIAGNOSTICO:
Utero: Adenosarcoma mulleriano con transformacion sarcomatosa.

Mullerian adenosarcomas are much less common than malignant mullerian mixed tumors in the uterus.

Clinical Features: The tumors usually occur in postmenopausal women (median 58 years), but in contrast to Malignant Mixed Mullerian Tumors, approximately 30% are found in-patients below 50 years of age. The occasional association of adenosarcomas with hyperestrinism (exogenous estrogen, ovarian thecoma, Stein-Leventhal syndrome) or prior pelvic radiation suggests their possible etiologic role in some cases. Tamoxifen therapy may have played a role in a few cases. The most common symptom is abnormal vaginal bleeding, often accompanied by lower abdominal or pelvic pain. Pelvic examination typically reveals an enlarged uterus, and in about half the cases, tumor protruding through the

external os. The diagnosis can frequently be made prior to hysterectomy by biopsy or dilatation and curettage. Patients with typical adenosarcomas are almost always stage I at presentation and the presence of extrauterine tumor suggest multicentricity or metastases from an adenosarcoma with sarcomatous overgrowth.

➢ *Occasional patients have presented on two or more occasions with lesions misinterpreted microscopically as benign polyps. Recurrent endocervical or endometrial polyps are uncommon, particularly in young women, and their occurrence should therefore suggest the possibility of adenosarcoma.*

Gross features: Typically form polypoid or villous broad-based masses arising from the endometrium (90%); frequently with secondary prolapse through the external os. Approximately 10% of the tumors originate in the endocervix. In rare cases, both the corpus and endocervix are involved by separate primary tumors. The cut surface is frequently spongy, with cystic spaces filled with watery or mucoid fluid, surrounded by white to tan tissue. Myometrial invasion, which is present in approximately one-sixth of adenosarcomas, may be grossly appreciable.

Microscopic features: The ***epithelial component*** has frequently cystically dilated glands scattered throughout the mesenchymal component. Occasionally a villous pattern, with the neoplastic epithelium lining thin papillae or broad polypoid fronds, and only a minor component of glands may be seen. The glands are lined more commonly by proliferative-endometrial type epithelium, although endocervical (mucinous), tubal (ciliated), secretory-endometrial (with subnuclear vacuoles), hobnail, or indifferent epithelia may also be seen. Metaplastic squamous epithelium, typically nonkeratinizing, is often present. In approximately one-third of adenosarcomas, the glandular epithelium exhibits focal architectural or cytological atypia, and small foci of endometrial adenocarcinoma may be rarely encountered. In such cases, the endometrium elsewhere in the uterus may be hyperplastic or carcinomatous. The frequent mitotic activity of the epithelial component, which is often in contrast to the inactivity or atrophy of the epithelium of the adjacent endometrium, the variety of epithelial cell types, the extensive distribution of glands throughout the stromal component and the occasional presence of glands within recurrent adenosarcoma are evidence of the neoplastic nature of the epithelial component of the tumor.

The ***stromal component*** typically has the appearance of a low-grade sarcoma, usually an endometrial stromal sarcoma, fibrosarcoma, or combinations thereof. Minor foci of smooth muscle differentiation have been occasionally described. The stroma is more cellular around the glands, creating a cuff-like appearance and intraluminal polypoid or papillary stromal projections are common. The stroma at a distance from the glands is often less cellular, and in some tumors, the stroma is composed predominantly of sparsely cellular, myxoid or hyalinized fibrous tissue, imparting a deceptively benign appearance to large areas of the tumor. The stromal cells exhibit mild or moderate nuclear atypia, but occasionally may be marked. Mitotic figures are an almost constant finding, and >80% of tumors exhibit a mitotic rate of 4 or more per 10HPFs.

Approximately one-sixth of adenosarcomas invade the myometrium; although in only 20% of such cases the invasion extends beyond the inner one-half of the myometrium. The invasive borders are usually well circumscribed but occasional tumors invade in irregular tongues. Rare adenosarcomas invade myometrial vessels in a pattern similar to that of low-grade endometrial stromal sarcoma.

Other microscopic features

✓ ***Heterologous elements*** in approximately 20% of adenosarcomas, which have varied from minor foci of fat, cartilage, or rhabdomyoblasts to embryonal rhabdomyosarcoma occupying most

or all of the stroma. Some of the cases with the latter type of stroma have also contained nodules of fetal-type cartilage similar to those occurring in some cases of embryonal rhabdomyosarcoma of the vagina and cervix.

✓ ***Foci of sex cord-like elements*** (SCLEs) within the stromal component. The SCLEs, which account for 5-50% of the tumors, are composed of benign-appearing epithelial type cells arranged in solid nests, trabeculae, and solid or hollow tubules. The cells may contain abundant eosinophilic or foamy, lipid-rich cytoplasm. The appearance of the SCLEs is similar to that of those encountered in some endometrial stromal tumors and in the rare uterine tumors resembling ovarian sex cord tumors.

✓ ***Sarcomatous overgrowth*** of the stromal component may occur in occasional adenosarcomas ("mullerian adenosarcoma with sarcomatous overgrowth") (MASO). In contrast to typical adenosarcomas, prominent myometrial invasion and also lymphovascular invasion are frequently present. ***To establish the diagnosis of MASO, the area of pure sarcoma has to occupy at least 25% of the tumor volume or one low-power field in one slide.*** The sarcoma in most cases is a high-grade sarcoma, but it can have a similar appearance to the low-grade sarcoma of the conventional adenosarcoma.

Useful criteria in diagnosing mullerian adenosarcoma alone or in combination include:

- Two or more stromal mitotic figures/10 HPFs
- Marked stromal cellularity
- Significant stromal cell atypia

Differential Diagnosis:

- ***Adenofibroma.*** Although may have a similar gross appearance, on microscopic examination the stromal component of the tumor is cytologically benign, with cells resembling fibroblasts or endometrial stromal cells exhibiting no or minimal nuclear pleomorphism and no mitotic activity. Zaloudek and Norris stated that the stromal mitotic rate is the most reliable criterion in the differential diagnosis. Because all the clinically malignant tumors in their series of cases had stromal mitotic counts of 4 or more MFs/10 HPFs, they concluded that only tumors with that degree of mitotic activity should be designated adenosarcomas. However, four of the 10 clinically malignant adenosarcomas in their series, had mitotic rates of only 4 or 5/10HPFs; the difference between such counts and a "benign" count of 3 MF/10 HPFs is within interobserver variation. Also, counting mitotic figures in these tumors may be difficult because of variations in cellularity. In contrast, Clement and Scully encountered a number of tumors with 2 or 3 MF/10HPF that had extrauterine disease at the time of presentation or that recurred after hysterectomy. Thus it appears that almost any measurable degree of stromal mitotic activity in these tumors can be associated with a malignant behavior.

Smooth muscle may be present focally in the stroma, but heterologous elements have not been described and most importantly no periglandular condensation of the stromal cells is identified. In contrast, adenofibroma are typically non-invasive

➢ *We diagnose as adenosarcoma tumors with 2 or more MF/10HPFs, a mitotic rate that will detect almost all tumors with a malignant potential.*

➢ *Because rare essentially amitotic tumors with marked stromal cellularity, stromal atypia or both have recurred after hysterectomy, we also consider tumors with these features low-grade adenosarcomas.*

➢ *Extensive sampling is required to exclude foci exhibiting mitotic activity, marked cellularity, or stromal cell atypia. This evaluation usually requires hysterectomy.*

▪ ***Benign endometrial polyps***. In those the stroma may resemble that of the adjacent endometrium or may be less cellular and often sclerotic. The stroma may be cellular but it is typically inactive. If its stromal component is unusually cellular or mitotically active, if its glandular cells differ in appearance from those of the adjacent endometrium, or if periglandular cuffing or intraglandular stromal papillae are present, the diagnosis of adenosarcoma should be seriously considered. Finally, bizarre stromal cells may be seen in an otherwise typical endometrial polyp. This feature should not be misinterpreted as cytologic atypia and accordingly the lesion should not be diagnosed as an adenosarcoma.

▪ ***Atypical polypoid adenomyoma***. The predominant stromal component is smooth muscle arranged in fascicles that may be cellular and mitotically active. The glandular component is less cystic and generally more atypical than that of an adenosarcoma and usually contains prominent numbers of squamous morules that may contain central areas of necrosis. There is absence of intraglandular polypoid projections or periglandular cuffing.

▪ ***Endometrial stromal sarcoma*** typically lacks the integral glandular component of the adenosarcoma, although their periphery may contain occasional entrapped glands, or in a minority of cases, there may be focal prominent glandular differentiation within the tumor and both tumors may have sex cord-like differentiation. Unlike adenosarcomas, endometrial stromal sarcomas typically have highly infiltrative borders with extensive myometrial and vascular penetration.

Behavior: Adenosarcomas frequently present with vaginal or abdominopelvic recurrence (approximately ¼ of the cases), while hematogenous spread occurs in less than 5%. Even in the clinically malignant cases, the recurrent tumor has often been indolent. In one-third of cases with recurrences in one large series, the recurrent tumor appeared 5 or more years after hysterectomy, and rare tumors recurred 10 or more years after hysterectomy. The recurrent tumor has been a pure sarcoma in 70% of the cases, an adenosarcoma in almost 30% and a carcinosarcoma in a single case. Rarely recurrent tumor contains heterologous elements or foci of carcinoma that were not present in the primary tumor. Blood-borne metastases have been pure sarcomas. The mitotic rate and grade of the recurrent tumor may be lower than, similar to, or higher than those of the original adenosarcoma.

➢ *The risk of recurrence in adenosarcomas correlates with the presence of myometrial invasion.*

➢ *Sarcomatous overgrowth is the other feature that correlates with an increased risk of recurrence. Those tumors have a behavior similar to that of other high-grade uterine sarcomas such as MMMT and leiomyosarcoma.*

➢ *The presence of heterologous elements was not associated with an increased risk of recurrence in one large study of typical adenosarcomas.*

➢ *Long-term clinical follow-up is therefore essential in these patients.*

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Caso 4:

Mujer de 40 años que acude al ginecólogo por metrorragia. El examen pélvico asi como la ecografia pélvica revelan un utero miomatoso. La paciente es sometida a histerectomia simple. El utero esta aumentado de tamaño y distorsionado por la presencia de múltiples nódulos, algunos firmes y blanquecinos y otros de menor consistencia y más amarillentos, cuyo tamaño oscila entre 0.2 y 2 cms.

DIAGNOSTICO:
Utero: Leiomiomatosis intravenosa celular.

Intravenous leiomyomatosis is defined as the presence of intravenous proliferations of benign-appearing smooth muscle in the absence of, or outside the confines of, a leiomyoma. The clinical presentation is usually similar to that of typical uterine leiomyomas. Extrauterine venous involvement, which occurs in about 30% of cases, is usually confined to the pelvis, but occasionally tumor can extend into the inferior vena cava and reach the right side of the heart, sometimes with fatal results. In rare

cases, patients with intact uteri and no pelvic manifestations present with cardiac involvement. Extrauterine extension may be diagnosed intraoperatively, on gross examination of the hysterectomy specimen, on postoperative imaging studies, or in some cases not until many years after hysterectomy when the patient presents with recurrent tumor. Rare patients have had a solitary metastasis (lungs, pelvic lymph nodes) ("benign metastasizing leiomyoma").

Gross features: The uterus is usually enlarged and bosselated with multinodular, rubbery, gray-white myometrial masses, at least some of which form worm-like plugs of tumor within myometrial or parametrial vessels, although this feature is often not appreciated on initial gross examination. Typical or hydropic leiomyomas are also usually present, but occasionally all discernible tumor is intravascular.

Microscopic features: The intravascular tumor (which is unsheathed by endothelial cells) usually, at least focally, resembles a typical leiomyoma, but rarely has the appearance of a leiomyoma variant, including cellular leiomyoma, leiomyoma with bizarre nuclei, lipoleiomyoma, myxoid leiomyoma, or epithelioid leiomyoma. The intravascular tumor often has a clefted or lobulated contour, extensive hydropic change or hyalinization, and a content of numerous thick-walled vessels, features that may obscure its smooth muscle nature. Mitotic figures are usually rare, but cellular intravenous leiomyomatosis may contain up to 4MFs/ 10 HPFs.

Differential Diagnosis

- ***Typical leiomyomas*** that are partially surrounded by compressed vascular spaces or typical leiomyomas with artifactual retraction from the surrounding myometrium. Stains for endothelial antigens may be useful in problematic cases.

- ***Leiomyoma with vascular invasion***. This term has been applied to rare otherwise typical leiomyomas or leiomyoma variants with microscopic intravascular growth confined to the tumor. In many patients, this intravascular growth is likely inconsequential, although no large series of these tumors with long-term follow-up has been reported. Several cases, however, have been associated with benign smooth muscle nodules in the lungs ("benign metastasizing leiomyoma") while some cases may represent an early stage of intravenous leiomyomatosis.

- ***Leiomyoma with perinodular hydropic change***. This is a common degenerative change seen in leiomyomas. If marked, it may result in cystic degeneration and may mimic the appearance of intravenous leiomyomatosis both grossly and microscopically, potential problems being accentuated by the fact that the smooth muscle component in that low malignant potential lesion often has hydropic change. In contrast to intravenous leiomyomatosis, immunohistochemical stains for endothelial markers confirm the absence of endothelial cells around the nodules or lining the pseudovascular spaces.

- ***Low-grade endometrial stromal sarcoma***, in contrast to cellular intravenous leiomyomatosis, usually lacks thick-walled vessels, lobulation, and hydropic degeneration in its intravascular extensions, and usually involves the endometrium as well as the myometrium.

Behavior: Rare patients experience pelvic or cardiac recurrences, as many as 15 years after hysterectomy, from continued growth of residual intravenous tumor. In some such cases, an initial diagnosis of a primary cardiac tumor is made, especially in women in whom the diagnosis was missed on a hysterectomy specimen. In women in whom the diagnosis of intravenous leiomyomatosis is made on a hysterectomy specimen, postoperative ultrasonic or magnetic resonance imaging studies may be useful in detecting and monitoring the growth of residual intravascular tumor. GnRH-agonists may be useful in controlling unresectable tumor.

A few words on *benign metastasizing leiomyoma,* a lesion related to intravenous leiomyomatosis. This disorder is characterized by the presence of single or multiple extrauterine nodules, usually pulmonary, composed of benign-appearing smooth muscle in women who have had typical uterine leiomyomas, or rarely leiomyomas with vascular invasion or intravenous leiomyomatosis. Other sites that may be involved in the presence or absence of pulmonary involvement include retroperitoneal and mediastinal lymph nodes, soft tissue and bone. The uterine tumors often have been removed by hysterectomy years earlier. The diagnosis of benign metastasizing leiomyoma should be rendered only in cases in which the uterine tumors have been thoroughly sampled to exclude leiomyosarcoma. An extrauterine leiomyosarcoma or gastrointestinal stromal tumor (GIST) (gastrointestinal tract, retroperitoneum) should also be excluded.

Gross features: The pulmonary tumors, which may be as large as 10 cm in diameter but are usually smaller, are circumscribed; solid or solid and cystic.

Microscopic features: Bundles of mature smooth muscle that may be surrounding fluid-filled cysts lined by entrapped bronchioalveolar epithelium.

Origin: The presence of estrogen and progesterone receptors in the metastatic tumor, a reduction in their size during pregnancy, and a cessation in their growth or complete regression after oophorectomy or the menopause, indicate hormone dependence in at least some cases. Although some investigators argue that cases of “benign metastasizing leiomyoma” represent hormonally induced hyperplastic primary pulmonary lesions, the rarity of smooth muscle proliferations in the absence of uterine leiomyomas, the association of the pulmonary lesions and uterine leiomyomas with vascular invasion or intravenous leiomyomatosis, and the occasional involvement of pelvic lymph nodes indicate that the pulmonary nodules are likely metastatic from the uterine tumors in most cases.

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Case N 5:

Mujer de 64 años que acude al medico general por observar la presencia de sangre en heces. La colonoscopia descubre un tumor exofítico y ulcerado en el sigma que se biopsia. Con el diagnóstico de carcinoma de colon la paciente es sometida a cirugia, durante la que se descrubre una masa ovárica izquierda; se opta por resecar el segmento de colon y extirpar ambos anejos. El examen macroscópico del ovario derecho es normal pero el ovario izquierdo mide 13 x13 x5 cm, es de superficie lisa y al corte se observan múltiples quistes que, en su mayoria, contienen material necrótico y hemorrágico.

DIAGNOSTICO:
Ovario: Metástasis de carcinoma de colon.

It is reported that approximately 7% to 17% of malignant tumors involving the ovary are metastatic although an accurate frequency is difficult to determine as studies have been based on different populations. The most common tumors that metastasize to the ovary arise in the colorectum, breast, endometrium, stomach, cervix, pancreas, appendix, and biliary tract. On routine microscopic examination, metastatic adenocarcinoma, particularly of gastrointestinal origin, may so closely mimic a primary ovarian adenocarcinoma that the correct diagnosis can be overlooked. Similarly, up to 45% of metastases from the large intestine are clinically interpreted as primary ovarian carcinoma. Several studies have evaluated various gross and microscopic features of metastatic and primary ovarian tumors in an attempt to establish diagnostic criteria that would reliably distinguish between them. The following findings have been found to be strongly suggestive of a metastatic process:

- Bilateral ovarian tumors
- Multinodular growth
- Surface involvement (surface implants)
- Lymphatic or vascular invasion
- Infiltrative pattern of stromal invasion
- Tumor size less than 10 cm
- Ovarian hilar involvement
- Single cell invasion

Other features such as the presence of "dirty" necrosis in association with a garland pattern should suggest, but are not diagnostic of, colorectal cancer. Arriving at the correct diagnosis is obviously important in that the prognosis and management of a primary ovarian tumor are often significantly different from those of a metastatic neoplasm. When possible, any tumors previously diagnosed in the patient should be reviewed and compared to the current one. If immunohistochemistry is required, the use of a panel of antibodies provides the most accurate immunophenotype and can usually assist in the correct identification of the site of origin.

Cytokeratins
They should be used as part of the initial immunohistochemical panel in the differentiation of primary from metastatic carcinomas of the ovary.

A frequent diagnostic problem is the differentiation of an ovarian adenocarcinoma, which is usually of endometrioid type (less often of mucinous type or rarely of clear cell type), from a metastatic colonic adenocarcinoma. The combined use of CK7 and CK20 allows the discrimination of most metastatic colorectal carcinomas from non-mucinous adenocarcinomas of the ovary. Non-mucinous ovarian

adenocarcinomas are almost always positive for CK7 and negative for CK20 whereas the vast majority of colorectal carcinomas are usually negative for CK7 and uniformly positive for CK20, with the exception of right-sided and high-grade colon cancers which more often express CK7. Ovarian mucinous tumors show an inconsistent immunophenotype but are almost always positive for CK7 and show variable positivity for CK20, which is often patchy in distribution, in 40 % to 73 % of tumors. Exceptions include mucinous tumors arising in mature cystic teratomas of the ovary which are negative for CK7 and positive for CK20 suggesting that they arise from gastrointestinal elements of the teratoma. Many other carcinomas, including those of lung, breast, thyroid, uterus, gallbladder, pancreas, and bladder origin are also CK7 positive, and thus the use of cytokeratins to distinguish between these tumors and a primary ovarian tumor is not useful. Studies of CK7 expression in gastric carcinomas vary greatly, with some studies showing up to 96% CK7 positivity and up to 40% CK20 expression. Similarly, in small bowel carcinomas, a very recent study has shown that these tumors are typically CK7 positive, although 75% of the cases also express CK20. Of note, adenocarcinomas of the appendix are CK20 positive and may show variable positivity for CK7, particularly the signet-ring and mixed types which are CK7 positive in 50% of the cases. Recent immunohistochemical studies of CK7 and CK20 in synchronous ovarian and appendiceal mucinous tumors with pseudomyxoma peritonei have found that the ovarian tumors are metastatic from the appendiceal tumor in most if not all cases. The appendiceal and ovarian tumors in cases of pseudomyxoma peritonei are both CK7 negative and CK20 positive. As CK7 and CK20 are not always discriminatory, particularly in mucinous tumors, the addition of CEA to the initial immunohistochemical panel may be helpful as colonic carcinomas are typically positive for CEA and approximately 35% of ovarian mucinous carcinomas are CEA negative.

CA-125 and HAM 56:

As single tests, their value in identifying ovarian adenocarcinoma is not reliable.

CA-125 is an antigen recognized by the monoclonal antibody OC-125 prepared against human serous carcinoma. CA-125 shows strong and diffuse staining of serous and endometrioid ovarian carcinomas with positivity ranging from 0 to 50% in mucinous tumors, and no staining reported in sex cord-stromal tumors or germ cell tumors. It also shows positivity in other carcinomas of mullerian origin, mesotheliomas, as well as carcinomas arising in the pancreaticobiliary tract, gastrointestinal tract, breast, thyroid, and other sites. Human alveolar macrophage 56 (HAM 56) is an antibody that identifies macrophages and endothelial cells and also stains many adenocarcinomas including those arising in the ovary, breast, lung, and uterus. Studies of the expression of HAM 56 in colon cancer have shown conflicting results with 21% to 39% of these tumors being positive. CA-125 and HAM 56 may be helpful as part of a diagnostic panel, but their use as a single test in identifying ovarian adenocarcinoma is not reliable.

Cdx-2:

A highly sensitive but relatively nonspecific marker of colorectal carcinoma.

Cdx-2 is a recent addition to the antibodies used to discriminate primary ovarian adenocarcinomas from metastatic colorectal carcinoma. Cdx-2 is a gene that codes for a transcription factor that is important in the development and differentiation of the large and small intestine. Several studies report consistent strong and diffuse nuclear positivity in colorectal carcinomas. Staining is also seen in ovarian carcinomas, most often in mucinous carcinomas (in up to 93% of cases), and rarely in endometrioid carcinomas. Cdx-2 expression is much less frequent and more heterogeneous in adenocarcinomas of the stomach, esophagus, pancreas, and endometrium. Cdx-2 is an extremely sensitive marker of colorectal cancer, but due to its relative lack of specificity, it is best used in conjunction with other stains.

***ß-catenin*:**

Its value in the diagnosis of metastatic colorectal carcinoma.

ß-catenin mutations play an important role in the development of colorectal cancer. Mutations in the adenomatous polyposis coli (APC) gene or in the ß-catenin gene cause ß-catenin protein to become localized in the nucleus, where it can be demonstrated by immunohistochemistry. Chou et al. found that 83% of colorectal carcinomas, 9% of primary ovarian mucinous carcinomas, and 4 non-mucinous carcinomas (2 endometrioid, 1 serous, 1 carcinosarcoma) showed positive staining for ß-catenin. Logani et al. analyzed the use of ß-catenin in conjunction with Cdx-2 and P504S and found that 59% of colorectal carcinomas showed strong diffuse positivity with ß-catenin. In contrast, only three endometrioid adenocarcinomas showed ß-catenin expression, which was confined to areas of squamous metaplasia in two of the tumors while all primary mucinous carcinomas were negative for ß-catenin. ß-catenin immunostaining also can be found in other metastatic adenocarcinomas including gastric carcinoma with a signet-ring morphology, endometrial carcinoma, and rarely in breast carcinoma and conventional pancreatic ductal carcinoma. These findings indicate that the use of ß-catenin is not helpful as a single diagnostic antibody in the distinction of primary and secondary adenocarcinomas in the ovary.

P504S:

A marker for colorectal carcinoma.

P504S is a mitochondrial and peroxisomal enzyme involved in the metabolism of fatty acids and in bile acid synthesis. Overexpression of P504S has been observed in several tumors particularly colorectal carcinoma and prostate cancer and in their precursor lesions, prostatic intraepithelial neoplasia and tubular adenoma. The frequency of P504S expression in colorectal carcinoma has ranged from 35% to 92% in different series. Some authors have found that the frequency of P504S expression is decreased in poorly differentiated colonic carcinomas. Studies of P504S in primary ovarian tumors are limited, and in two studies, only 2 of 33 ovarian carcinomas were positive. In one study, the subtypes of ovarian carcinoma were not mentioned and in the other study six of six serous carcinomas were negative. In another study, Zhou and colleagues reported that some ovarian carcinomas overexpressed P504S, but they provided neither the number of cases nor the subtypes studied. Although there appears to be value in the use of P504S in the diagnosis of colorectal cancer, its expression in primary ovarian tumors requires additional evaluation.

***MUC2 and MUC5AC*:**

Their utility in differentiation of primary ovarian mucinous tumors from mucinous tumors of appendix and in determining the origin of pseudomyxoma peritonei.

Several mucin genes have been identified and their expression has been found to be relatively specific to the tissue type. MUC2 is expressed by goblet cells of intestinal and colonic epithelium and MUC5AC is expressed by endocervical, respiratory, and gastric glandular epithelium. Colon cancers metastatic to the ovary are usually positive for MUC2 and may rarely express MUC5AC with the degree of expression related to tumor differentiation. However, in a recent study, MUC5AC expression was seen in 89% of signet-ring cell carcinomas of the colon. Borderline mucinous tumors and mucinous carcinomas show MUC5AC staining with focal MUC2 staining limited to goblet cells of intestinal type. MUC5AC is not helpful in the differential diagnosis of a mucinous carcinoma from the cervix or pancreas metastatic to the ovary as these tumors are also MUC5AC positive. Differential MUC2 and MUC5AC expression has also been studied in cases of pseudomyxoma peritonei with synchronous mucinous tumors of the appendix and ovary. MUC2 is expressed in appendiceal and ovarian tumors with pseudomyxoma peritonei, supporting an appendiceal origin of the pseudomyxoma peritonei. Although

these findings support the use of mucin immunohistochemistry in the differential diagnosis of ovarian and colon adenocarcinoma, it is recommended that these antibodies be used as part of a panel.

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Caso N 6:

Mujer de 20 años que acude al ginecólogo por dolor pélvico. El examén ginecólogico y una ecografia pélvica denotan una masa de aproximadamente 10 cm en el area del ovario izquierdo. Se realiza una anexectomia izquierda. El ovario mide 9 x 8 x 6cms y está casi completamente reemplazado por un tumor predominantemente sólido con pequeños quistes, de superficie de corte lobulada y coloración relativamente amarillenta.

DIAGNOSTICO:
Ovario: Tumor de células de Sertoli-Leydig con componente retiforme.

Sertoli-Leydig cell tumors (SLCTs) account for < 1% of ovarian neoplasms. They are classified into five major categories: well, intermediate, and poorly differentiated, retiform, and mixed. Any of the last four categories may be associated with heterologous elements. They typically occur in reproductive age women (average age 25 years) while retiform SLCTs usually occur at a younger age (average 15 years). One third of the patients present with signs of virilization (retiform SLCTs and SLCTs with heterologous elements). Occasionally the tumors may be estrogenic or have a-fetoprotein elevation.

Gross features: Solid yellow masses with focal cyst formation, except SLCTs with heterologous or retiform components more commonly cystic. In the latter, the cysts contain multiple papillae and polypoid excrescences. Only 2% of tumors are bilateral.

Microscopic features: ***Well-differentiated tumors*** have a predominant tubular pattern forming lobules with the tubules being solid or hollow whereas the stromal component consists of bands of fibrous tissue with Leydig cells (Reinke crystals present in 20% of cases). ***Intermediate differentiated SLCTs*** often have a lobulated growth with densely cellular areas intersected by hypocellular edematous tissue The Sertoli cells within the lobules are arranged diffusely or in tubules, nests or cords, and they have small round to oval nuclei, and typically scanty cytoplasm. Occasionally they contain abundant, pale or vacuolated cytoplasm. Clusters of Leydig cells may be seen in the lobules but they are more often conspicuous at the periphery of the lobules, as well as at the periphery of the tumor as a whole. ***Poorly differentiated SLCTs*** are characterized by a diffuse or sarcomatoid growth of poorly differentiated Sertoli cells with very scant or absent Leydig cells. The appearance may suggest that of a fibrosarcoma or even undifferentiated carcinoma. The ***retiform variant*** is characterized by growth patterns that simulate those of the rete testis and it is seen in approximately 15% of SLCTs, typically intermediate and poorly differentiated tumors. There is an irregular network of elongated, often slit-like tubules and cysts often containing papillae. The papillae may be short and rounded or blunt, often containing hyalinized cores, or are larger with fibrous or edematous cores. Tubules, papillae, and cysts are usually lined by a single layer of cuboidal epithelial cells with round to oval nuclei. The cytoplasm is typically scanty and mitotic activity variable. The stromal component varies from moderately cellular fibrous tissue (which is occasionally focally hyalinized) to markedly edematous (accounting for the soft, spongy consistency) to very cellular, immature mesenchyme.

Heterologous elements occur in approximately 20% of SLCTs, the most common being mucinous epithelium of gastrointestinal type, present in almost 90% of these tumors which is usually benign, but is occasionally borderline or low-grade carcinoma. In approximately half of the cases with argentaffin cells, microscopic foci of carcinoid are present, which may be easily overlooked. Mesenchymal heterologous elements include cartilage, which typically appears fetal, or skeletal muscle Mesenchymal heterologous elements are usually found in tumors with a sarcomatoid background.

Unusual features include:

- Grooved or bizarre nuclei (either in Sertoli or Leydig cells).
- Cysts of varying size, sometimes containing eosinophilic secretion mimicking thyroid tissue.
- Hepatic differentiation.
- Prominent edema during pregnancy distorting the typical architecture.
- Conspicuous Leydig cell aggregates during pregnancy.

Differential Diagnosis

- ***Sertoli cell tumors.*** As SLCTs and Sertoli cell tumors share histologic features, they may be confused with each other. The presence of Leydig cells or heterologous elements is highly suspicious for SLCT. Extensive sampling is very important.

- ***Endometrioid carcinoma with sex-cord features*** (EC) may contain cords and tubules and the stroma is frequently fibromatous and may contain luteinized stromal cells. Typical areas of EC are almost always present, even with an adenofibromatous background. In difficult cases inhibin and EMA are helpful.

- ***Krukenberg tumor*** (KT) may mimic a SLCT as it is typically associated with stromal luteinization and secondary virilization and may show tubular formation. However, KTs are typically bilateral, and are associated with atypical cells including signet ring cells with mucin.

- ***Serous borderline tumor/carcinoma.*** The retiform SLCT may mimic the growth of a serous tumor. However, conventional areas of intermediate differentiation associated with Leydig cells as well as the absence of ciliated cells should be helpful in the differential diagnosis.

- ***Yolk sac tumor*** (YST). The retiform SLCT may mimic a YST as both occur in young patients, may have a prominent hypocellular stroma with marked edema and a papillary growth. However, about 1/3 of the patients with SLCTs have androgenic manifestations, while YSTs even though may have peripheral stromal luteinization usually do not have androgenic manifestations. Finally, the cells in YSTs are more primitive and they stain with a-fetoprotein.

- ***Mixed malignant mesodermal tumors***. The admixture of retiform tubules with immature mesenchymal tissue which may show heterologous differentiation can suggest the diagnosis of a malignant mixed mesodermal tumor.

- ***Immature teratoma***. Heterologous SLCTs are most often misdiagnosed as teratomas, but the common constituents of teratomas, such as squamous epithelium, skin appendages, and respiratory epithelium, have not been reported in SLCTs. In addition, neuroectodermal tissues are very rare in these neoplasms in contrast to their frequency in teratomas. Heterologous SLCTs containing prominent amounts of mucinous epithelium may be confused with pure mucinous cystic tumors on gross and microscopic examination. Although a history of virilization is much more suggestive of a SLCT, occasional mucinous tumors containing luteinized stromal cells are masculinizing. The diagnosis of heterologous SLCT rests on finding a Sertoli-Leydig cell component, which is almost always of intermediate differentiation, between the glands and cysts or at the periphery of the tumor. Heterologous SLCTs with mesenchymal elements may be confused with sarcoma when recognizable Sertoli-Leydig cells are scarce. Before a pure ovarian sarcoma is diagnosed, particularly in a young woman, heterologous SLCT should be excluded by thorough sampling.

Behavior: Approximately 12% of SLCTs are clinically malignant. Almost all of the malignant tumors have been, alone or in combination, poorly differentiated, retiform, or contained heterologous mesenchymal elements.

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Caso N 7:

Mujer de 28 años que durante la semana 29 de embarazo acude al ginecólogo por disconfort abdominal y dificultad para respirar. El examén físico descubre la presencia de ascitis y derrame pleural. Una ecografia evidencia una masa de aproximadamente 20 cms en el ovario derecho. La paciente es sometida a cirugia con excisión de la masa ovárica al mismo tiempo que se toman múltiples biopsias peritoneales. El tumor pesa 1600 gr y mide 21 x 15 x 12 cms, su superficie externa es lisa y al corte tiene una apariencia heterogénea con áreas blancas, grisaceas o amarillentas y abundantes zonas de necrosis y hemorragia.

DIAGNOSTICO:

Ovario: Carcinoma de células pequeñas de tipo hipercalcémico.

This is a distinctive form of undifferentiated ovarian cancer, which is probably the most common form of undifferentiated ovarian carcinoma in women under 40 years of age. The tumor is associated with paraneoplastic hypercalcemia in two-thirds of the cases and accounts for slightly more than half of the reported cases of hypercalcemia associated with ovarian cancer (Table 1). The patients range from 9 to 44 (mean, 24) years of age. Most patients present with signs and symptoms related to the presence of an abdominal or pelvic mass, but in rare cases, the clinical presentation has been related to the hypercalcemia. Rare familial cases have been encountered.

Gross features: The tumors are usually large and predominantly solid and soft with frequent areas of necrosis and hemorrhage.

Microscopic features: The most common pattern is a more or less diffuse arrangement of small, closely packed epithelial cells, punctured by, in 80% of cases, follicle-like spaces containing weakly eosinophilic fluid. The tumor cells also grow as small islands, cords and clusters. The tumor cells have scant cytoplasm and small nuclei containing single nucleoli. Mitotic figures are numerous.

Unusual features include:

- ***Component of cells with abundant eosinophilic cytoplasm*** in about half of the cases, referred to as "large cell variant" of small cell carcinoma when this is the predominant, component. The large cells often have eccentric nuclei and dense globular cytoplasm. Ultrastructural examination in some of these cases has shown numerous whorls of microfilaments.

- ***Mucinous epithelium*** as a minor component in about 10% of these tumors. The latter may resemble a mucinous cystadenoma, typically standing out sharply from the background sea of small cells. Occasionally, however, the mucinous epithelium is less conspicuous and more cytologically atypical, and may merge with the small cells. Rarely it may take the form of signet-ring type cells. One might hope that the presence of mucinous epithelium would help one ascribe a specific cell of origin to this tumor but, as mucinous epithelium may be seen in common epithelial tumors, germ cell tumors and sex cord-stromal tumors, this is unfortunately not the case.

Immunohistochemical profile: These tumors usually stain for keratins. The tumor cells also stain for EMA in one-third of the cases. They are frequently positive for WT1 and CD10. Approximately 50% of the tumors stain for vimentin and two-thirds stain for NSE. All tumors are negative for inhibin, a relatively new marker for sex cord stromal tumors, however they are frequently positive for calretinin, a much less specific marker of se-cord differentiation. Overall is felt that small cell carcinoma of the hypercalcemic type probably represents a variant of surface epithelial tumor rather than a type of sex cord-stromal tumor.

Differential diagnosis

- ***Granulosa cell tumor of either adult or juvenile types*** **(AGCT/JGCT)** are frequently mentioned in the differential diagnosis. However, the cells of the small cell carcinoma do not have the characteristic pale grooved nuclei of the AGCT and the mitotic rate in the small cell carcinoma far exceeds that encountered in AGCTs. Distinction from the JGCT is generally easy, because the cells of the small cell carcinoma usually lack the abundant eosinophilic cytoplasm that is an almost invariable feature of the cells of the JGCT. Even in cases of small cell carcinoma in which there are cells with abundant eosinophilic cytoplasm, distinction can usually be made because such cells are most often a

focal finding and, in addition, they differ in appearance from the cells of the JGCT, because of the dense, sometimes globular cytoplasm. Additionally, in cases of small cell carcinoma containing cells with abundant cytoplasm, there is generally a more disorderly architecture than seen in the JGCT. Finally, with regard to distinction from both forms of granulosa cell tumor, it is often helpful that the small cell carcinoma has spread beyond the ovary at presentation, something, which would be exceptional for either variant of granulosa cell tumor.

- ***Small cell malignant tumors that may involve the ovaries in young women***. These include primitive neuroectodermal tumors, primary or metastatic neuroblastoma, malignant lymphoma and leukemia, metastatic round cell sarcomas, metastatic small cell carcinomas, most of which are of pulmonary origin, metastatic malignant melanoma, the intra-abdominal desmoplastic small round cell tumor, and ovarian small cell carcinomas of pulmonary type.

- ***Highly malignant monodermal teratomas of central nervous system type, resembling neuroblastoma and primitive neuroectodermal tumors***, occur in the same age group as the small cell carcinoma. In cases of neuroblastoma, the presence of Homer-Wright rosettes is often diagnostic, although such structures may be few in number. Appreciation of fibrillar material may also be important in the diagnosis in these cases. Although follicles are not a feature of neuroblastoma or primitive neuroectodermal tumors, the rare neuroblastoma that spreads to the ovary from elsewhere, like many metastatic tumors of the ovary, may contain follicle-like spaces that may be misconstrued as the follicles of the small cell carcinoma. In these cases, other microscopic features and the clinical findings, alone or in combination, should enable the diagnosis to be established.

- ***Intra-abdominal desmoplastic small round cell tumor*** **(DSRCT)**. The three examples of ovarian involvement of this neoplasm all occurred during the teenage period when the hypercalcemic form of small carcinoma may occur. The ovarian involvement was bilateral in two of the three cases of DSRCT, in contrast to the rarity of bilaterality of the hypercalcemic small cell carcinoma. Although the hypercalcemic tumor may have an insular pattern, it is generally absent or only focal, whereas in the DSRCT discrete nests of tumor cells are characteristic. Additionally, the latter tumor has, as its name implies, a typically prominent desmoplastic stroma, which is either absent, or only a focal finding in the hypercalcemic small cell carcinoma. The nests in the DSRCT often have a basaloid appearance, which is not a feature of the hypercalcemic tumor and its cells, although small, are more reminiscent of those of the pulmonary form of small cell carcinoma than the hypercalcemic tumor. Finally, if any difficulty in the distinction of the DSRCT and hypercalcemic small cell carcinoma remains on the basis of the examination of routinely stained sections, immunohistochemical examination will be diagnostic as the staining of the DSRCT for desmin is not a feature of the hypercalcemic tumor.

- ***Metastatic alveolar rhabdomyosarcoma***, because the follicle-like spaces of the small cell carcinoma may be simulated by cystic changes in the alveolar spaces of the rhabdomyosarcoma. However, the distinctive and prominent alveolar pattern of rhabdomyosarcoma is not a feature of small cell carcinoma. The distinctive giant cells that are seen in some rhabdomyosarcomas have not been encountered in the hypercalcemic small cell carcinoma. The age distribution of these two tumors is similar, although the youngest patient with small cell carcinoma of whom we are aware was nine years old, whereas patients with alveolar rhabdomyosarcoma are occasionally younger.

- ***Malignant lymphoma and leukemia***. The cells of these neoplasms may grow in a variety of patterns, such as insular, cord-like, and alveolar. The cytologic features, however, differ from those of the cells of the small cell carcinoma, and the frequent follicle-like spaces of the latter are helpful in this differential.

- ***Small cell carcinomas of the lung with metastasis to the ovary*** may be the presenting manifestation of the disease. Although these tumors may exhibit degenerative spaces when growing in the ovary, they lack the distinctive follicles of the small cell carcinoma and have the characteristic cytologic features of small cell carcinomas of pulmonary type, which are unlike those of the hypercalcemic small cell carcinoma.

- ***Small cell carcinomas of pulmonary type*** may be primary in the ovary. These tumors resemble typical (oat) cell carcinoma of the lung and typically occur in older patients. They are often bilateral. On microscopic examination, it is helpful that they are often associated with a component of surface epithelial neoplasia, such as an endometrioid carcinoma or Brenner tumor. Their nuclear features tend to differ from those of the hypercalcemic tumors, with more finely dispersed chromatin and generally inconspicuous nucleoli. They have been aneuploid in 5 of 8 cases.

Behavior: In the largest series in the literature, the stage of the tumor was IA in 33%, while 44% of patients had stage III or stage IV tumors. The prognosis is dismal with the overall survival rate being of approximately 16% (33% for Stage 1A tumors and 7% for tumors >stage IA). Favorable prognostic factors in the largest study included:

- Age >30 years
- Normal preoperative serum calcium
- Bilateral oophorectomy
- Tumors <10 cm
- No large cell component
- Administration of adjuvant radiotherapy

TABLE 1

OVARIAN TUMORS ASSOCIATED WITH HYPERCALCEMIA

Small cell carcinoma	59%
Clear cell carcinoma	18%
Serous carcinoma	6%
Dysgerminoma	6%
Squamous cell carcinoma arising in dermoid cyst	6%
Mucinous carcinoma	3%
Undifferentiated Carcinoma	1%
Mixed clear cell/endometrioid carcinoma	1%
Steroid cell tumor	1%

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Caso N 8:

Mujer de 50 años que acude al ginecólogo por distensión abdominal. El examén físico descubre ascitis y una ecografia pélvica denota una masa ovárica en el lado derecho. La paciente es sometida a histerectomia y anexectomia bilateral. El ovario derecho está sustituido por una tumoración predominantemente sólida de consistencia blanda, con superficie de corte homogénea donde alternan áreas blanquecinas con otras más rojizas.

DIAGNOSTICO:
Ovario: “Struma” de celulas claras.

Struma ovarii is the most common monodermal teratoma.

Definition: It refers to a tumor in which thyroid tissue is the predominant or sole component or forms a grossly recognizable component of a more complex teratoma. Neoplasms composed of struma and carcinoid tumor are classified separately as strumal carcinoids. Although meticulous examination of dermoid cysts has revealed thyroid tissue in 20% of the cases, this component is recognized grossly in considerably less than 5% of the cases. The peak frequency is in the fifth decade, although occasional cases have been reported in prepubertal and postmenopausal females.

Aside from the usual manifestations relating to the presence of a mass, struma may be associated with a number of unusual clinical manifestations. Ascites occurs in approximately one-third of the cases, and occasionally Meigs' syndrome (ascites and hydrothorax associated with a benign ovarian tumor) is present. Although many, if not most, strumas probably produce thyroid hormones at subclinical levels, clinical evidence of hormone production by these tumors occurs in only about 5% of cases. In one study, a correlation was noted between the presence of thyrotoxicity and the size of the struma; evidence of hyperthyroidism was rare in cases of struma in which the tumor was less than 3 cm in diameter.

Gross Features: It is usually recognizable as brown or greenish-brown, predominantly solid, gelatinous tissue, usually in pure form and less often associated with a dermoid cyst or mixed with a solid carcinoid tumor as a strumal carcinoid. Rarely struma is found within the wall of a mucinous or serous cystadenoma or is admixed with a Brenner tumor. Some strumas appear as unilocular or multilocular cysts containing brown to green, mucked or gelatinous fluid. Occasionally, the opposite ovary contains a dermoid cyst, and rarely, another struma.

Microscopic Features: Struma may resemble normal thyroid tissue or a thyroid adenoma, with patterns including macromolecular, microfollicular, sheetlike (embryonal), solid tubular, or trabecular, alone or in combination. Cystic strumas may have only scant recognizable thyroid tissue that is easily overlooked, especially if the pathologist is unaware that strumas can be predominantly or entirely cystic. Oxyphil cells may be present and occasionally the tumor has the appearance of an oxyphilic thyroid tumor, and rare strumas have a prominent component of clear cells. Foci of "thyroiditis" are occasionally encountered. Colloid within the follicles often contains birefringent calcium oxalate crystals. The colloid and cytoplasm of the tumor cells are typically immunoreactive for thyroglobulin.

Uniformly accepted criteria for malignant change in struma have not been established. As in the thyroid gland, a papillary pattern with typical nuclear characteristics of papillary thyroid carcinoma, or similar nuclear features in tumors with a follicular pattern, provide microscopic evidence of carcinoma. Tumors with these features, however, are often clinically benign.

Differential Diagnosis

- ***Mucinous cystic tumors.*** On gross examination, cystic strumas can be mistaken for; the green to brown color of the former helps in the differential diagnosis. The wide variety of microscopic patterns that can be encountered in struma ovarii can result in diagnostic confusion with ovarian tumors of diverse types. Oxyphilic strumas with solid or tubular patterns may be mistaken for other oxyphil cell tumors, such as steroid cell tumors or Sertoli cell tumors, respectively. Similarly, clear œll strumas may be misdiagnosed as clear cell carcinoma. One struma with a microfollicular and trabecular pattern, which was clinically malignant, was misdiagnosed and reported in the literature as a granulosa cell tumor.

- ***Clear cell carcinomas***
- ***Endometrioid carcinomas***
- ***Sertoli-Leydig cell tumors***
- ***Pregnancy luteomas***

The last four tumors may contain follicle-like spaces filled with material resembling thyroid colloid, but other features of such tumors almost always permit their identification. In problematic cases, an association with a dermoid cyst or teratomatous elements of another type, the demonstration of foci of typical thyroid follicles, the presence in the colloid of birefringent calcium oxalate crystals, and

immunoreactivity for thyroglobulin may be helpful in confirming the thyroid nature of the tumor. Occasionally a struma is admixed with mucinous neoplasia or contains luminal mucin, as might be expected in a mixed endodermal teratoma. Finally, exceptional cases of follicular carcinoma of the thyroid gland have metastasized to the ovary, a differential diagnosis facilitated by knowledge of the primary tumor, the typical patterns of a metastatic tumor in the ovary, and the absence of an associated dermoid cyst.

Behavior: The treatment of benign struma is oophorectomy. Cases of malignant struma should be treated by oophorectomy and the removal of any extraovarian tumor to the extent that is technically feasible. Some cases of malignant struma with extraovarian spread have been treated successfully with postoperative 131 -I. Although 5 to 10% of strumas have been considered malignant, less than half of such tumors have been associated with extraovarian spread to sites including the peritoneum, the contralateral ovary, regional lymph nodes, bone, liver, brain, lungs, and mediastinum. In the remaining cases, the diagnosis has been made on microscopic criteria alone, and many such cases are now known to be strumal carcinoids. More recently, Devaney and colleagues have found that most cases of struma with atypical or malignant features on microscopic examination are not associated with a clinically malignant course. These investigators studied 54 cases of struma which were subdivided into "proliferative" struma (41 cases) and "malignant" struma (13 cases). The former group were composed of densely packed follicles or papillary formations, but lacked the distinctive nuclear features of papillary carcinoma, vascular invasion, and mitotic activity. After a mean follow-up interval of 8.7 years, all the patients were clinically free of disease. Eleven of the 13 malignant strumas were papillary carcinomas of thyroid type, whereas two resembled follicular carcinoma with "capsular" and vascular invasion. One of the patients with papillary carcinoma had peritoneal involvement by similar tumor at the time of oophorectomy; the peritoneal lesions were incompletely resected. None of the patients received adjuvant therapy. On follow-up examination (mean follow-up interval 7.3 years), none of the patients had clinical evidence of recurrent disease, including the patient with Stage III disease at presentation.

Preliminary data are available from another study of 34 cases of malignant struma with 20-year follow-up data (Robboy & Scully, in preparation). Criteria for inclusion in the study were microscopic evidence of papillary or follicular carcinoma by the criteria described above, clinical evidence of malignant behavior, or both. On follow-up examination, local or distant spread of tumor occurred in 14 patients. Factors that were predictive of recurrence in this study included tumor size, the presence of adhesions or ascites, and a solid microscopic architecture. None of the tumors that were less than 5 cm in maximal dimension recurred, whereas the risk of recurrence for tumors that were 5 to 6 cm, 7 to 15 cm, and over 15 cm was 40, 60, and 75 percent, respectively. Recurrences developed in 8 of the 9 patients with tumors that were associated with extensive adhesions, and in 7 of the 9 patients with ascites. Features that were not useful in predicting behavior included mitotic activity, the presence of an infiltrative border, and the presence of vascular invasion. This study indicates the need for prolonged follow-up examination is assessing the frequency of malignancy of struma ovarii, as some of the tumors recurred late, up to 27 years postoperatively. Another observation from this and other studies is that occasional cases of struma associated with extraovarian spread may have a histologically benign appearance, as can the extraovarian tumor. In some of these cases, the term "strumosis" has been applied to benign appearing peritoneal implants present at the time of oophorectomy or at a second operation. Some of these cases may be associated with a very indolent clinical course, with the metastases appearing many years after oophorectomy, and with a prolonged survival. No study of an unselected series of cases of struma has been reported to date to determine the frequency of malignant behavior.

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Caso N 9:

Mujer de 42 años con masa pélvica derecha descubierta en un examen ginecólogico de rutina; es intervenida practicandosele una anexectomia derecha. El examen macroscópico muestra un tumor de 12 x 10 x 10 cm de diámetro que parece originarse o estar adherido a la trompa de Fallopio. Al corte el tumor es sólido, vagamente lobulado y de consistencia firme.

DIAGNOSTICO:
Trompa de Fallopio: Tumor wolfiano.

This is a distinctive female genital tract tumor that was designated "female adnexal tumor of probable wolffian origin" (FATWO) by Kariminejad and Scully in 1973. They are judged to be of probable wolffian origin because their features are different from those of mullerian type tumors and because of a location predominantly in sites where wolffian remnants are distributed. Approximately 60% of these tumors occur in the broad ligament with most of the remainder in the ovary. Rare examples have also been encountered in the retroperitoneum and paravaginal region. The recently proposed designation of "retiform wolffian adenoma" for these tumors is in our opinion, not entirely appropriate

considering that not all of these tumors have a retiform pattern, and that a minority of them have been clinically malignant. Although the term "FATWO" was initially used to refer only to tumors occurring in the broad ligament, in the following discussion, it is used to refer to tumors in the latter site and within the ovary.

Clinical Features: Patients typically present with nonspecific clinical manifestations such as abdominal pain (occasionally due to torsion of the mass) and swelling, or have asymptomatic masses discovered on physical examination or at operation. They ranged from 15 to 79 years of age (median between 40 and 50 years). Rarely FATWOs have been associated with spread at the time of operation: one tumor, or with postoperative recurrence, hematogenous metastases, or both (thus approximately 10% of the reported FATWOs have been clinically malignant).

Gross features: The tumors range from 1 to 25 cm in diameter (median 6 cm in the largest series) and are typically rounded masses with bosselated external surfaces. Their cut surface may be solid or solid and cystic. The solid tissue varies from gray-white to tan or yellow and is usually firm or rubbery. Hemorrhage and necrosis are rare.

Microscopic features: The low-power appearance varies from cystic, to solid and cystic, to solid, depending on the relative proportion of cysts, closely packed tubules and diffuse sheets of epithelial cells. These patterns usually coexist in the same tumor, but generally one predominates. When cysts predominate there is often a striking sieve-like appearance. Many of the cysts are empty but others contain watery eosinophilic fluid that is mucin-negative. The cysts are usually lined by flattened cells but occasionally by hobnail cells. Some tumors have a focally prominent hyalinized stroma and fibrous bands may separate cellular foci into lobules. The tubules may be solid or hollow and may be essentially indistinguishable from those of a Sertoli cell tumor. Occasionally, the tubules are large and dilated and may simulate the glands of an endometrioid adenocarcinoma. The cells lining the tubules are mostly cuboidal with scant cytoplasm but some are columnar and a few contain abundant pale cytoplasm. When the tumor cells grow diffusely they typically have scanty cytoplasm and may be spindle-shaped, sometimes focally simulating a spindle cell tumor. A reticulum stain may be helpful in showing an epithelial pattern in the solid areas. In otherwise solid foci, small spaces that resemble the vacuoles seen in adenomatoid tumor may be seen. In typical FATWOs, the nuclei lack significant atypicality and mitotic figures are rare. In contrast, most, but not all of the malignant tumors have had worrisome histologic features, including a high mitotic rate, focal nuclear atypicality, or areas of undifferentiated carcinoma.

Immunohistochemistry: The cells are immunoreactive for cytokeratin, but typically negative for EMA, B72.3, and CEA. Recently it has been shown that these tumors are also positive for calretinin and for CD10.

Differential Diagnosis

- ***Endometrioid carcinomas*** **(ECs)** of the fallopian tube have patterns mimicking those of the FATWO and some ovarian ECs may show an spindled growth pattern that may simulate the solid growth of FATWO. However, ECs when originating in the fallopian tube are intratubal and involve the tubal mucosa. Most ECs either in the fallopian tube or ovary contain foci of typical EC, abortive squamous elements, intraluminal mucin, and focal nuclear atypicality and mitotic activity exceeding that seen in most FATWOs. . Additionally, ECs are immunoreactive for EMA and B72.3, findings absent in FATWOs.

- ***Sertoli or Sertoli-Leydig cell tumors* (SLCT),** as FATWO may have a tubular pattern. However, the other patterns in FATWOs, are incompatible with a diagnosis of SLCTs. The absence of cells resembling Leydig cells and the absence of hormonal manifestations in the FATWO also facilitate the diagnosis.

- ***Adult granulosa cell tumor***. The diffuse pattern of FATWO may resemble on low-power examination the growth pattern of a typical granulosa cell tumor, but the cells of the former lack the angular appearance and grooved nuclei of the granulosa cell tumor, and other patterns seen in FATWOs are incompatible with the latter diagnosis. Inhibin stain is helpful when strong and multifocal or diffuse to establish the diagnosis of granulosa cell tumor. In contrast, calretinin is not helpful in this differential diagnosis.

Behavior: Most of these tumors behave in a benign fashion. However, occasional tumors with highly atypical microscopic features have been clinically malignant.

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Caso N 10:

Mujer de 30 años que acude al ginecólogo por metrorragia de 3 meses de duración. El examen pélvico revela un útero aumentado de tamaño mientras que la ecografia pélvica denota una masa miometrial. La paciente es sometida a histerectomia que revela una masa blanda de 6 cms de márgenes poco definidos y localización preferentemente miometrial en la que alternan áreas de hemorragia con otras blanquecino-amarillentas.

DIAGNOSTICO:
Utero: Tumor del lugar de implantación placentaria.

Placental site trophoblastic tumor (PSTT) is a rare form of trophoblastic tumor composed predominantly of IT. In the past it was named trophoblastic pseudotumor because the benign course seen in the initial cases despite of deep myometrial invasion. It almost always occurs in reproductive years, although occasional cases have been seen in postmenopausal women. In contrast to choriocarcinoma it rarely is associated with a recent pregnancy, and very few occur after a hydatidiform mole. The interval from the previous known pregnancy has been as long as 18 years. Some patients have been reported to develop an unusual complication similar to the nephritic syndrome. The renal biopsies on these cases show a distinctive glomerular lesion consisting of eosinophilic deposits in the capillary lumens which stain for fibrinogen-related products and IgM. It has been hypothesized that chronic intravascular coagulation from factors synthesized by the tumor may be involved in the pathogenesis of this lesion. This is supported by the fact that at least in two cases, resolution of the renal disease occurred after resection of the uterine tumor.

Clinical features: The most common presenting symptom is uterine bleeding or amenorrhea of up to 18 months, one third of the latter group also develop subsequent abnormal bleeding. The hCG levels are usually low, but they are elevated in 75 to 80% of the cases. The presence of uterine enlargement, abnormal bleeding, and positive pregnancy test often leads to the erroneous diagnosis of pregnancy, and lack of an identifiable fetus may result in the diagnosis of missed abortion or ectopic pregnancy.

Gross features: These tumors form a mass that may be small (1 to 2 cm) or may largely replace most of the uterus. They may be grossly well circumscribed, infiltrative or poorly defined. Cut section reveals a soft, tan-white to yellow tumor with areas of necrosis and hemorrhage. PSTTs are deeply invasive in 60% of the cases.

Microscopic features: They are composed of a monomorphic population of IT that grows in cohesive sheets. These tumors also show an irregular and infiltrating growth into the myometrium, typically splitting muscle bundles. Another characteristic feature of PSST is that the IT cells surround and replace the vessel walls preserving the lumen and this phenomenon is associated with extensive fibrinoid deposition. This eosinophilic fibrinoid material may be seen in a patchy distribution throughout the tumor. Most cells are polygonal although in the myometrium the cells tend to be spindle-shaped. They usually have abundant amphophilic or eosinophilic cytoplasm, but a second population of clear cells may also be found. Most cells have a single irregular hyperchromatic nucleus and with nuclear foldings, but binucleated and scattered multinucleated cells may be present. Some nuclei have grooves and others may have large cytoplasmic pseudoinclusions. Mitotic in activity is variable, often low. Atypical mitotic figures may be seen in up to 90% of PSTTs. Areas of necrosis are found to some degree in two thirds of the cases and it is significant in 40%. Histologic features associated with a more aggressive behavior include the presence of extensive necrosis, large sheets of clear cells and mitotic rates higher than 5 per 10 high power fields. Abnormal mitotic figures are seen in either clinically benign or malignant tumors.

Rare PSTTs occur at extrauterine sites, such as fallopian tube and ovary. Their histologic appearance is similar to that seen in their uterine counterparts. Metastatic tumors are also composed of similar cells associated with hemorrhage.

Immunohistochemistry: Typically PSTTs show intense immunoreactivity for hPL, inhibin, keratins and Mel-CAM and focal immunoreactivity for hCG.

Differential diagnosis

- ***Exaggerated implantation site***. As discussed earlier, they never form a mass and tend to have more syncytiotrophoblast giant cells when compared to the more monotonous cell population seen in PSTT. The differential diagnosis may be difficult in small curettings.

- ***Placental site nodule*** When studying the margin of the lesion especially in a curettage composed of small fragments of tissue it may be difficult to know if there are cells that are infiltrating the surrounding tissues. As mentioned earlier PSNs have a hyalinized center and the IT cells tend to be located at the periphery of the nodules. PSN is overall hypocellular and the cells widely spaced when compared to a PSST.

- ***Epithelioid trophoblastic tumor***. On gross examination, one important feature that distinguishes ETT from PSTT is the finding of an expansile growth. On microscopic examination, ETTs are often well circumscribed, although minor infiltrating areas may be seen at the periphery of the tumor. The cells are arranged in nests, cords and masses intimately associated with eosinophilic, hyaline-like material and necrotic debris with a lymphocytic infiltrate surrounding the tumor in half of the cases. These areas of necrosis are quite extensive and surround islands of viable tumor imparting a "geographic" pattern of necrosis. Blood vessels within the tumor are preserved with focal deposition of amorphous fibrinoid material, but vascular invasion is not a striking feature of these tumors in contrast to the characteristic vessel invasion seen in PSTTs. The cells in general are smaller than the IT cells from the implantation site, and smaller than the cells of PSTT, showing less nuclear pleomorphism when compared with the latter. Although this is the typical architecture of an ETT, the tumor may show areas that overlap with those seen in a PSTT. The immunohistochemical profile of ETT shows focal expression of hPL, b-hCG, PlAP and Mel-CAM (CD146), contrasting with the immunoprofile of PSTT that shows diffuse positivity for hPL and Mel-CAM. These tumors are diffusely positive for keratin EMA and inhibin. P63 may be also helpful in distinguishing between PSTT and ETT, being positive in the latter.

- ***Choriocarcinoma***. Characterized by an intimate admixture of cyto and syncytiotrophoblast cells. The IT cells may be present but represent a minor component of the tumor.

- ***Epithelioid leiomyosarcoma***. When the bulk of the tumor is in the wall of the uterus, this differential diagnosis may be difficult and immunohistochemical stains may be necessary. It is important to remember that epithelioid smooth muscle tumors are frequently positive for cytokeratins, but they are negative for hPL and inhibin.

- ***Keratinizing squamous cell carcinoma***. Especially in curettage/biopsy specimens in young women, this differential diagnosis may be a problem, as keratin has an appearance similar to that seen in the amorphous eosinophilic fibrinoid material deposited in the PSST. The latter is typically located in the uterine corpus while squamous cell carcinomas occur in the cervix. Immunohistochemical stains may also be of help.

Behavior: Most of these tumors are benign, despite destructive growth in the myometrium. Because they extensively infiltrate the myometrium, the uterus can be perforated during curettage. About 15-20% PSTTs have shown an aggressive behavior associated with distant metastasis and death of the patients, although one recent series from the New England Trophoblastic Disease Center (NETDC) reported a recurrence rate of 43%, which is substantially higher. Sites of metastases in order of frequency are lungs, liver, vagina, gastrointestinal tract, pelvis, bladder, brain and others. Brain metastases tend to be fatal due to associated hemorrhage. Overall, there is still controversy in recognizing the features that may be associated with a poorer prognosis. *Clinical features that have been shown by some investigators to be associated with aggressive behavior* include older age at presentation and higher levels of hCG. *Histologic features associated with a poorer prognosis* include necrosis, clear cells and high mitotic activity. In the study by Feltmate and colleagues (NETDC), they found that mitotic activity was the most important adverse prognostic indicator among the histologic factors. Conservative treatment has been used in patients that want to preserve fertility and in general still remains the mainstay of treatment. In contrast to the exquisite chemosensitivity of choriocarcinoma, PSTT seems to respond poorly to chemotherapeutic agents. Although there are no consistent results, the most effective combination would seem to include methotrexate, actinomycin-D and at least one more agent, and may be indicated when the mitotic index is >5 mitosis/10 high power fields.

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