California Tumor
Tissue Registry

114TH SEMI-ANNUAL CANCER SLIDE SEMINAR

"ADVANCES IN SURGICAL PATHOLOGY
OF TUMORS"

Richard L. Kempson, M.D.
Michael R. Hendrickson, M.D.

Stanford University Medical Center

June 8, 2003

Westin South Coast Plaza
Costa Mesa, California
8:30 a.m. – 4:30 p.m.

Drs. Kempson and Hendrickson are Co-Directors of Surgical Pathology at Stanford University Medical Center, and are Professors of Pathology at Stanford University School of Medicine. They are widely recognized as authorities in all aspects of surgical pathology. Together they have published nearly 200 articles and have authored or co-authored nearly 60 books and/or book chapters. This is the second time that each of our speakers has addressed the Registry. Dr. Kempson was a prelector in 1974, and Dr. Hendrickson in 1982.

Objectives:
At the conclusion of this seminar, attendees will have up-to-date criteria for diagnosing tumors and tumor-like conditions, and will be able to formulate appropriate differential diagnoses for common and uncommon neoplasms. The participant will be able to better distinguish cellular atypias, especially in pre-malignant conditions, and will be able to confidently interpret immunohistochemical and molecular tools in the diagnosis of neoplasms.
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CASE 1

Presented by Dr. Hendrickson

HISTORY: This 59-year-old woman presented with pelvic pain and examination revealed a large left ovary. At surgery the left ovary had been replaced by a 35.0 cm. mass. A hysterectomy and left salpingo-oophorectomy was performed. In the distant past the patient had a right oophorectomy for an “abnormal looking leaky” ovary.

HISTOLOGIC FINDINGS:

Low power: The low power appearance of the neoplasm has the typical sponge-like, multicystic look of a mucinous LMP. There is nothing to suggest destructive stromal invasion or a nodular overgrowth of epithelium.

Medium power: Most of the cysts are lined by simple cuboidal-to-columnar epithelium. There are scattered foci possessing a thicker lining due to the jumbled stratification of larger cells. In areas, this epithelium is thrown up into jumbled tufts.

High power: The stratified areas are lined by a proliferation of high N-C ratio cells with atypical nuclei, prominent nucleoli and moderate nuclear pleomorphism. There are scattered mitotic figures in this epithelium.

IMMUNOHISTOCHEMISTRY:

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This is a pattern that favors an ovarian primary over a metastasis from the gastrointestinal tract.
DIFFERENTIAL DIAGNOSIS:

MUCINOUS SURFACE EPITHELIAL NEOPLASMS
36% of SEN's

- Benign: 80% of Mucinous Series
- M-LMP: 15% of Mucinous Series
- Carcinoma: 5% of Mucinous Series

M Ilerian Mucinous
- Endocervical mixture of ciliated cells and mucin-containing cells
- Association with endometriosis
- Implants (like serous LMPs)
- With this histology, don't have to worry about metastasis and PMPB

STROMAL INVASION
- Expansive
- Invasive
- Microinvasion 5.0 mm

PSEUDOMYXOMA SYNDROME

PERITONEAL MORPHOLOGY
- dpam: Disseminated peritoneal adenomucinosis
- PMCA: Peritoneal mucinous carcinomatosis

- Pseudomyxoma ovarii
- Pseudomyxoma peritonei
- Primary mucinous neoplasms
  - Appendix
  - Pancreas
  - Biliary Tract

OVARIAN MORPHOLOGY
- The ovarian proliferations in patients with this syndrome is notoriously bland and usually has cytological and architectural features no more atypical than a mucinous benign or LMP neoplasm
Any intestinal mucinous neoplasm of the ovary raises the possibility of a metastasis to the ovary from the gastrointestinal tract or biliary tract. Metastases may simulate any type of primary mucinous neoplasm of the ovary, even mucinous cystadenoma. Findings that raise this possibility include bilaterality, multifocality, ovarian surface involvement and significant dissection of free mucin in the ovarian stroma (pseudomyxoma ovarii). None of these findings were present in this case.

So, under the assumption that the neoplasm is an ovarian primary, given the complexity of the epithelial lining, the tumor is at least an LMP. Moreover, there is sufficient cytological atypia of the cells in the stratified zones to warrant a diagnosis of intraepithelial carcinoma (IEC). There is no destructive stromal invasion and there is insufficient crowding of glands to raise the possibility of ‘expansive’ invasion.

**DIAGNOSIS:** OVARY: Mucinous Low Malignant Potential Tumor (LMP) with Intraepithelial Carcinoma

**DISCUSSION:**
A number of issues are raised by this case. First, the taxonomy of mucinous neoplasms presenting in the ovary has undergone a substantial revision in recent years. The general trend has included: 1) downgrading the malignant potential of the mucinous LMP; 2) the recognition that essentially all pseudomyxoma-associated ovarian neoplasms are metastases and 3) the recognition that most mucinous carcinomas that occur in the ovary are also metastases from, most commonly, the gastrointestinal tract. These points are covered below.

**What is the natural history of mucinous LMPs?**
As currently defined, carefully sampled mucinous neoplasms that fall into the LMP category are clinically benign. Reported cases of high stage mucinous LMPs most likely are really cases of metastasis to the ovary from an occult gastrointestinal primary or inadequately sampled primary mucinous carcinoma of the ovary. Many have suggested that the term LMP or ‘borderline’ be dropped; Kurman and associates have suggested the term ‘atypical proliferative tumor.’

**What difference does the presence of intraepithelial carcinoma make in the prognosis of an LMP?**
This term is used to when there are, in an otherwise typical LMP, foci of marked cytologic atypia and/or marked stratification. The limited experience with neoplasms of this type suggest that their behavior is essentially that of mucinous LMPs without this finding. The two large recent series of primary mucinous neoplasms of the ovary differ in the number of cases assigned to this category. Riopel et al had 4/44 cases with this finding; none of these four cases failed. The Lee and Scully study had 90/164 with this finding. All 90 mucinous borderline tumors that had foci of intraepithelial carcinoma were recorded as stage I, but two of the 69 patients with follow-up data (3%) had fatal recurrences. Both of these tumors were incompletely staged, however, and one had ruptured intraoperatively.

The lesson that we extract from this is that the behavior of LMP with IEC is essentially that of LMP without IEC.
Background fact: Note that Stage I, Grade I adenocarcinomas (judged to be so after compulsive staging) have a relapse free survival of in excess of 90 percent.

What is the morphologic definition of ‘invasion’ in mucinous surface epithelial neoplasms?
The morphologic definition of invasion in these neoplasms remains problematic. Destructive stromal invasion is easy to identify; this pattern features jagged infiltration of single cells or cords of cells into an inflamed stroma. The problem arises in defining ‘expansive’ invasion and is completely analogous to the problem of defining ‘invasion’ in endometrial proliferations (e.g., confluence) or in endocervical glandular proliferations (e.g., ‘microinvasive’ adenocarcinoma). The general idea is this: there are glandular foci in, what is otherwise a mucinous LMP, that are ‘too crowded’ and ‘too budded’ to be benign. Translating that impression into rules that someone else can follow is very difficult and usually unsuccessful. The best way to get a feel for what the authors who use this terminology are talking about is to go to the articles and scrutinize the figures.

Microinvasion is defined as ≤ 5 mm. of invasion (as defined above); essentially all of these patients are cured by adnexectomy.

A brief summary of changing concepts of mucinous neoplasms involving the ovary
There are two types of mucinous neoplasms of the ovary: intestinal and müllerian. It’s important to remember this distinction. Briefly, müllerian mucinous neoplasms look, at low power like serous LMPs, but the papillae are lined by cervical type mucinous epithelium. They feature a mixture of cell types- ciliated, pink cells etc.-and are often mixed with serous LMP. The importance of recognizing this mucinous subtype is that the possibility of metastasis (and pseudomyxoma syndrome) is eliminated. This histology is diagnostic of an ovarian primary. Like their close relatives serous LMPs, müllerian mucinous tumors may present with, or later develop, implants.

Given a mucinous neoplasm in the ovary that is, morphologically, obviously malignant, there is a better than even chance that it is a metastasis from another site. Bilaterality, multinodularity, and surface involvement of the ovary are features of metastatic involvement. Immunohistochemical strategies for recognizing a metastasis are described in the abstract below.

Pseudomyxoma peritonei (PMP)
An ovarian mucinous neoplasm associated with pseudomyxoma peritonei (PMP) is essentially always a manifestation of the metastatic spread of a gastrointestinal or biliary tract primary carcinoma. The ovarian component may be architecturally non-complex and cytologically bland. One clue is the dissection of naked mucin into the ovarian stroma (pseudomyxoma ovarii). The histology of the peritoneal component has been divided into two prognostically relevant patterns: Disseminated peritoneal adenomucinosis (DPAM) and peritoneal mucinous carcinomatosis (PMCA). The survival after vigorous treatment is much better in patients who have DPAM.

Intraoperative consultation
Adequate sampling of large mucinous neoplasms in the LMP-carcinoma range is essential before assignment to a diagnostic category. An intraoperative diagnosis should always be of the form: “At least an.....” and defer final classification for permanent sections. The background issue at the time of surgery is the possibility of a metastasis; the surgeon should be alerted to this possibility and explore the patient appropriately.
REFERENCES:

General References

The problem of metastasis
The authors evaluated the immunohistochemical expression of cytokeratins 7 and 20 (CK 7, CK 20), Dpc4 (nuclear transcription factor inactivated in 55% of pancreatic carcinomas), and MUC5AC (a gastric mucin gene) in 57 primary ovarian mucinous tumors (41 atypical proliferative tumors and 16 carcinomas) and 46 metastatic mucinous carcinomas in the ovary.
Primary ovarian mucinous tumors were usually always diffusely positive for CK 7 (98%), Dpc4 (100%), and MUC5AC (98%) and often focally to diffusely positive for CK 20 (68%).
Colorectal mucinous carcinomas were diffusely positive for CK 20 (100%) and Dpc4 (89%) and were distinguished from primary ovarian mucinous tumors by their frequent lack of expression of CK 7 and MUC5AC (67% were negative for each marker).
Appendiceal carcinomas were diffusely positive for CK 20 (100%) and often negative for CK 7 (71%) but were often positive for MUC5AC (86%) and Dpc4 (100%).
When primary ovarian and metastatic colorectal or appendiceal carcinomas shared expression of both CK 7 and CK 20, they could usually be distinguished by the pattern of positivity (diffuse CK 7 and patchy CK 20 in ovarian tumors and patchy CK 7 and diffuse CK 20 in colorectal and appendiceal tumors).
Pancreatic carcinomas shared the same pattern of diffuse positivity for CK 7 (100%) and MUC5AC (92%) and focal to diffuse positivity for CK 20 (71%) as primary ovarian mucinous tumors but were negative for Dpc4 in 46%. Loss of Dpc4 expression is useful for distinguishing metastatic pancreatic carcinomas in the ovary from both primary ovarian mucinous tumors and metastatic mucinous carcinomas derived from other sites.

Clinicopathology of primary intestinal mucinous neoplasms of the ovary

Pseudomyxoma peritonei
Müllerian mucinous vs. Intestinal
CASE 2

Presented by Dr. Hendrickson

HISTORY:
The patient is a 59-year-old woman found to have a right pelvic mass. Hysterectomy and salpingo-oophorectomy was performed.

HISTOLOGIC FINDINGS:
Low power: A prominent fibrous matrix populated by irregular acini into which papillary structures project. Even at this power the epithelium has a hobnail appearance.
Medium power: The papillae possess prominent eosinophilic hyaline cores. Scattered more delicate papillae are covered by hobnail epithelium.
High power: Nuclear pleomorphism, prominent nucleoli, mitotic figures are all evident.

DIFFERENTIAL DIAGNOSIS:
DIAGRAM: Spectrum of clear cell neoplasms:

A number of diagnostic possibilities are suggested:
1) A primary ovarian clear cell neoplasm that is something less than carcinoma: benign, intermediate or microinvasive clear cell adenofibromatous neoplasm. These possibilities feature a prominent fibrous stroma but the nuclear pleomorphism is too extreme for any of these possibilities.
2) A neoplasm in another differentiated series of surface epithelial tumors. Other surface epithelial neoplasms may have cleared cells. Mucinous neoplasms are usually obvious in virtue of the goblet cells present. Endometrioid carcinomas with secretory change can be identified by looking for more typical areas (particularly squamous elements) and by failing to find pleomorphic hobnail of the sort found in abundance in this case.

3) Endodermal sinus (yolk sac tumor). This is a very important differential diagnostic consideration because the management of the clear cell carcinoma and EST are so different. In this case the patient is too old for EST and the pattern doesn't particularly suggest that diagnosis. In younger patients with sheet-like clear cell growth, this is a real problem.

4) Metastatic renal cell carcinoma. The patient is the right age. We lack a history of this and one would expect a more prominent vascular pattern and necrosis.

**DIAGNOSIS:** OVARY: Clear cell carcinoma (CCCa)

**DISCUSSION:**

General comments on clear cell histology.

In spite of the name, the defining feature of clear cell ovarian neoplasms is the protrusion of large cells with irregular nuclei and cleared or eosinophilic cytoplasm into glands, tubules and/or spaces. Such cells are often referred to as "hobnail" cells or "tombstone" cells. The low power appearance of clear cell tumors is distinctive with cells appearing as "bumps" or protrusions along the luminal surface of the glands.

If it's a primary ovarian neoplasm with clear cell histology, it's overwhelmingly likely to be carcinoma.

Almost all clear cell tumors meet the morphologic criteria for malignancy and almost all behave as carcinomas, but a handful of benign and LMP clear cell tumors have been reported. Because of the rarity of benign clear cell tumors and clear cell tumors of low malignant potential, these two diagnoses should be made with caution and only after thorough sectioning of the tumor to rule out areas of clear cell carcinoma. All benign clear cell tumors and clear cell tumors of low malignant potential thus far reported have been adenofibromatous tumors, i.e., they have a predominant cellular stroma containing cysts of varying sizes.

**Benign Clear Cell Neoplasms – very rare**

Probably less than two dozen benign clear cell tumors have been reported. All have been adenofibromatous and this has become a requirement for the diagnosis. Grossly, benign clear cell tumors are almost always smooth on the outside but occasionally protuberant cysts are noted. On cut surface the abundant stroma is interrupted by cysts. The usual microscopic pattern features simple round-to-oblong glands, cysts or tubules set within abundant, often cellular, fibrous stroma. Not allowed in the definition of benign clear cell tumors are papillae, sheet-like growth, closely packed glands or irregularly shaped glands. Additional exclusionary features include glandular crowding and complexity. If any of these features are present in a clear cell tumor it should be relegated to either the LMP category or classified as carcinoma (see below). The epithelium lining the cysts in the benign clear cell tumor is usually one cell thick and by definition can be no more than two cells thick. The cells are not infrequently flattened to cuboidal but somewhere in the lesion they must develop large nuclei that protrude into glands or cystic spaces. In benign tumors the nuclei may have dense chromatin but it is finely granular or smudged and evenly distributed even if the nuclei are enlarged. Mitotic figures must be absent.
Clear Cell Tumors of Low Malignant Potential – very rare

Somewhat less than 50 clear cell tumors of low malignant potential have been reported so these are only slightly more common than the vanishingly rare benign clear cell tumors. All LMP clear cell tumors have been adenofibromatous and grossly all have had variable numbers of cysts set within abundant fibrous stroma. The microscopic features that mark clear cell tumors of low malignant potential include focal crowding of glands, mild glandular complexity manifested by budding and irregular channels, occasional solid cords of cells, a few small solid nests of cells (less than 1 high power field) and cysts with stratification of more than two cells. None of these features are allowed in benign clear cell tumors. Mild nucleomegaly, mild pleomorphism, minor degrees of chromatin clumping, occasional prominent irregular nuclei and some shift in NC ratios are also features that have been used to place clear cell tumors into the LMP category; moderate to marked degrees of these features should cause the prudent observer to reconsider clear cell carcinoma (see below). The mitotic index of the epithelial component by definition must be less than 1 mf/10 hpf (as it is for benign tumors). Hobnail (tombstone) cells with nuclei protruding into cystic lumens are the marker of this form of clear cell tumor as it is of others and usually the hobnail pattern is prominent at least focally. Papillae and extensive sheet-like growth are not features of clear cell LMP but small intracytic tufts are acceptable. The tumor cells typically produce abundant glycogen and may demonstrate luminal mucin, but intracytoplasmic mucin is distinctly unusual. The stroma is cellular and often resembles the stroma of a cellular fibroma. The vast majority of clear cell LMPs contain morphologically benign clear cell areas.

Clear cell LMPs may have foci of microinvasion. This has been defined by Bell and Scully as "microscopic foci of glands, epithelial islands, or single cells with nuclear features of malignancy scattered haphazardly in the stroma". The stroma around the infiltrating cells should be altered and most often resembles granulation tissue. This definition specifies the earliest changes must be "microscopic" but it underspecifies the dividing line between microinvasion and frank invasion. Endometriosis is found in approximately one third to one half of clear cell tumors of low malignant potential and often the endometriosis is near or associated with the clear cell tumor.

The tumors thus far reported as clear cell LMPs without microinvasion have not caused patient death nor have they recurred with one possible exception. Bell and Scully reported one patient with clear cell LMP who developed a lung nodule of unknown type four years after therapy for her ovarian tumor. This was not removed and she was alive and well at last follow-up 4.7 years after the initial therapy. Thus, clear cell LMPs, like the endometrioid type, are morphologically borderline but have not yet manifested clinical behavior that differs from that of benign tumors; however, the number of cases reported is too small to insure that this morphologically atypical group of lesions is not capable of recurrence on occasion. Bell and Scully argue that because microinvasive carcinoma can occasionally be found in the group of tumors they designate as LMP on morphologic grounds, the designation "LMP" or of "borderline malignancy" is appropriate even though the tumors are not known to behave aggressively. One patient with microinvasion in the Bell and Scully series suffered a recurrence but the size of the focus of microinvasion and the number of foci of microinvasion were not specified. One of the two patients with microinvasion reported by Roth and colleagues died of her tumor.
As noted above, invasion is an ominous finding in any clear cell adenofibromatous lesion and the limits of invasion not associated with recurrence or metastasis are uncertain. Consequently all tumors considered to be benign clear cell adenofibromas and clear cell tumors of low malignant potential should be subjected to extensive sectioning in a search for invasion and we think any clear cell tumor with more than 4-5 mm of invasion in the aggregate should be considered to be carcinoma.

CLEAR CELL CARCINOMA: Selected Comments

1) Clear cell carcinoma may have several different patterns and, accordingly, CCCa has a long differential diagnosis.

Clear cell carcinoma may grow in sheets or, more commonly, has a tubulo-papillary architecture. Sometimes, as in this case, there is a prominence of stroma. Again, more than just a rare papilla, stratification greater than 3 cells, more than minute foci of cribriform or closely packed glands, sheet-like growth of any extent and marked nuclear atypia individually are sufficient to warrant a diagnosis of clear cell carcinoma. More than 1 mf/10 hpf and more than a rare abnormal mitotic figure are also markers of malignancy.

Benign clear cell adenofibromas are vanishingly rare and clear cell LMPs are rare, so all tumors that are considered candidates for these two diagnoses should be thoroughly sectioned to exclude areas of clear cell carcinoma which may manifest only focally as invasion or any of the morphologic features mentioned immediately above. It is not uncommon for an adenofibromatous clear cell tumor to contain areas that are morphologically LMP or benign and other areas that are carcinomatous. The stroma in benign clear cell tumors and clear cell LMPs is characteristically cellular whereas it tends to be paucicellular and hyalinized in areas of carcinoma.

The variety of patterns that CCCa may assume raises a long differential diagnosis.

Endometrioid neoplasms with an early secretory pattern or glycogen rich squamoid areas may be mistaken for CCCa. Endodermal sinus tumor is an important consideration in young women. Strategies for distinguishing the two include a sampling to find more characteristic EST patterns (Schiller-Duvall bodies, network pattern with hyaline globules) and immunohistochemistry (αFP +ve, -ve LeuM1 in EST). Information about serum markers is also helpful. The solid pattern of CCCa may mimic dysgerminoma. Other clear cell lesions that occasionally cause problems include steroid cell tumors and struma ovarii.

2) The prognostic significance of clear cell histology in a surface epithelial carcinoma.

There is ongoing debate about the prognostic significance of the clear cell subtype and whether it is useful to grade this variant. Most series of CCCa don't correct for confounding factors. Two series that did stratify for stage and grade and found a slightly worse prognosis are listed in the references (Pecorelli, 1998; Sugiyama, 2000).

3) The reproducibility for the clear cell category is relatively poor.

Just as in the endometrium, there are many surface epithelial histologies that feature cleared cells including mucinous, squamous and endometrioid. We insist on high grade cytology and a hobnail appearance of the cells for the diagnosis of clear cell carcinoma.

4) Clear cell carcinoma is commonly associated with endometriosis

Approximately one-half of clear cell carcinomas are associated with endometriosis, and many (nearly one quarter) are found in the wall of endometriotic cysts. Mixtures of clear cell carcinoma and endometrioid carcinoma are not uncommon; mixtures of clear cell and mucinous
or serous carcinoma are distinctly unusual. Beware of atypia and Arias-Stella type reaction in endometriosis that can simulate clear cell carcinoma!

The intraoperative management of a clear cell neoplasm in a young woman.

In a premenopausal woman clear cell histology raises the possibility of endodermal sinus tumor and, less commonly, a dysgerminoma. It is extremely important to distinguish these possibilities. The clinical threat posed by clear cell carcinoma usually outweighs reproductive conservation considerations. This is not true for EST which is highly sensitive to modern germ cell chemotherapy. EST is essentially always unilateral and the other ovary can be preserved. This suggests that extreme caution be taken in making a definitive diagnosis of CCCa intraoperatively in this age group; we usually defer for permanent sections. We suggest that the surgeon draw serum markers (aid in diagnosis, provide a baseline for following therapy).

Thromboembolic episodes. Such episodes are more common in clear cell carcinoma than other subtypes in patients treated with platinum based therapy.

REFERENCES:

General References

Clear cell adenofibroma, clear cell LMP, microinvasion

Ruling out endodermal sinus tumor

Ruling out metastatic renal cell carcinoma

Is clear cell carcinoma worse than other histologies

**Thromboembolic complications with CCCa**

CASE 3

Presented by Dr. Hendrickson

HISTORY:
The patient is a 62-year-old woman with post-menopausal bleeding.

HISTOLOGIC FINDINGS:
Low power: One's first impression is that there is too much epithelium; there are scattered macroglands with papillary infoldings separated by abundant stroma.
Medium power: Much of the complexity of architecture appreciated at low power turns out to be due to stratified epithelium exhibiting a variety of differentiated types: mucinous, ciliated, squamous.
High power: Cells are 'active' but not particularly atypical. Certainly cytologic features that would allow a diagnosis of carcinoma are not present.

IMMUNOHISTOCHEMISTRY:

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DIFFERENTIAL DIAGNOSIS:

There are three general possibilities:
1) Primary benign endometrial proliferation: complex metaplasia, complex atypical metaplasia.
2) Primary endometrial proliferation: malignant.
3) Local extension (or metastasis) from elsewhere; the 'elsewhere' is suggested by the histology: mucinous, endocervix; serous, fallopian tube or ovary; squamous, cervix.

While the presence of mucinous epithelium should always raise the possibility of a cervical primary, the overall 'endometrial look' to this proliferation makes this unlikely. By the 'endometrial look' I understand a stroma that is more cellular than endocervical stroma, a merging of the mucinous elements with more typical endometrial glandular epithelium and the striking mixture of mullerian epithelial types.

Under the assumption that this is an endometrial primary then the algorithm set out in the Longacre study (Longacre, 1995 or the Sternberg version) is appropriate to distinguish complex hyperplasia/metaplasia from well differentiated carcinoma.
A Problematic Endometrium

Cytology

No atypia
- Cytologic features at level of:
  - Atrophy
  - Weakly proliferative
  - Normal proliferative
  - Disordered proliferative

"Benign"
- Cystic or architecturally complex atrophy (or weakly proliferative)
- Disordered proliferation
- Hyperplasia / metaplasia without atypia
  - Simple
  - Complex

Mid range atypia
- Features intermediate between no atypia and marked atypia
- Noticeable nuclear pleomorphism
- Mild to moderate nuclear pleomorphism

Architectural Index

Low
- "Benign"
  - Atypical hyperplasia
  - Atypical metaplasia

Indeterminate
- "Borderline"
  - Grade I carcinoma
  - "Villoglandular" carcinoma
  - Grade I mucinous carcinoma

High
- "Cancer"
  - Marked nuclear pleomorphism
  - Prominent nucleoli
  - Noticeable at low power

Marked atypia
- Grade I carcinoma with focal marked atypia
- Grade II carcinoma
- Grade III carcinoma
- UPSC
- Clear cell carcinoma

Whenever the following are present, carefully re-check cytology & architectural index:
- Granulation tissue host response
- Smooth muscle around glands
- Extensive morules / squamous metaplasia
- Papillary architecture
- Scanty sample
- Extensive necrosis
FIG. 29. A: Architectural index for well-differentiated endometrial carcinoma. Endometrial proliferations with gland patterns that map to the lower half of the chart are associated with a negligible risk of myometrial invasion and are regarded as benign. These proliferations fall within the range of endometrial hyperplasia/metaplasia and are further designated as atypical when they are associated with cytologic atypia, as depicted in Figs. 23 and 25. Occasionally, endometrial proliferations with a low architectural index contain foci with cytologic atypia sufficiently severe to warrant a diagnosis of carcinoma on the basis of cytologic features alone (usually manifest by prominent nucleoli and marked nuclear pleomorphism). In contrast, endometrial proliferations with gland patterns that map to the top half of the chart are associated with myoinvasion with sufficient frequency to warrant a diagnosis of carcinoma regardless of the cytologic features. In unusual cases, endometrial proliferations may feature architectural patterns that are ambiguous in morphologic characteristics, and these patterns are positioned along the borderline zone above the solid line in the lower half of the chart; in these cases, the diagnosis "borderline" is warranted.
In this case neither the cytologic atypia nor the architectural complexity is sufficiently to warrant a diagnosis of carcinoma.

**DIAGNOSIS:** ENDOMETRIUM: Mixed complex metaplasia without atypia

**DISCUSSION:**

Endometrium featuring alternative differentiation (see diagram)

At times, benign cells with differentiation typically encountered elsewhere in the female genital tract may be discovered in endometrial proliferations. Similarly, carcinomas arising in the endometrium may, on occasion, demonstrate differentiation found more often in neoplasms arising in other parts of the female genitalia. The concept of the extended müllerian system is a useful construct for understanding these observations. The ovarian surface “epithelium,” fallopian tubes, uterus, and upper third of the vagina share a common embryologic history, and all of these structures act, in many ways, as a single extended organ system. Many of these components show similar changes during pregnancy, develop comparable epithelial metaplasias, and share a common set of differentiated neoplasms. Furthermore, several neoplasms (often of identical histologic types) may arise in different components of the müllerian system metachronously or synchronously.

Although the full range of müllerian epithelial neoplasms may develop at any site within the female genitalia, the incidence of a particular differentiated type varies from one anatomic site to another. For example, most of the surface epithelial carcinomas that arise in the ovary may also be primary in the endometrium. In the endometrium, however, endometrioid carcinomas are by far the most common type; in the ovary, endometrioid carcinomas identical to those arising in the uterus are less common than serous neoplasms. In general, there is nothing in the intrinsic histological characteristics of a müllerian neoplasm that pinpoints its anatomic site of origin. Papillary serous carcinoma looks much the same whether it arises in the endometrium (an infrequent occurrence) or in the ovary (a common occurrence).

These considerations have certain important implications for the histopathologist. First, clinicopathologic correlation is often required to establish the primary site of a gynecologic malignancy. In the endometrium, this is particularly true for neoplasms exhibiting mucinous (endocervical primary?) or papillary serous (ovarian primary?) differentiation. Second, the diagnosis of benign or malignant, given a particular type of differentiation, may depend on the primary site. For example, considerably more cytologic atypia, mitotic activity, and epithelial stratification is allowed in benign endometrial proliferations with mucinous areas (mucinous metaplasia) than in benign endocervical proliferations with mucinous areas. Finally, the occurrence of synchronous, primary, müllerian neoplasms at several sites in the female genital tract has important implications for staging, prognosis, and therapy.
What are metaplasias and what are they good for?

In a variety of circumstances, benign endometrial cells may exhibit epithelial differentiation other than the well-known differentiated patterns seen in proliferative and secretory endometria. The commonly encountered alternative epithelial types ("metaplasias") are discussed here. It is important to realize that these benign alternative epithelial types may be present in association with any of the nonsecretory endometria (i.e., atrophic; weakly proliferative; disordered proliferative; hyperplastic, including AH; and endometrioid carcinoma). The clinical significance that attaches to these patterns is, as far as we know, that of the underlying associated nonsecretory pattern.

For example, patients with AH containing squamous metaplastic areas presumably have the same risk of endometrial carcinoma as those patients with hyperplasia with the same degree of cytologic atypia but uncomplicated by this differentiated feature. Benign metaplastic cells often cause diagnostic difficulties because of their unusual appearance and because they may grow in architectural arrangements also found in complex hyperplasia and in carcinoma. In particular, they may stratify (e.g., morules), or they may have cribriform patterns (e.g., ciliary metaplasia). When benign metaplastic epithelium coexists with carcinoma, the metaplastic cells do not warrant a change in the classification of the carcinoma; the classification of the carcinoma is based on the morphologic features of the malignant epithelium.

Cells with aberrant differentiation may themselves be malignant, however. In this circumstance, the term metaplasia is no longer appropriate; instead, the designation special variant carcinoma is employed. A final important differential diagnostic point: the subclassification of metaplasias into a variety of types is for descriptive and differential diagnostic purposes. Once a proliferation is determined to be a metaplasia and its degree of atypia determined, an unequivocal assignment to a particular metaplastic type is of little clinical (and probably less scientific) interest. Indeed, most metaplastic endometria are of mixed type, and it is likely that many of the patterns overlap (e.g., morules and syncytial papillary metaplasia).

What are special variant carcinomas?

The endometrium gives rise to a wide variety of differentiated carcinomas, but more than 80% are glandular neoplasms that resemble the epithelium found in endometrial hyperplasia. Squamous or squamoid ("morular") differentiation is commonly encountered in this endometrioid or usual adenocarcinoma. Other müllerian-differentiated types make up the remainder of endometrial carcinomas, the so-called special variants. Papillary serous carcinoma and clear-cell carcinoma are important because of their notorious aggressiveness. Mucinous carcinoma raises questions concerning localization, since both the cervix and the endometrium give rise to mucinous neoplasms and the treatment of carcinomas at these two sites differs. Carcinomas composed predominantly or exclusively of ciliated cells define the category of ciliated cell carcinoma and are a curiosity; however, scattered ciliated cells are frequently found in ordinary endometrioid carcinomas.
Problems raised by metaplasias

Metaplasia vs. Endometrial Carcinoma, NOS

The metaplasias were, historically, entities created for differential diagnostic purposes. An early study of clinical stage I endometrial carcinoma at Stanford persuaded us that carcinoma was over diagnosed. There were many patterns that were labeled carcinoma because they looked peculiar but for which there was no good evidence that they were fully developed carcinomas or that they had anything to do with the development of carcinoma (i.e., were precursor lesions).

Over the years, this has become less of a problem and the differential diagnosis is more focused: metaplasia vs. the analogous special variant carcinoma.

Metaplasia vs. special variant carcinoma

This distinction is made using architectural complexity and/or cytologic atypia of an extreme degree (Longacre, 1995). Our architectural criteria are set out in the chart below. That study included all types of metaplasia and low grade special variant carcinomas.

Non-standard epithelium: Did it originate from the endometrium or some other site

The particular problem depends upon the type of differentiation present. Mucinous differentiation (relatively common in endometrial primaries) raises the possibility of an endocervical primary. Confusingly, cervical primaries commonly have endometrioid histology. Strategies for distinguishing these possibilities are set out in the following table.
Table: Strategies for distinguishing endometrial from endocervical primary

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<tr>
<th>Clinical Localization studies</th>
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<td>Hysteroscopy, culposcopy, imaging studies</td>
<td>Merging with normal endocervical structures</td>
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<td>H&amp;E</td>
<td>• Merging with more typical endometrial glands and stroma</td>
<td>• Fibroblastic, chronically inflamed stroma</td>
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<td>• Stromal foam cells</td>
<td>• Precursor lesions: ACIS</td>
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<td>• Heterogeneity of epithelial patterns</td>
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<td>• Precursor proliferation: AH</td>
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<td>IPOX</td>
<td>ER+ve; Vim +ve, CEA-ve</td>
<td>ER-ve; Vim -ve, CEA+ve</td>
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One metaplasia vs. another metaplasia

Metaplasias are commonly mixed and nothing depends upon which metaplasia is present. Again, the pattern serves chiefly to raise a differentiation-specific differential diagnosis.

REFERENCES:

General


Metaplasias and their separation from carcinoma


Distinguishing between endocervical and endometrial primaries


McCluggage WG, Sumathi V, McBride HA, Patterson A. A panel of immunohistochemical stains, including carcinoembryonic antigen, vimentin, and estrogen receptor, aids the distinction between primary endometrial and endocervical adenocarcinomas. Int J Gynecol Pathol 2002;21:11-5.


CASE 4

Presented by Dr. Hendrickson
[In the Seminar, Case 5 presented before Case 4]

HISTORY:
The patient is a 50-year-old woman who was seen by her physician because of abnormal vaginal bleeding and pelvic pain. A pelvic mass was detected and hysterectomy and bilateral salpingo-oophorectomy was performed.

HISTOLOGIC FINDINGS:
Low power: Sheets of cells in this compressive myometrial lesion; nothing to suggest vascular involvement (which would suggest intravenous leiomyomatosis). Many foci featuring vacuolated cells: start thinking of cleared epithelioid myocytes (in epithelioid smooth muscle neoplasm, benign or malignant) or fatty differentiation. Other areas composed of smooth muscle cells exhibiting standard smooth muscle differentiation.
Medium power: Both vacuoles and probably adipocytes.
High power: Minimal cytologic atypia and only rare mitotic figures.

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DIAGNOSIS: MYOMETRIUM - Epithelioid Leiomyoma with Probable Lipomatous Differentiation

DIFFERENTIAL DIAGNOSIS
The differential diagnosis for this case falls into two parts: 1) is this epithelioid smooth muscle differentiation or something else and 2) under the assumption that we are in the presence of epithelioid differentiation, is this benign, STUMP or malignant?

Distinguishing epithelioid smooth muscle neoplasms from carcinoma can sometimes be a problem. The cells of epithelioid neoplasms fail to produce convincing glands and lack the cytologic atypia and mitotic activity of carcinoma. Immunohistochemical stains for keratin may be unreliable discriminators, since smooth-muscle cells can express keratin and EMA (Rizeq, 1994). However, it is unheard of for carcinoma cells to express desmin, and only rarely do they express muscle actin. An HMB45 stain is warranted for epithelioid uterine tumors because PEComas closely resemble epithelioid smooth muscle tumors. A good strategy is to cut more H&E sections, searching for areas of more characteristic smooth-muscle differentiation within the tumor. Stromal sarcomas with epithelial structures, adenosarcomas, and adenofibromas possess convincing tubular, glandular, or sex-cord-like structures. Placental site trophoblastic tumor (PSTT) sometimes figures in the differential diagnosis; immunohistochemical markers for intermediate trophoblast such as PLAP or HLA-G are helpful in this setting (Seidman, 1992, Shih, 1998, Singer, 2002, Young and Scully, 1984).
Once we have decided that the phenotype is epithelioid smooth muscle, we now have to place it in a risk category. For reasons set out below, we think that this is benign. Briefly, it lacks tumor cell necrosis, lacks significant atypia and has only rare mitotic figures.

This tumor features scattered lipocytes; these are not uncommon in ordinary leiomyomas and can be seen smooth muscle neoplasms — both benign and malignant — with alternative differentiation.

**DISCUSSION:**

As mentioned in Case 5, an initial step in the evaluation of the malignant potential of a uterine smooth muscle neoplasm is a determination of smooth muscle cell type. The rules are different for diagnosing malignancy in each of the differentiated patterns: standard, epithelioid and myxoid. The discussion will focus on alternative differentiated types of smooth muscle and the use of the term STUMP.

**Differentiated Cell Types revisited**

**Epithelioid differentiation:** Epithelioid smooth-muscle cells have a round configuration, with eosinophilic to colorless cytoplasm. They may have perinuclear cytoplasmic vacuoles or a perinuclear rim of eosinophilic cytoplasm with the rest of the cytoplasm clear. When the cytoplasm is totally clear, the label clear cell is used. This case exhibits marked vacuolization focally.

**Myxoid differentiation:** Myxoid smooth muscle neoplasms feature stellate cells embedded in abundant mucoid matrix. This pattern must be distinguished from the very common hydropic degeneration seen in leiomyomas. The latter features nodules of smooth muscle seemingly afloat in an edematous fibrovascular matrix in which large muscular-walled vessels are also suspended.

**Lipomatous differentiation in uterine neoplasms.** The finding of scattered foci of adipocytes in an otherwise typical leiomyoma is not unusual. Conspicuously fatty fibroids is unusual and the term lipoleiomyoma or, if extreme, lipoma is used. Malignant neoplasms of the uterus may have a fatty component; these include leiomyosarcomas and carcinosarcomas. The issue of fatty differentiation in this case is not straight-forward given the spectrum of vacuolization in this case.

**Criteria for epithelioid leiomyosarcoma**

Epithelioid differentiation in more than a few foci of a uterine smooth-muscle tumor is an ominous finding, because the absence of cytologic atypia and necrosis is no guarantee of a clinically benign course when the tumor contains more than 5 mf per 10 hpf. All epithelioid tumors with tumor cell necrosis in our series behaved in a malignant fashion. On the other hand, all seven epithelioid tumors in our study with an MI of less than 5, with at most minimal cytologic atypia and without necrosis, were clinically benign. The experience with epithelioid tumors as a group is limited, even when all the literature is considered. Indeed, those tumors with moderate to severe atypia without necrosis and an MI of less than 5 should be classified as STUMP, because our experience is too limited to guarantee a benign outcome.

**Criteria for myxoid leiomyosarcoma**

Myxoid differentiation coupled with enlarged and atypical cells is an ominous finding. Four of seven such uterine tumors failed in our series. Our diagnostic terminology is as follows. Benign (myxoid leiomyoma): myxoid neoplasms possessing whose constituent cells are small, uniform, have at most mild atypia; and the MI is ≤ 5 mf /10 hpf. Malignant (myxoid leiomyosarcoma): any myxoid neoplasms whose cells feature moderate to marked atypia with or without necrosis,
with any MI. The tumor margins are usually infiltrative. In myxoid leiomyosarcomas, not only is the stroma myxoid but the cells are also enlarged, with hyperchromatic nuclei, and pleomorphism is typically obvious. The usual case of myxoid leiomyosarcoma bears a striking resemblance to soft-tissue myxoid malignant fibrous histiocytoma. Both myxoid malignant fibrous histiocytoma and myxoid leiomyosarcoma are composed of cells that exhibit a range of cytologic abnormalities from bland to obviously malignant.

**Are there any STUMPs (Smooth Muscle Tumors of Uncertain Malignant Potential) left?**

STUMPS will always be with us; the term gestures toward that ineliminable fringe of cases for which insufficient clinicopathologic information is available to be dogmatic about the characteristics of the lottery the patient is in. We chiefly use the term when there is ambiguity about one of the evaluated standard features (mitotic index, type of necrosis, type of differentiation etc.) and the diagnostic possibilities straddle an important managerial boundary. For example, in case of that combines marked atypia and any MI. The tumor margins are usually infiltrative.

**REFERENCES:**

**General**


**Epithelioid Smooth Muscle Neoplasms and their differential diagnosis**


**Trophoblast references (Differential diagnosis of epithelioid smooth muscle neoplasms)**


Myxoid Smooth Muscle Neoplasms

Lipomatous differentiation
CASE 5

Presented by Dr. Hendrickson
[In the Seminar, Case 5 presented before Case 4]

HISTORY:
Four years prior to the current admission this 47-year-old woman had a hysterectomy and bilateral salpingo-oophorectomy. The diagnosis was well-differentiated adenocarcinoma of the endometrium with a single uterine serosal implant and invasion into the inner one third of the myometrium, well-differentiated endometrioid carcinoma of the right ovary and endometriosis. Lymph nodes were negative for tumor. At the time of this admission a pelvic mass was found.

HISTOLOGIC FINDINGS:
- **Low power**: Pale featureless zones and highly cellular zones.
- **Medium power**: On closer examination, the pale zones are seen to represent coagulative tumor cell necrosis (CTN) and are directly adjacent to highly cellular zones of malignant spindled cells.
- **High power**: Marked nuclear atypia (of the uniform sort), high mitotic index and individual cell necrosis.

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DIFFERENTIAL DIAGNOSIS:
There are ‘primary-site’ problems with this case. One possibility is that the tumor in the endometrium was, in reality, a carcinosarcoma and this case represents metastasis from a uterine carcinosarcoma. Another is that this is a primary retroperitoneal leiomyosarcoma unrelated to the patient’s prior adenocarcinoma.

Setting aside the primary site ambiguities and focusing on the tumor’s phenotype, there are two possibilities: 1) The tumor is differentiated as smooth muscle but is something other than malignant: leiomyoma or atypical leiomyoma. 2) The tumor is malignant, but has a phenotype other than smooth muscle, e.g. undifferentiated sarcoma, a component of a carcinosarcoma.

The first possibility is unlikely: under the assumption that one is dealing with a smooth muscle neoplasm, CTN forces a diagnosis of malignancy. If there is any doubt, the MI and the atypia resolve the problem.

More difficult, is the problem of determining differentiated type. In this case the conventional light microscopic appearance is quite typical of leiomyosarcoma; the positive desmin stain confirms this impression. Sampling would be required to rule out a benign or malignant epithelial component; adenosarcoma and carcinosarcoma respectively.

The case is complicated by the ambiguity of anatomic primary site. Under either interpretation-primary pelvic /retroperitoneal or uterine-this tumor is malignant.
DIAGNOSIS: PELVIC MASS: Leiomyosarcoma

DISCUSSION:

Introduction

Morphologically, this is a completely typical example of leiomyosarcoma and provides an opportunity to discuss criteria for diagnosing leiomyosarcoma and the clinicopathology of leiomyosarcoma. The discussion that follows relates to uterine smooth muscle neoplasms. The criteria are a reasonable starting point for separating benign and malignant smooth muscle neoplasms in other sites but must be used with extreme caution. The relevant clinicopathologic studies are required to validate uterine criteria elsewhere. In this case, the diagnosis of leiomyosarcoma is secure whatever the primary site. In summary: CRITERIA FOR SMOOTH MUSCLE NEOPLASMS ARE NOT TRANSPORTABLE.

The Diagnosis of Leiomyosarcoma

A Vocabulary for Discussing Prognosis and Clinical Management in uterine smooth muscle neoplasms

It is important to distinguish, on the one hand, between terms used to label clinical outcomes and, on the other hand, terms used to label groups defined on the basis of their gross and microscopic features. Histopathologic nomenclature is ambiguous in this respect. For example, “benign” is a free-floating term usefully employed in every organ system to mean, more or less, that after adequate removal of the offending lesion, the patient is cured. The same term is also employed as a morphologic label for a particular group of neoplasms all of which conform to a set of histopathologic rules or criteria. To decide if a tumor or neoplastic process is benign in the morphologic sense, one simply turns to a list of features set out in the relevant text to determine whether or not the case in hand counts as a benign example. To be sure, the specific morphologic definitions of benign that have been settled upon were fashioned by keeping one eye on clinical outcome and the other on morphologic characteristics. We sometimes make clinicopathologic terms less ambiguous by prefacing them with such clarifying descriptors as “clinically benign” and “morphologically benign.”

Several observations about clinical outcome terminology are also required. Traditionally, the clinical behavior of neoplasms has been characterized dichotomously as benign or malignant, with the corollary that benign implies an absolute guarantee that the neoplasm so labeled will never behave in a clinically malignant fashion. Those tumors that are clinically malignant, then, comprise all those that are not benign. As is widely recognized, this simple-minded approach, not surprisingly, is inadequate to the task of usefully describing the wide variety of clinical behavior of human neoplasms observed in actual practice. Nonbenign behavior can be expressed in terms of the magnitude of the failure rate, the tempo of disease progression, the sites of failure, and the death rate, to name but a few variables.

The biologic correlate of this dichotomous clinical classification is a model that envisions malignant transformation as a kind of on/off switch at the genetic level that propagates in a clean yes/no fashion to the light microscopic level, where histopathologic diagnosis takes place. Increasingly, from a scientific point of view, this dichotomous classification does less and less justice to what is known about the biology of cancer. The following discussion focuses on three of the inadequacies of the “benign or malignant” paradigm that are particularly relevant to uterine smooth-muscle neoplasms: its unrealistic definition of the term benign, its failure to
provide a useful conceptual framework for low-grade tumors, and its failure to provide a terminology to express degrees of confidence in a clinical prediction.

First, since every rational decision-maker knows that there are no guarantees in this life (with the exceptions of death and taxes), a more realistic rendering of "clinically benign," is something along the lines of "the failure rate after removal is sufficiently low that the prudent clinician would act as if the failure rate were zero." For example, uterine smooth-muscle tumors that are unremarkable in gross features and bland in histologic characteristics and that are indistinguishable from run-of-the-mill leiomyomas may very rarely metastasize to bone, lymph nodes, or the lungs. Quite sensibly, our impulse on receipt of this information is not to label all former leiomyomas as malignant but to fashion a new term—"benign metastasizing leiomyoma"—that draws attention to this phenomenon without forcing an unwarranted relabeling of leiomyomas to reflect this insignificant failure rate.

Second, the wide range of clinical behaviors that neoplasms exhibit has forced attention on the awkwardness of equating the labels "not clinically benign" and "clinically malignant." Two factors have been chiefly responsible for this focusing of our attention. (a) There exist neoplasms that are, in a number of senses, low grade. Low-grade behavior (relative to other members of the same differentiated group) may manifest itself in a number of ways, for example, by a lower failure rate, a slower tempo of disease progression, or, perhaps, a high recurrence rate but lower death rate with recurrence. (b) Then there is the fact that knowledge of this low-grade behavior not only is important for prognosis but also can be exploited to treat patients more effectively. As is well known in gynecologic oncology, the identification of "low grade" ovarian neoplasms has resulted in effective treatment strategies, the aim of which is to preserve fertility in young patients. We use the descriptor "low malignant potential" for these low-grade ovarian neoplasms.

The term we use for an analogous set of uterine smooth-muscle neoplasms is atypical leiomyoma with low risk of recurrence. The smooth-muscle tumors we include in this group are those with morphologic features that are associated with failure rate estimates that lie between 1% and 10%. Patients with such tumors could be treated with reasonable safety by myomectomy combined with careful clinical and radiologic follow-up, if they desire uterine preservation and are capable of understanding the small risk. Our experience also suggests that the neoplasms we have gathered under this heading tend to have a slower rate of progression, even if they do recur. Neoplasms with an estimated failure rate of more than 10% form the "high malignant potential" (HMP) group. Whereas a patient might reasonably opt for uterine conservation (after myomectomy) for a tumor with a less than 10% risk of recurrence, the designation HMP is used for tumors having a failure rate that overrides fertility considerations for all but the most risk-seeking patients.

The third point to be made is that groupings like "benign," "LMP," and "HMP" for purposes of clinical treatment are associated not only with a best guess of clinical outcome ("the estimated failure rate is 10% for tumors with this appearance") but also with some measure of the reliability of that guess [Diamond, 1983 #891; Diamond, 1989 #959]. The correlate of this guess in more numeric enterprises is, of course, a confidence interval, standard deviation, or variance. Many variables, in principle, enter into an estimate of reliability. One important factor, certainly, is the number of cases of the sort under consideration that have been studied and the length of the follow-up. When the number of investigated cases is small, the morphologic predictors being used are relatively weak, and the intra- and interobserver agreement on feature evaluation is not
thought to be high, we append the label “limited experience” to the best guess, to alert the clinician to this problem.

A diagnosis that might be used is “leiomyoma but limited experience.” The message being conveyed with such wording is that the few cases we have seen or know about with these morphologic features have been clinically benign, but, alert to the problems of small samples, we would not be shocked if, in the fullness of time and with the acquisition of more experience, this tumor turned out to be one of LMP. Again, the diagnosis “leiomyosarcoma of HMP but limited experience” would be an appropriate way of summarizing the following clinicopathologic state of affairs. We have seen ten tumors more or less similar to the one your patient harbors, and in that group of ten the failure rate was 30%. I would not be shocked if the “true” failure rate (e.g., if there were 1,000 cases available for follow-up) was in the range bracketed by 10% and 60%. With more experience, we might discover either that this is an LMP tumor or, more likely, that we were right in judging this to be an HMP neoplasm.

**Definitions of Morphologic Terms**

Morphologic features other than the mitotic index (MI) are powerful predictors of clinical outcome and have been incorporated into the diagnostic criteria for uterine smooth-muscle neoplasms. These features include epithelioid histologic features, myxoid stroma, cytologic atypia, and coagulative tumor cell necrosis. They are defined in the following sections.

**Differentiated Cell Type**

*Usual smooth-muscle* cells resemble normal myometrial cells in that they are elongated, with easily seen eosinophilic and sometimes fibrillar cytoplasm, and often have distinct cell membranes. These cells have a tendency to be arranged in bundles.

Other patterns of smooth muscle differentiation are discussed in connection with Case 4.

**Atypia**

Our study and several others have established a relationship between cytologic atypia and outcome for uterine smooth-muscle tumors. The problem, as always, is defining significant atypia in a way that is reproducible and can be communicated to others. We found that a two-tiered scheme of absent to mild atypia and moderate to severe atypia is reasonably reproducible. Moderate to severe atypia is defined by several features. Nuclear hyperchromatism and pleomorphism are obvious at scanning power, and cells with huge nuclei are common. Enlarged and sometimes abnormal mitotic figures are a typical finding. Most often, moderate to severe atypia is diffuse, but it can be focal. In contrast, absent or mild atypia is characterized by uniform cells with no more than mild pleomorphism. Chromatin is usually fine to granular. The nuclei may be enlarged compared with the surrounding myometrium, but the enlargement is uniform throughout the lesion. More than one or two enlarged abnormal division figures place the tumor in the group with moderate to severe atypia.

**Mitotic Index**

The MI is based on the number of mitotic figures per 10 hpf. Only definite mitotic figures are counted. As will be seen later, compulsive counting of mitotic figures is not always necessary, depending on the presence or absence of significant atypia and/or tumor cell necrosis.

**Necrosis**

In our experience, the presence or absence of necrosis and the type of necrosis are powerful predictors. We distinguish two types of necrosis in uterine smooth-muscle tumors: coagulative tumor cell necrosis and hyalinizing necrosis. Coagulative tumor cell necrosis features an abrupt
transition between necrotic cells and preserved cells. The nuclei of the necrotic cells often retain their hematoxyphilia, and inflammatory cells are unusual. A cuff of viable cells may be seen around blood vessels. This pattern of necrosis is common in clinically malignant smooth-muscle tumors and should never be ignored. In contrast, hyalinizing necrosis exhibits a zone of usually eosinophilic collagen interposed between the dead cells and the preserved cells, a pattern reminiscent of an infarcted region being organized by granulation tissue. Eosinophilic collagen matrix is characteristic, in contrast to the necrotic debris seen in tumor cell necrosis.

If dead nuclei can be discerned in areas of hyalinization, they are uniform, with often faint chromatin, compared with the nuclear hyperchromatism and pleomorphism still barely visible in tumor cell necrosis. Necrosis stemming from ulceration in submucous leiomyoma features acute inflammatory cells and a peripheral reparative process, while ghost outlines of nuclei are usually inconspicuous or absent. “Apoplectic” leiomyomas are distinguished by areas of hemorrhage, but necrosis is absent. Since the advent of leuprolide therapy to shrink leiomyomata, there has been controversy concerning the mechanism of shrinkage and the morphologic correlates of this process. Most investigators have not been able to detect striking differences in leuprolide-treated leiomyomas compared with controls.

Our Approach to the Diagnosis of Uterine Smooth-muscle Tumors

Our approach to the diagnosis of uterine smooth-muscle tumors, outlined here, is based on our personal experience of 213 difficult cases and a review of recently published cases. These guidelines do not necessarily apply to nonuterine smooth-muscle tumors. The first step in the evaluation of a uterine smooth-muscle tumor is to be sure that the lesion in question is composed of cells demonstrating smooth-muscle differentiation.

Smooth-muscle Tumors of the Usual Sort Confined to the Uterus Without Intravascular Extension

The crucial observations to be made in this subset of tumors are to assess the presence or absence of necrosis and, if necrosis is present, to distinguish its type; to determine whether moderate to severe atypia is present; and to evaluate the MI. If the histologic appearance is that of the usual leiomyoma, with neither coagulative tumor cell necrosis nor significant atypia (as defined previously), nothing clinically useful is gained by determining the MI. The recent literature and our experience indicate that for practical diagnostic purposes, neoplasms without these two features behave in a benign fashion even if the MI is up to 20 mφ per 10 hpf.

Although the reported experience with bland smooth-muscle neoplasms without coagulative necrosis and with mitotic counts ranging from 5 to 20 mφ per 10 hpf is limited to approximately 200 patients, as rare tumors go, this is a substantial experience; accordingly, we think that it is appropriate to label these neoplasms as leiomyomas with increased mitotic figures. The mitotic figures should be small and normal, with no more than one or two abnormal forms in a well-sampled tumor. The same benign behavior is to be anticipated for otherwise characteristic leiomyomas that exhibit hyalin necrosis. Whereas the majority of leiomyomas contain, at most, a few normal mitotic figures, examination of grossly undistinguished and cytologically bland leiomyomas removed during the secretory phase of the menstrual cycle often turn up tumors with mitotic counts in the range of 4 to 5 normal mφ per 10 hpf.

Submucous leiomyomas with surface necrosis may also contain increased numbers of cells in division near the necrosis. Even higher mitotic counts can be found in some, but not all, leiomyomas removed from women receiving progestational agents. Thus, there appear to be
reasons other than neoplastic transformation for an increased MI. If low-power examination reveals significant diffuse, moderate to severe atypia, but no tumor cell necrosis, the mitotic counts serve to stratify the cases into two groups – atypical leiomyomas with an MI of fewer than 10 mf per 10 hpf (one of 46 failed in our group) and leiomyosarcomas with an MI of 10 or more mf per 10 hpf (four of ten failed in our group). When low-power examination reveals more than just minute foci of coagulative tumor cell necrosis (not hyalinizing necrosis - see definitions given earlier), our experience indicates that the tumor has a strong chance of behaving in a malignant fashion and should be labeled leiomyosarcoma (29 of 39 failed) if focal or diffuse, moderate to severe atypia is present - regardless of the MI. If coagulative tumor cell necrosis is evident in the absence of atypia and the presence of an MI of less than 10, the tumor should be placed in the UMP category owing to our limited experience.

The clinicopathology of leiomyosarcoma

General Comments
The mean age of patients with uterine leiomyosarcoma is about 50 years; they may be found in women in the fourth decade, but leiomyosarcoma is very rare in women younger than 40 years of age. Although leiomyosarcoma is among the most common of the sarcomas that arise in the uterus, it almost certainly does not evolve from "malignant degeneration" of a leiomyoma.

Staging uterine sarcomas
The staging system for uterine corpus carcinoma is used for uterine sarcomas, although this has not been officially sanctioned. Most leiomyosarcomas are clinically confined to the uterus on presentation; when extraterine disease is present it is likely to involve the lung. Leiomyosarcoma spreads intraperitoneally, to regional lymph nodes and hematogenously, particularly to the lungs, liver, brain, kidney and bone. Recurrences in a recent large series of Stage I and II leiomyosarcomas were hematogenous in 57% and pelvic in 20%. The incidence of lymph node metastasis varies from series to series but is substantially lower than found in clinical stage I and II high risk endometrial carcinomas (Major, 1993).

Clinical behavior and therapy
Leiomyosarcoma is a highly malignant neoplasm; survival is worse with this disease than with carcinosarcoma. For postmenopausal women, primary therapy for early stage leiomyosarcoma is total abdominal hysterectomy and bilateral salpingo-oophorectomy. Therapy in premenopausal women is more controversial. The ovaries are only rarely the site of metastatic disease in clinically low stage leiomyosarcoma; in the GOG study only two of 59 patients had this finding (Major, 1993). Moreover, there is no evidence that oophorectomy influences the results of therapy. Accordingly, ovarian conservation is reasonable in premenopausal women. On the other hand, patients with low grade smooth muscle neoplasms metastatic to the lung have responded to oophorectomy alone. The role of radiotherapy would appear to be limited given the conflicting reports on the radiosensitivity of leiomyosarcoma and its noncontroversial tendency to spread hematogenously. Advocates of adjuvant radiotherapy have argued that although survival is not changed, pelvic radiation prevents local and regional recurrence and thereby is associated with an improvement in the quality of remaining life.

Prognosis
The prognosis of leiomyosarcoma depends chiefly upon stage. The three year progression free interval was 31% in a GOG series of 59 early stage leiomyosarcomas; the first recurrence was in
the pelvis in 14% of cases and in 41% in the lung (Major, 1993). Most recurrences are detected within 2 years.

For Stage I tumors, some investigators have found the size of the neoplasm to be an important prognostic factor. In Evans' series all patients with tumors larger than 5 cm. died of disease while only three of eight patients with tumors smaller than 5 cm. died of disease (Evans, 1988). In another series of metastasizing leiomyosarcomas only 20% were less than 5 cm. (Jones, 1995).

Premenopausal women have a more favorable outcome in some series.

**Grading leiomyosarcomas**

There is controversy as to whether the histologic features of stage I leiomyosarcomas provide additional prognostic insight.

Historically, grading was held to be useful; this had to do with the inclusion of cases we would no regard as benign (or having low risk of recurrence) in the malignant category. These cases, of course, were the Grade I cases. With the morphologic redefinition of leiomyosarcoma to exclude these cases the value of grading is more difficult to establish.

That said, several recent series, including the large GOG study of early stage leiomyosarcoma, have found mitotic index to be of prognostic significance (Gadducci, 1996; Larson, 1990; Major, 1993; Pautier, 2000); while others have not (Evans, 1988). A modification of the classification of Bell et al (Bell, 1994) has been employed as a grading scheme and found to provide independent prognostic information (Blom, 1998). A grading scheme designed for soft tissue neoplasms has been applied to uterine sarcomas but was not of prognostic significance (Pautier, 2000). We do not grade leiomyosarcomas.

**What should the clinician do with a diagnosis of STUMP?**

If, with a firm diagnosis of leiomyosarcoma, the clinical team is inclined to give adjuvant therapy, they probably shouldn’t with a diagnosis of STUMP.

We discuss the uses of the term STUMP in connection with Case 4.

**REFERENCES:**

**General**


**Diagnostic criteria**


**Clinicopathology of leiomyosarcomas**


CASE 6

Presented by Dr. Hendrickson

HISTORY:
This 37-year-old woman was found to have a pelvic mass. At surgery the mass was in the pelvic retroperitoneum and involved the mesentery of the sigmoid colon. The mass was resected and hysterectomy and bilateral salpingo-oophorectomy was performed. A section of sigmoid colon was also excised. The uterus contained a leiomyoma; otherwise the uterus and adnexa were unremarkable. The section is from the pelvic mass, which was attached to the muscularis of the sigmoid.

HISTOLOGIC FINDINGS:
Low power: Highly variegated appearance: some areas resemble an ordinary uterine leiomyoma; some areas are densely hyalinized and entrap rows of stubby spindled cells; other areas have an endometrial stromal appearance but are associated with thick-walled vessels.
Medium power: The rope-like collagen is suggestive of that seen in endometrial stromal neoplasms.
High power: The cells in all areas are cytologically bland and only rare mitotic figures are encountered.

IMMUNOHISTOCHEMISTRY:

<table>
<thead>
<tr>
<th>CD 117</th>
<th>HMB45</th>
<th>CD 10</th>
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DIFFERENTIAL DIAGNOSIS
The differential diagnostic possibilities for the general problem of monomorphous spindled neoplasms in the pelvis include a large number of possibilities. Some of these are set out below:

<table>
<thead>
<tr>
<th>Differential diagnosis of pelvic monomorphous spindle-cell neoplasms</th>
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</thead>
<tbody>
<tr>
<td><strong>Uterus</strong></td>
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<tr>
<td>&quot;Parasitic&quot; leiomyoma</td>
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<tr>
<td>Subserosal leiomyoma</td>
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<tr>
<td><strong>Ovary, adnexa</strong></td>
</tr>
<tr>
<td>Fibroma</td>
</tr>
<tr>
<td>Smooth muscle neoplasm</td>
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<tr>
<td>Endometrial stromal neoplasm</td>
</tr>
<tr>
<td><strong>Urogenital tract</strong></td>
</tr>
<tr>
<td>Smooth muscle neoplasms</td>
</tr>
<tr>
<td><strong>Gastrointestinal tract</strong></td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor (GIST)</td>
</tr>
<tr>
<td>Fibromatosis</td>
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</tbody>
</table>
### Peritoneal surfaces

<p>| | |</p>
<table>
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<tr>
<td>Fibrous mesothelioma</td>
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<tr>
<td>Solitary Fibrous Tumor</td>
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<tr>
<td>Leiomyomatosis peritonealis disseminata (LPD)</td>
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### Pelvic Soft tissues, NOS

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<table>
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<tbody>
<tr>
<td>Leiomyoma</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td></td>
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<tr>
<td>Endometrial stromal sarcoma (ESS)</td>
<td></td>
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<tr>
<td>Mixed müllerian neoplasms (stromal overgrowth in an adenosarcoma, for example)</td>
<td></td>
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<tr>
<td>Low grade sarcomatous overgrowth of atypical lipomatous tumor</td>
<td></td>
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</table>

### Vasculature

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<tbody>
<tr>
<td>Intravenous leiomyomatosis (IVL)</td>
<td></td>
</tr>
<tr>
<td>Endometrial stromal sarcoma (ESS)</td>
<td></td>
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</tbody>
</table>

The differential diagnosis in this case can be simplified. The major considerations are set out below:

**Differential Diagnosis in this case**

<table>
<thead>
<tr>
<th></th>
<th>Conventional Light Microscopy</th>
<th>Immunohistochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyoma</td>
<td>Fascicles of cigar-shaped spindled cells; Looks like usual uterine leiomyoma</td>
<td>Typical case: CD 10+ve; Desmin, Calponen -ve Other combinations: leave you up in the air</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>High grade neoplasms with +ve muscle marker; low grade neoplasm with some combination of necrosis, cytologic atypia and high MI</td>
<td>Muscle profile</td>
</tr>
<tr>
<td>Endometrial Stromal Sarcoma (ESSa)</td>
<td>Blunt spindled cells; Plexiform vasculature; May be sex cord or glandular foci</td>
<td>Typical case: CD 10+ve; Desmin, Calponen -ve Other combinations: leave you up in the air</td>
</tr>
<tr>
<td>Fibromatosis</td>
<td>Fascicles of spindled cells; Mitotic index low; Infiltrates muscle; May have myxoid areas</td>
<td>Desmin, calponen -ve; Actin may be focally and weakly positive</td>
</tr>
<tr>
<td>Nerve sheath tumor</td>
<td>Bent wire nuclei; plexiform neoplasms have ‘braided’ appearance</td>
<td>S100 +ve</td>
</tr>
<tr>
<td>Solitary Fibrous Tumor (see case 11)</td>
<td>Laminated appearance: alternating blunt spindled cell layer with collagen layer</td>
<td>CD 34 +ve</td>
</tr>
</tbody>
</table>

This patient's neoplasms is problematic because it exhibits smooth muscle areas and endometrial stromal like areas.

As we shall see in the discussion section, women can develop clinically benign smooth muscle neoplasms in the pelvis/retroperitoneum. So, if this neoplasms look just like an ordinary fibroid but was detached from the uterus, leiomyoma would be the reasonable diagnosis. Alternatively, were this a straightforward ESSa the prognosis would be that of a low-grade chronically recurring neoplasm and might eventually be responsible for the patient's death.

Unfortunately, we are in the middle; the tumor has features of both. This problem is discussed below.
DIAGNOSIS: PELVIC RETROPERITONEUM: Leiomyoma with focal areas of stromal differentiation

DISCUSSION:
Introduction

This case of a cytologically bland, mitotically inactive, predominately smooth muscle pelvic neoplasm raises a number of controversial issues.

1) If we view this as a morphologically bland smooth muscle neoplasm, it raises the question: “Is there a pelvic/retroperitoneal leiomyoma?”

2) Focal cellular areas with a suggestion of plexiform vasculature raise the issue of endometrial stromal differentiation either mimicking or commingled with a smooth muscle neoplasm.

“Is there a retroperitoneal/pelvic leiomyoma?”

Rephrasing: Is there ever a morphologic justification for declaring that a smooth muscle neoplasm of the retroperitoneum/pelvis will never metastasize or recur? One quibble: The term of art: “benign metastasizing leiomyoma” suggests that this sort of guarantee is not available for the humble fibroid. This uterine problem is solved by reserving this oxymoronic label for this vanishingly rare phenomenon and calling the vast sea of ‘non-metastasizing’ leiomyomas, benign. That said, we will now turn to non-uterine pelvic smooth muscle neoplasm in women.

In the case of retroperitoneal/pelvic smooth muscle neoplasms, the experience reported in the literature, though limited, suggests that recurrence of smooth muscle neoplasms with nothing morphologically to recommend a diagnosis of malignancy occurs with sufficient frequency to encourage caution. One response to this situation is to withhold a diagnosis of leiomyoma for all such neoplasms and to call them at least STUMPs. There are reasons to believe that the situation might be different in women. The smooth muscle neoplasms arising in the female genital tract are peculiar in a number of respects. They are exquisitely sensitive to steroid hormones, waxing and waning in response to changing levels. They may synchronously or metachronously involve multiple sites in the genital tract and/or pelvic peritoneum and, nevertheless, pursue a benign clinical course. In light of these phenomena, the dictum that ‘all pelvic pelvic/retroperitoneal smooth muscle neoplasms should be regarded as malignant’ is difficult for gynecologic pathologists. A typical situation might involve the following: Multiple uterine smooth muscle neoplasms that look like completely ordinary leiomyomas and one or more identical tumors, morphologically identical, but in the pelvis with no connection to the uterus. One traditional way of dealing with this is to invoke the parasitic leiomyoma story. We’ve never found this particularly convincing but we, and others, dutifully list this unicorn in our chapters. Perhaps LPD provides us with a clue. This rare, benign, and probably hormone-induced lesion is characterized by multiple peritoneal nodules composed of an admixture of fibroblasts and bland smooth-muscle cells. The nodules are usually small (less than 2 cm), and they stud the surface of the peritoneum. There may be an associated decidual reaction. One theory about LPD: the submesothelial mesenchyme retains the capacity to differentiate along müllerian lines as evidenced by peritoneal decidual reaction, pelvic endosalpingiosis, extraovarian surface epithelial neoplasms etc. Why should this not also extend to localized benign smooth muscle neoplasms? Indeed, we have seen a number of cases that bridge LPD and isolated pelvic smooth muscle neoplasms.

Enough speculation and anecdote. Someone has looked at the situation. The results of two relatively large recent series suggest that, in women at least, smooth muscle neoplasms with no
significant atypia, no coagulative tumor cell necrosis (CTN) and a mitotic index below 1 mitosis/10HPF can be regarded as benign.

More specifically, Billings, Folpe and Weiss (2001) reviewed 23 tumors: retroperitoneum (20) or abdominal cavity (3) of 22 women and one male. The study requirement entailed anatomic separation from the uterus. In four cases the tumors were multiple and in three occurred up to years after hysterectomy. Four cases occurred with synchronous uterine leiomyomas.

The mean mitotic index was 1 mitosis/50 HPF (range <1-10 mitoses/50 HPF). No patient developed metastasis within the follow-up period (mean 42.5 months, range 6-120 months); one tumor with a positive margin recurred at 10 months. In the six cases tested, five of six were positive for the estrogen receptor protein and all were positive for progesterone receptor protein.

Paal & Miettinen (2001) obtained similar results in their study of 56 tumors. Long-term follow-up (mean 140 months) did not reveal metastases, but two patients had local recurrence; however, neither patient with recurrence demonstrated disease progression in follow-up.

**Endometrial stromal sarcoma in extra-genital site.**

Although most commonly a uterine neoplasm, endometrial stromal sarcoma is well known to occur in extra-genital sites. They behave like high stage primary uterine ESS.

Most cases of ESS estrogen and progesterone receptors and the tumor is responsive to hormonal therapy.

**What is the behavior of neoplasms whose differentiation is ambiguous (i.e., there are conflicting signals as between ES and SMus differentiation)**

The behavior of neoplasms with mixed endometrial stromal / smooth muscle differentiation is not well established. The reported literature suggests that the behavior is that of the stromal component.

If there is convincing stromal differentiation in a pelvic neoplasm it should be managed as if it were stromal sarcoma.

**REFERENCES:**

**General**


**Deep soft tissue leiomyomas.**


**Extraterine stromal sarcoma**

Distinguishing stromal from smooth muscle differentiation;

Mixed smooth muscle stromal neoplasms
CASE 7

Presented by Dr. Kempson

HISTORY (CTTR Acc. #28679): This 61 year old woman experienced sharp severe left abdominal pain while playing golf. An immediate CT scan revealed a retroperitoneal hematoma medial to the spleen. At surgery multiple yellow masses and a hematoma were found involving the left kidney.

HISTOLOGIC FINDINGS: This tumor is composed mainly of epithelioid cells with round nuclei which have granular to clear cytoplasm. Pleomorphism is striking and some of the nuclei are quite large and hyperchromatic. Mitotic figures are very difficult to find. Intranuclear inclusions are prominent. Mixed among these epithelioid cells are numerous clear vacuoles, at least some of which are fat cells with nuclei distorted by the clear vacuoles. Focally within the tumor there are elongate cells with eosinophilic cytoplasm resembling smooth muscle. Many of the blood vessels show fibrillary change of their smooth muscle walls and in some vessels smooth muscle cells seem to stream off of the vessels into the neoplasm.

IMMUNOHISTOCHEMISTRY: The following stains are diffusely and strongly positive: HMB45, caldesmon, and smooth muscle actin. A desmin stain is negative.

DIFFERENTIAL DIAGNOSIS: The differential diagnostic considerations in this case include angiomyolipoma, pleomorphic liposarcoma, and carcinoma. The abnormal blood vessels and the mixture of fat and smooth muscle are indicative of angiomyolipoma. The epithelioid appearance of the majority of tumor cells is unusual because most angiomyolipomas are composed of spindled smooth muscle cells, fat and abnormal vessels. However, angiomyolipomas composed focally or predominately of epithelioid cells are well recognized. The strong diffuse HMB45 staining also supports angiomyolipoma. This staining pattern provides no support for pleomorphic liposarcoma and the paucity of mitotic figures is very much against sarcoma. The histologic and immunohistochemical findings provide no support for carcinoma.

DIAGNOSIS: Angiomyolipoma (PEComa).

DISCUSSION: Classically angiomyolipoma is trilineage with vascular, smooth muscle and lipidic components although any of these three may predominate in a given tumor. Until recently angiolipoma was considered to be a hamartomatous lesion often associated with tuberous sclerosis but recently cases that were locally aggressive and some that demonstrated metastasis have been reported. Molecular techniques have demonstrated that the lesion is clonal. Angiomyolipoma most commonly affects the kidney but it has also been reported in a number of sites, most commonly in the liver but also the heart, lung, palate, vagina, and gastrointestinal tract as well as the soft tissues of the retroperitoneum. In its classic form the mixture of abnormal vessels with fibrillary disrupted walls, smooth muscle and fat mixed together with variable numbers of epithelioid cells is distinctive and seldom causes diagnostic problems. However, when one or the other component predominates, the diagnosis can become more difficult. When fat predominates and the tumor is in the retroperitoneum, one would consider
atypical lipomatous tumor and when smooth muscle predominates, considerations are often given to a smooth muscle neoplasm. When epithelioid cells predominate as in this case, the lesion can mimic both sarcoma and carcinoma. The paucity of mitotic figures and the abnormal blood vessels are most helpful clues to the correct diagnosis which can be confirmed with positive HMB45 or melan A stains. Essentially 100% of angiomyolipomas are positive for these antibodies.

Marked cellular pleomorphism is common in angiomyolipomas that pursue a benign clinical course, but when this is coupled with easily found mitotic figures and necrosis, the tumor should be considered potentially malignant. However, ordinary angiolipomas may involve regional lymph nodes and spleen or even invade the renal vein and not pursue a malignant clinical course, if they are completely removed. Epithelioid angiomyolipomas have been reported to pursue a more aggressive clinical course.

Epithelioid cells in angiomyolipoma may be centered around blood vessels and these have been given the label perivascular epithelioid cells. The characteristic features of perivascular epithelioid cells (PECs) are positive staining for HMB45 and abundant clear to eosinophilic granular cytoplasm. Other features include expression of the other melanoma-associated antigen melan A, co-expression of muscle markers without cytokeratin or S-100 expression and premelanosomes. Other lesions containing variable number of PECs occur in the kidney, lung and liver and include epithelioid angiomyolipoma, clear cell sugar tumor, some examples of lymphangioleiomyomatosis, clear cell myomelanocytic tumor of the ligamentum teres/falciform ligament, and abdominopelvic sarcoma of perivascular epithelioid cells. Because all of these tumors contain PECs, or may be exclusively composed of PECs, they are grouped together and classified as PEComas. A subset of patients; with one or more of the PEC family of lesions, have the tuberous sclerosis complex.

In the past, some epithelioid smooth muscle tumor tumors of the uterus have been reported to be partially or completely composed of cells with pale or clear cytoplasm. It is interesting that these tumors have a histologic similarity to clear cell sugar tumors and epithelioid angiomyolipoma and recently HMB45 and melan A expression has been observed in some of these neoplasms. Those that express this antigen have been given the label uterine PEComa and we recently reported eight examples. Morphologically, the tumors could be divided into two groups. The first demonstrated a tongue-like growth pattern similar to that seen in low grade endometrial stromal sarcoma and were composed of cells that tended to have abundant clear to eosinophilic pale granular cytoplasm, diffuse HMB45 expression and focal muscle marker expression. The other group was composed of epithelioid cells with less prominent clear cell features, smaller numbers of which were HMB45 positive. They also featured extensive muscle marker expression and a lesser degree of the endometrial stromal sarcoma like pattern seen in the first group. Two of the four patients in the second group had pelvic lymph nodes involved by lymphangioleiomyomatosis. One of these patients had the tuberous sclerosis complex. All eight of the patients are alive and well after hysterectomy although followup time is short.

It could be argued that uterine PEComa merely represents a subset of epithelioid smooth muscle tumors that are distinguished by HMB45 and melan A expression rather than a tumor related to epithelioid angiomyolipoma. The answer is unknown, but until we know more about the clinical
outcome of these lesions, we think it wise to stain epithelioid smooth muscles of the tumor with HMB45, melan A, and S-100 and identify those that are positive for HMB45 and melan A but negative for S-100 as PEComas. Until more information is available we consider uterine PEComas to be of uncertain malignant potential unless they have cytologically malignant features.

REFERENCES:


CASE 8

Presented by Dr. Kempson

HISTORY (CTTR Acc. 28503): A 12.0 cm mass was palpated in this 44 year old woman who saw her physician because of menometrorrhagia. The uterus was anterior to the mass. Past history revealed that she had had a thyroidectomy for papillary carcinoma. At surgery the mass was separate from the uterus, but was attached to the large bowel.

HISTOLOGIC FINDINGS: The most striking features of this case are the cells with enlarged nuclei and dense smudgy chromatin. Many of these have eosinophilic cytoplasm and in some the nuclei become enormous. These cells are mixed with much smaller spindle cells that form a delicate fibrillar background as well as fat cells of variable sizes. Focally thicker collagen fibers are noted. Many of the enlarged cells are multinucleated and some have multiple vacuoles in the cytoplasm. A few clear vacuoles distort the nucleus. Intranuclear pseudoinclusions are present in some of the enlarged cells.

IMMUNOHISTOCHEMISTRY: The lesional cells are positive for S-100 and CD34. An actin stain is negative.

DIFFERENTIAL DIAGNOSIS: The differential diagnosis in this case includes atypical lipomatous tumor (formerly known as well differentiated liposarcoma), pleomorphic liposarcoma, dedifferentiated liposarcoma, myxofibrosarcoma, and angiomylipoma. The tumor is, in part, composed of adult fat cells as well as the cells with enlarged smudgy nuclei. These are the features of atypical lipomatous tumor. Fat is a part of the neoplasm so dedifferentiated lipoma is excluded because it is a non-lipogenic sarcoma seen in conjunction with atypical lipomatous tumor. The tumor lacks the sarcomatous stroma of pleomorphic liposarcoma and because the fat cells are part of the neoplasm myxofibrosarcoma is excluded.

DIAGNOSIS: Atypical lipomatous tumor.

DISCUSSION: Atypical lipomatous tumor is a neoplasm composed of mature fat cells and almost always fibrous or myxoid tissue. A variable number of the tumor cells, whether in the fat or the fibrous or myxoid tissue have enlarged irregular hyperchromatic nuclei. In the past this neoplasm has often been classified as well differentiated liposarcoma because in certain locations, such as the retroperitoneum, it can recur destructively and relentlessly resulting in patient death. However, the neoplasm does not have metastatic potential unless it dedifferentiates to dedifferentiated liposarcoma, hence the name well differentiated liposarcoma is inappropriate. The WHO classification of soft tissue tumors published several months ago has now recognized this and places atypical lipomatous tumor in the intermediate (locally aggressive) category rather than among the liposarcomas. Until clinicians are fully aware of this change in terminology it is prudent to explain in the comment section of the Surgical Pathology report that atypical lipomatous tumor was formerly known as well differentiated liposarcoma.

Microscopically atypical lipomatous tumors are made up at least partially of adult type fat cells, some of which are usually smaller than the usual adult adipocyte. Scattered among the fat cells
are variable numbers of cells with enlarged irregular dense nuclei. Almost always there is a component of myxoid or fibrous tissue (or both) which varies from slight to extensive and not infrequently this component also contains some of the cells with enlarged nuclei. Whether in the fat or the fibrous or myxoid stroma these enlarged cells are required for the diagnosis and their distinguishing feature is their large irregular nucleus which is composed of dense often smooth chromatin. When the cytoplasm of these cells contain clear vacuoles that distort the nucleus, the term lipoblast is appropriate but not all of them contain fatty vacuoles. Clear nuclear pseudoinclusions are commonly present. Some atypical lipomatous tumors feature extensive sheets of paucicellular fibrous tissue, which feature the atypical cells; these tumors are classified as the sclerosing variant.

In general cellularity is low, both in the myxoid and fibrous areas of atypical lipomatous tumors and mitotic figures are uncommon although they may be atypical. Moderately cellular fibrous or myxoid areas may be present and raise concern for dedifferentiated liposarcoma (see below). The fat cells in atypical lipomatous tumors may be S-100 protein positive and some of the spindle cells may be CD34 positive. Over 90% of tumors are composed of cells that have variable clonal chromosomal abnormalities, the only consistent one of which is the presence of supernumerary ring chromosomes derived from the 13-15 region of chromosome 12.

The most common differential diagnostic problem involving atypical lipomatous tumor is their distinction from lipomas. Essentially lipomas do not occur in the retroperitoneum so this is not a problem in that site although this differential diagnostic problem rises rather frequently in other soft tissue sites. What is required for a diagnosis for a diagnosis of atypical lipomatous tumor is identification of the cells with large nuclei and smudged chromatin. Other clues that one may be dealing with an atypical lipomatous tumor rather than lipoma include large amounts of fine fibrillar connective tissue and adult type fat cells of variable size. Atypical lipomatous may have large areas indistinguishable from lipoma because the atypical nuclei may be present in only a few areas of the tumor. Thus, it is necessary to take a large number of sections of any lipomatous tumor which demonstrates fibrosis and variation in the size of the fat cells or is in the retroperitoneum but seems to lack the diagnostic large cells.

Rarely what appears to be a lipoma is found in the retroperitoneum and thorough search fails to find cells diagnostic of atypical lipomatous tumor. Because such tumors can recur we think it prudent to use the diagnostic term “atypical lipomatous tumor cannot be excluded.”

The distinction of atypical lipomatous tumor from the usual spindle cell lipoma is based on the dense ropy collagen, uniform spindle cells and usual subcutaneous location in the back neck or shoulders that characterize spindle cell lipoma as well as the lack of the enlarged atypical cells which characterize atypical lipomatous tumor. Pleomorphic lipoma is distinguished from atypical lipomatous tumor by location; examples that rise in the subcutaneous tissue of the neck, back and shoulder are classified as pleomorphic lipoma while those that occur elsewhere are classified as atypical lipomatous tumor. Atypical lipomatous tumors are distinguished from non-lipogenic malignant mesenchymal neoplasms that contain enlarged atypical cells by the presence of neoplastic adult type fat cells.
Dedifferentiated liposarcoma is a non-lipogenic sarcoma arising within an atypical lipomatous tumor. It is characterized by a cellular stroma and mitotic activity above 3-4/10 hpf. This has been labeled as high grade dedifferentiated liposarcoma by Goldblum and associates. They consider non-lipogenic areas in an atypical lipomatous tumor with the cellularity of desmoid fibromatosis to be low grade dedifferentiated liposarcoma. However, these latter tumors probably do not metastasize until they have recurred locally as high grade dedifferentiated liposarcoma. Whether to use the term low grade de-differentiated liposarcoma is controversial and we prefer to label such changes as non-lipogenic fibrous or spindle cell areas with the notation that some investigators have classified such lesions as low grade de-differentiated liposarcoma.

REFERENCES:
Evans HL, Soule EH, Winkelmann RK. Atypical lipoma atypical intramuscular lipoma, and well-differentiated retroperitoneal liposarcoma: a reappraisal of 30 cases formerly classified as well-differentiated liposarcoma. Cancer 1979;43:574-84.
Fukunaga M. Histologically low grade dedifferentiated liposarcoma of the retroperitoneum. Pathol Int 2001;51:392-5.


CASE 9

Presented by Dr. Kempson

HISTORY (CTTR Acc. #29864): This 52 year old male was found to have a 10.0 cm mass in the deep tissues of the thigh. The tumor involved most of the vastus lateralis.

HISTOLOGIC FINDINGS: Two different patterns are found within this neoplasm. In some areas the stroma is myxoid and features delicate arching capillaries and cells with uniform small nucleoli. Occasional cells with enlarged nuclei are also present. In other areas the capillary pattern persists but the cells are much more closely approximated, the nuclei are larger and pleomorphic and they have granular-chromatin. Mitotic figures including abnormal forms are easily found. These areas appear more solid. The tumor is widely infiltrating.

IMMUNOHISTOCHEMISTRY: The following stains were negative: AE1/CAM 5.2, EMA, desmin, smooth muscle actin and S-100.

DIFFERENTIAL DIAGNOSIS: The main considerations in the differential diagnosis are myxofibrosarcoma, myxoid liposarcoma, myxoid chondrosarcoma, neural neoplasms, pleomorphic malignant fibrous histiocytoma, metastatic mucinous carcinoma, myxoid melanoma, and bland myxoid tumors composed of uniform cells. This differential diagnosis is discussed below following the discussion of myxofibrosarcoma.

DIAGNOSIS: Myxofibrosarcoma, intermediate grade (Myxoid variant of MFH).

DISCUSSION: Two problems have arisen with the concept of myxofibrosarcoma (myxoid variant of MFH): the variable definitions of the tumor provided by different investigators and the different labels used to identify this neoplasm. In their 1977 paper proposing a category of myxoid MFH, Weiss and Enzinger define this variant as having "varying proportions of myxoid and cellular components" and state that "over three-quarters of the tumors...had areas indistinguishable from typical malignant fibrous histiocytoma", implying that one-quarter did not and thus were purely myxoid. They suggested that only tumors that were more than 50% myxoid be included in the myxoid MFH category. In their textbook they define the tumor as follows: "this form of malignant fibrous histiocytoma is characterized by myxoid areas in association with cellular areas indistinguishable from ordinary malignant fibrous histiocytoma". Their requirement that more than 50% of the tumor be myxoid before applying the name myxoid MFH was retained. This leaves unanswered the question of how to designate purely myxoid sarcomas and how much atypia a purely myxoid lesion must have to be included in the myxoid MFH category.

Angervall and associates reported similar myxoid neoplasms under the rubric of myxofibrosarcoma. They divided the myxoid neoplasms they studied into four groups designated as grades I-IV. Their grades III and IV myxofibrosarcoma correspond reasonably well to the definition of myxoid MFH proposed by Weiss and Enzinger because for these grades they required solid and myxoid areas with cellular pleomorphism although there is no mention of areas resembling pleomorphic MFH. Their grade I tumors are described as paucicellular, or no
more than moderately cellular, with uniform cells and minimal mitotic activity but they were more cellular than myxomas. Their grade I tumors did not metastasize. Grade II myxofibrosarcomas as defined by Angervall and associates also have no more than moderate cellularity (i.e., there are no areas as cellular as those found in pleomorphic MFH) but the cells must be pleomorphic and mitotic figures, sometimes including abnormal forms, are easily found (2-10 mf/10 hpf). These tumors have significant metastatic potential.

In 1996 Mentzel and associates reported 75 myxoid neoplasms which they designated myxofibrosarcoma. They divided these into low, intermediate and high-grade types based on the degree of atypia and the presence or absence of pleomorphic MFH within the tumor. Tumors in the low-grade group were purely myxoid but had to have at least mildly pleomorphic cells with hyperchromatic irregularly shaped nuclei while the high-grade tumors contained areas of pleomorphic MFH as well as myxoid tumor. They did not address the purely myxoid lesions with uniform bland cells that are more cellular than myxomas, although subsequent publications from a number of investigators suggested the label cellular myxoma for such lesions. Although their low-grade myxofibrosarcoma group is labeled as “sarcoma” none of the tumors metastasized.

While it may seem that all of this leads nowhere but to confusion, several things seem important. First, the main reason to distinguish purely pleomorphic MFH from lesions with a mixture of myxoid areas and pleomorphic MFH is because the prognosis of patients with the latter is supposed to be better than for patients with the former. As it turns out in most studies the better prognosis applies to patients whose lesions are low grade and purely myxoid. Therefore, no matter whether the myxoid MFH or the myxofibrosarcoma label is used, the lesion should be graded. Second, a threshold needs to be set to separate non-metastasizing myxoid lesions from myxoid sarcomas. The definition used by Mentzel et al. required at least some degree of pleomorphism before placing a malignant label on a purely myxoid neoplasm currently this seems a good starting point, but as noted their low grade lesions did not metastasize. Therefore, further refinement of the nomenclature will be needed in the future if follow-up continues to demonstrate a non-metastasizing course for Grade I myxofibrosarcomas. Third, the percentage of myxoid stroma that should be present before placing a tumor in the myxofibrosarcoma category is controversial but we follow the lead of Mentzel et al and use greater than 10% of the volume of the tumor rather than the 50% or more volume of myxoid stroma required by Weiss and Enzinger. However, the percentage of myxoid stroma may be relatively unimportant because, as noted above, a significantly better prognosis does not seem to accrue unless the lesion is low grade and practically myxoid throughout and prognosis also depends on the size of the tumor and whether it is superficial or deep.

Some discussion about the definition of myxoid stroma is in order because it is key to recognizing myxofibrosarcoma. A tumor cannot have much in the way of a myxoid stroma if it is highly cellular, i.e. if the tumor cells are closely packed together. A myxoid stroma requires spaced apart cells set within a variable amount of either fluid or finely fibrillar matrix between cells rather than cells in apposition to each other or cells in a collagenous or hyalinized stroma. Cellularity in myxoid areas varies from paucicellular (nuclei spaced far apart) to moderately cellular (the amount of fluid or fibrillar matrix between cells is small but recognizable).
The most recent (2002) WHO classification officially changes the label of this tumor from myxoid variant MFH to myxofibrosarcoma and moves the tumor to the fibrous tumor category.

**GROSS FINDINGS:**
Myxofibrosarcoma, as its name would suggest, is gelatinous or frankly mucinous, either diffusely or focally, and when the myxoid areas are diffuse these tumors are grossly indistinguishable from other myxoid neoplasm such as myxoid liposarcoma. Myxofibrosarcomas tend to form multiple macroscopically visible nodules of tumor.

**MICROSCOPIC FINDINGS:**
The classic myxofibrosarcoma is composed of variable proportions of pauci- to moderately cellular myxoid tumor mixed with cellular tumor often identical to that found in pure pleomorphic MFH. The myxoid areas that count toward classification of the tumor as the myxoid variant may be diffuse or focal, but in the aggregate make up greater than 10% or greater than 50% of the tumor volume depending on whether one uses the definition of Mentzel et (10%) or the definition of Weiss and Enzinger (50%). The cells in the myxoid areas vary from small and bland to enlarged, bizarre, and pleomorphic. Either type of cell may predominate but in most tumors there is a mixture. The small bland cells have elongate to round regular nuclei and scant cytoplasm. These blend imperceptibly into cells with larger, often irregular nuclei and more abundant eosinophilic or vacuolated cytoplasm. Finally, bizarre, enlarged, often huge cells with round to jagged irregular nuclear outlines, abundant cytoplasm, and marked hyperchromasia round out the roster of cells that can be found in the myxoid areas. Any of these cells may have vacuolated or bubbly cytoplasm and thus come to resemble lipoblasts; however, their nuclei are characteristically central, the strands or spikes of chromatin that extend from the indented nucleus of a lipoblast are absent and the vacuoles are not usually sharply circumscribed and clear as are fat vacuoles. The cytoplasmic vacuolar material often stains with alcian blue. Mitotic figures are almost always easy to find and abnormal forms are the rule in pleomorphic areas. Blood vessels are prominent and may take on an arborizing pattern of the type found in myxoid liposarcoma or, more often, they form arcs or curves. Acute and chronic inflammation is found in some tumors, particularly those that have areas of pleomorphic MFH. Necrosis is generally limited to tumors with areas of pleomorphic MFH.

The minimum requirement for inclusion as myxofibrosarcoma is an otherwise undifferentiated tumor with a myxoid stroma throughout in which the constituent cells demonstrate at least mild pleomorphism, that is, at least some tumor cell nuclei are enlarged and hyperchromatic and have irregular outlines. Mitotic figures including abnormal forms are often present. Blood vessels are numerous and arranged in gently curvilinear arches or in a plexiform pattern reminiscent of the vessels found in myxoid liposarcoma. Rarely a pericytic vascular pattern is present. The tumor cells tend to condense around the vessels. The lesions of pure myxofibrosarcoma vary from hypocellular to moderately cellular and there is a continuum of nuclear atypia, pleomorphism, abnormal mitotic figures, and increasing cellularity that blends into the solid pattern of pleomorphic MFH. Myxoid lesions composed of cells that do not meet these requirements should not be placed in the myxofibrosarcoma category (see differential diagnosis below).

Because of the significant differences in patient outcome between purely hypocellular myxofibrosarcoma and those that are more cellular and pleomorphic, myxofibrosarcomas should
be graded. The grading criteria provided by Mentzel and associates utilize a three-tier scheme and are easy to apply. Low grade myxofibrosarcomas are hypocellular throughout and their matrix is entirely myxoid. High grade myxofibrosarcomas have solid pleomorphic areas indistinguishable from pleomorphic MFH in addition to myxoid areas. Intermediate grade lesions are myxoid throughout but they are more cellular than the low grade ones and pleomorphism is more obvious. Giant cells and abnormal division figures are often present. Tiny areas of solid tumor are acceptable in intermediate tumors.

In summary, in order for a tumor to qualify as myxofibrosarcoma the neoplastic cells must not be differentiated except as fibroblasts, myofibroblasts or histiocytes-like cells, the myxoid areas used to make the diagnosis must account for over 10% of the volume of the tumor and at least focally significant pleomorphism with enlarged cells must be present in the myxoid areas, the cellular areas or both. Whenever myxofibrosarcoma is diagnosed a grade should be specified. We use the terms low, intermediate, and high grade.

SPECIAL STUDIES:
CD68 and Factor XIIA may be focally positive and some tumors contain actin positive cells. As is the case for pleomorphic malignant fibrous histiocytoma the main value of immunohistochemistry is to exclude other neoplasms.

DIFFERENTIAL DIAGNOSIS:
The prime entities in the differential diagnosis are myxoid liposarcoma, myxoid chondrosarcoma, neural neoplasms, pleomorphic malignant fibrous histiocytoma metastatic mucinous carcinoma, myxoid melanoma and bland myxoid tumors composed of uniform cells. A diagnosis of pleomorphic malignant fibrous histiocytoma versus high grade myxofibrosarcoma is based on the amount of myxoid stroma in the neoplasm (> or <10%). The stromal cells, particularly those in the hypocellular areas, in myxofibrosarcoma may be indistinguishable from the undifferentiated stromal cells in myxoid liposarcoma, but myxoid liposarcoma also contains lipidic cells and it does not contain the pleomorphic cells required at least focally for diagnosis of myxofibrosarcoma. Myxoid liposarcoma practically never arises in the subcutaneous tissue whereas myxofibrosarcoma not infrequently develops in this site. S-100 protein stains can help exclude neural neoplasms and knowledge about the relationship of the tumor to a nerve (malignant peripheral nerve sheath tumors arise from a nerve or a neurofibroma or develop in a patient with neurofibromatosis). S-100 protein will also identify almost all myxoid melanomas. Keratin, EMA and mucin stains are adjuncts that often help identify metastatic carcinoma. Myxoid chondrosarcoma has microscopic lobular architecture and the chain-like arrangement of uniform cells extending from the periphery of the lobules to the center is unlike the cellular pattern in myxofibrosarcoma. Moreover, the cells in myxoid chondrosarcoma are usually small and uniform and do not demonstrate the degree of pleomorphism and anaplasia found at least focally in myxofibrosarcomas.

Aggressive angiomyxoma, juxta-articular myxoma, intramuscular myxoma, and superficial angiomyxoma lack the pleomorphism and nuclear atypia required for low grade myxofibrosarcoma. Evans has reported a type of bland fibromyxoid tumor that has metastatic potential even without significant cellular pleomorphism. This he has labeled low-grade fibromyxoid sarcoma, and it is characterized by not only paucicellular myxoid stroma, bland cells and low mitotic count, but also abundant fibrous tissue and a whorled or storiform
arrangement of the constituent cells. Almost all are deep and large and they are slow growing even when metastatic. Nodular fasciitis may have a myxoid stroma but it lacks the pleomorphism required for even low-grade myxoid malignant fibrous histiocytoma. The line between cellular myxoma and low grade myxofibrosarcoma is poorly defined but we require at least focal pleomorphism before putting a tumor in the myxofibrosarcoma category. Cellular myoid lesions without pleomorphism, and mitotic figures are placed in the cellular myxoma category. These have a 10% recurrence rate.

The reason for distinguishing myxofibrosarcoma from pleomorphic MFH is the supposedly better prognosis for patients with the former as compared to the latter. As it turns out the prognosis for patients with high grade myxofibrosarcoma is for practical purposes the same as for pleomorphic MFH (approximately 50-60% recurrence rate, 20-30% metastasis rate). However, low grade myxofibrosarcoma practically never metastasizes, although it has a recurrence rate in the same range as high grade myxofibrosarcoma and pleomorphic MFH and it may become more pleomorphic and cellular (and hence higher grade) in recurrence. Intermediate grade myxofibrosarcoma appears to behave as does the high grade variety although the number of cases with followup is small. As in the case for pleomorphic MFH the prognosis depends on size and location and whether superficial or deep. Patients with large deep-seated lesions do significantly worse than those with superficial tumors but of course most superficial tumors are small when discovered.

REFERENCES:
Nielsen GO, O'Connell JX, Rosenberg AE. Intramuscular myxoma. A Clinicopathologic study of 51 cases with emphasis on the hypercellular variant. Mod Pathol 1997;10:13A.
CASE 10

Presented by Dr. Kempson

HISTORY (CTTR 23087): This 49 year old male presented with a “large” unresectable soft tissue mass in his thigh. An amputation was performed.

MICROSCOPIC FINDINGS: This epithelioid neoplasm is composed of cells with enlarged nuclei and granular eosinophilic cytoplasm. Mitotic figures are numerous and tumor cell necrosis is prominent. The tumor cells tend to grow in sheets although they are somewhat discohesive and in some areas tend to form nodules with central necrosis.

IMMUNOHISTOCHEMICAL FINDINGS: The following stains were negative: CD34, desmin, CD31, AE1/CAM 5.2, EMA, and S-100. There were positive internal controls for the S-100.

DIFFERENTIAL DIAGNOSIS: This malignant epithelioid neoplasm is undifferentiated histologically so the differential diagnosis is large and includes carcinoma, melanoma, epithelioid sarcoma, epithelioid smooth muscle tumor, a neural tumor, and malignant rhabdoid tumor. Immunohistochemical stains provide no support for any direction of differentiation. Most importantly, the keratin stains and the S-100 protein stains are negative providing no support for metastatic carcinoma or melanoma.

DIAGNOSIS: Undifferentiated malignant neoplasm.

DISCUSSION: The classification of neoplasms is based on the direction of cellular differentiation or upon recognition of histologic pattern that has previously been described. It is not uncommon to encounter a neoplasm particularly in the soft tissue in which the direction of cellular differentiation of the constituent cells, whether determined by H&E morphology, immunohistochemistry or molecular techniques, cannot be determined and the pattern is not recognizable as a previously described tumor. When faced with this situation, pathologists should ask themselves several questions. First is the tumor a benign lesion mimicking a sarcoma? A number of benign reactive proliferations occur in the soft tissues and mimic sarcomas. They do so clinically because of their rapid growth, grossly because they may infiltrate normal structures and microscopically because they may be cellular, cytologically atypical or mitotically active. The full range of nuclear alterations encountered in dividing and synthetically active cells may be seen in these benign soft tissue lesions. These include nuclear and nucleolar enlargement, coarsening of chromatic and some degree of nuclear pleomorphism. These morphologically atypical but clinically benign lesions include such well-known entities as nodular fasciitis, neurofibroma with cellular atypia, atypical fibroxanthoma, pleomorphic lipoma and papillary endothelial hyperplasia. Features which favor a benign lesion are small size, paucicellularity and if mitotic figures are present, they are normal. Features favoring a malignant neoplasm are high cellularity, abnormal mitotic figures, and large size.
After determining that a soft tissue lesion is indeed malignant, the second question to be asked is whether the tumor is primary or a malignant neoplasm mimicking sarcoma. Two major considerations apply. First is to exclude lymphoma and metastatic melanoma, and carcinoma and to determine that the neoplasm is not extending into the soft tissues from a nearby organ. Immunohistochemistry has been extremely helpful in resolving the first issue and modern imaging techniques are very useful for the second.

When the pattern of a soft tissue tumor does not fit a well recognized category and when direction of differentiation cannot be discerned histologically and by judicious use of antibodies, the question arises as to how much clinical care funds should be expended in an attempt to classify a difficult to identify tumor. The answer lies in the difference that classification will make in therapy. Certainly every effort should be made to identify lymphomas so they can be treated and metastatic carcinoma and melanoma so patients are not treated for a primary soft tissue tumor. It is very important to correctly classify childhood sarcomas. However, adults with most pleomorphic sarcomas are treated in a similar manner regardless of type so expending large amounts of patient care dollars to try to determine direction of differentiation for a pleomorphic high grade sarcoma may not always be warranted. For example, it makes no difference in patient management whether a pleomorphic sarcoma is leiomyosarcoma, rhabdomyosarcoma or pleomorphic liposarcoma but what does make a difference is whether the lesion is high grade and fully capable of metastasis rather than having only recurring potential or very low metastatic potential.

Considerable effort has gone into constructing the elaborate scientific classifications of soft tissue tumors and the time and financial recourses are often spent in detecting differentiation that allows placement of hard to classify soft tissue tumors. However, pathologists also need to give full attention to the important task of determining the lesion’s biologic potential. In recent years it has become apparent that there are degrees of clinical malignancy and the simplistic and clinically unhelpful view that neoplasms can be sorted into benign and malignant is archaic. In response to this problem both the authors of the AFIP fascicle Tumors of the Soft Tissues and the authors of the recently published WHO Tumors of Soft Tissues have divided soft tissue neoplasms into several different managerial categories. WHO has four categories, benign, intermediate (locally aggressive), intermediate (rarely metastasizing), and malignant. Benign tumors are almost always cured by excision and while recurrences may rarely occur, they are not destructive. Benign tumors never metastasize. Locally aggressive neoplasms commonly recur and recurrences may be destructive. Rarely metastasizing neoplasms frequently recur but in addition to recurrence, which may be destructive, there is a low risk of metastasis, which has been defined as less than 2% by WHO. A category for tumors that may recur and recur destructively but do not metastasize unless they dedifferentiate is not included in the WHO categories and these are very important to recognize (e.g. atypical lipomatous tumor). Finally the label sarcoma is used for tumors that have a significant risk of metastasis, which in most cases is 10-100%. WHO suggests that tumors with a 2-10% metastasis may be classified as low grade sarcomas. We prefer that they be kept in the locally aggressive category and labeled as having a low risk of metastasis.
We think it important that pathologists be aware that the managerial categories have been expanded beyond benign and malignant and utilize this terminology. In particular clinicians should be made aware that the benign/malignant paradigm is no longer viable. Determining the direction of a neoplasm often provides the managerial classification. However when a tumor’s location in a scientific classification cannot be established with certainty, a distinctive managerial category may still be provided. In this circumstance careful evaluation of cellular features often but not always allows proper managerial classification into one of the categories above.

Gene expression is an emerging technology that holds promise as an adjunct for classifying soft tissue and other neoplasms that defy morphologic and immunologic classification. Technical advances that allow large numbers of DNA sequences to be attached to various substrates have led to the development of gene microarray analysis. This technology allows genome-wide screening of tens of thousands of genes in a single experiment. Experiments carried on in many institutions including our own have demonstrated that this technology can distinguish between tumors that are also distinguishable by histologic or immunohistochemical techniques. Whether, this currently very expensive technology will provide important therapeutic and prognostic information about tumors that are, by current techniques, undifferentiated remains to be seen.

While gene microarrays can classify lesions accurately that are morphologically distinct such as synovial sarcoma vs. pleomorphic MFH, it is important to recognize that it is not the purpose of gene arrays to classify lesions that can also be classified morphologically with or without the acid of immunohistochemistry. The fact that arrays can correctly distinguish among tumors is merely a verification that gene arrays work - i.e. they verify what is seen with the light microscope. In fact it is comforting that every new technology thus far developed validates the pre-existing histologic classification system. The potential of gene microarray analysis lies in the promise that this technology will identify important prognostic and therapeutic sub-groups of tumors not identified by morphology. Additionally, gene arrays may identify molecular pathways that can be targeted therapeutically. However, it will take time to determine the role of gene microarrays in practice. New tests will be developed based on gene array studies and then integrated with traditional microscopic evaluation. The combination of the two will undoubtedly provide additional information about prognosis and guide the treatment process in selected cases.

Clonal non-random chromosomal abnormalities are common in both benign and malignant soft tissue tumors, including tumors that occur predominantly in children. This is also true for many leukemias and some lymphomas but only a handful of carcinomas. However, currently this technology is expensive and time consuming so, with the possible exception of childhood tumors, it is used only when the morphologic diagnosis is uncertain.

Categorization and exploration of gene products proteomics for diagnosis and possibly therapeutic use is emerging as the next technologic advance that will probably have an impact on diagnostic pathology.
REFERENCES:
Fletcher CDM, Unni K, Mertens F. *Tumors of Soft Tissue and Bone* eds. WHO IARC Press, Lyon, France 2002.
CASE 11

Presented by Dr. Hendrickson

HISTORY:
A 62-year-old male sought medical care because of difficulty in swallowing and a choking sensation. CT scan revealed a 9.0 cm mediastinal mass; subsequently a FNA yielded spindled cells that were not diagnostic. Concomitantly the patient was found to have adenocarcinoma of the prostate. A prostatectomy was performed and following recovery from this procedure the mediastinal mass was resected. The sections are from the mediastinal mass.

HISTOLOGIC FINDINGS:
Low power: Uniform appearing paucicellular, collagenized proliferation
Medium power: Alternating layers of collagen and bland spindled cells
High power: Cytologically bland, uniform spindled cells; no mitotic figures.

IMMUNOHISTOCHEMISTRY:

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD45</td>
<td>+++</td>
</tr>
<tr>
<td>AE1/cam 5.2</td>
<td>-</td>
</tr>
<tr>
<td>Calretinin</td>
<td>-</td>
</tr>
<tr>
<td>Ck 5/6</td>
<td>-</td>
</tr>
<tr>
<td>S100</td>
<td>-</td>
</tr>
<tr>
<td>Desmin</td>
<td>-</td>
</tr>
<tr>
<td>Actin</td>
<td>-</td>
</tr>
</tbody>
</table>

DIAGNOSIS: MEDIASTINUM: Solitary Fibrous Tumor with nothing to suggest malignancy (see comment)
DIFFERENTIAL DIAGNOSIS:

<table>
<thead>
<tr>
<th>As a primary pleural monomorphic spindle-cell neoplasm</th>
<th>Comments relative to this case</th>
</tr>
</thead>
<tbody>
<tr>
<td>The fibrous series</td>
<td></td>
</tr>
<tr>
<td>Solitary fibrous tumor (SFT)</td>
<td>YES CD34 +ve</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>Not cellular enough</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>No pleomorphism, not cellular enough</td>
</tr>
<tr>
<td>Nerve sheath tumor</td>
<td>$100 -ve</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>Cells not right, CD34 +ve; no pleural synovial sarcomas</td>
</tr>
<tr>
<td>Benign fibrohistiocytic neoplasm</td>
<td>Monomorphic cell population rather than the mixed population usual in fibrohistiocytic neoplasms</td>
</tr>
<tr>
<td>Hemangiopericytoma</td>
<td>Nothing to suggest this; sometimes this is an issue since both SFT and HP can have stag-horn vessel pattern and are CD34 +ve</td>
</tr>
<tr>
<td>Smooth muscle neoplasms</td>
<td>Desmin, actin -ve</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>Keratin -ve</td>
</tr>
<tr>
<td><strong>Metastatic sarcoma</strong></td>
<td></td>
</tr>
<tr>
<td>Endometrial stromal sarcoma</td>
<td>Not cellular enough; wrong sex!</td>
</tr>
<tr>
<td>Other soft tissue sarcomas</td>
<td>No history of sarcoma, good to check though</td>
</tr>
<tr>
<td>Thymoma</td>
<td>Keratin negative</td>
</tr>
</tbody>
</table>

DISCUSSION:

Introduction

SFT is the most common mesenchymal neoplasm of the pleura. It used to be called localized fibrous mesothelioma but showed none of the ultrastructural or immunophenotypic features of mesothelial cells (Said, 1984). Accordingly, the name was changed to reflect these observations and a variety of alternatives have since been employed: submesothelial fibroma, localized fibrous tumor, or solitary fibrous tumor. The latter is the current designation for this neoplasm. These are tumors of adults and are typically asymptomatic. A minority of patients will present with symptoms related to pulmonary compromise. Unusually (but strikingly) some patients present with hypoglycemia. SFT is usually a grossly well-circumscribed mass and can attain a size of up to 20 cm. in maximum dimension. SFT is usually attached to the pleura by short pedicle; diffuse infiltration is one sign suggesting malignancy.

SFTs typically have a variegated histological appearance which leads to substantial differential diagnostic difficulties many of which have been resolved by immunohistochemistry.

Since the advent of CD34, the woodwork has emptied of closeted SFTs and now they have been reported in about every site in the body.
Histological Growth Patterns in Benign and Malignant Fibrous Tumors of the Pleura
(Moran et al, 1992)

<table>
<thead>
<tr>
<th>Solid spindle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short storiform (‘patternless’)</td>
</tr>
<tr>
<td>Angiofibroma- and Hemangiopericytoma-like</td>
</tr>
<tr>
<td>Fibrosarcoma-like (herringbone)</td>
</tr>
<tr>
<td>Monophasic Synovial sarcoma-like</td>
</tr>
<tr>
<td>Neural (wavy nuclei, palisading)</td>
</tr>
</tbody>
</table>

Diffuse sclerosing
Other less frequently observed features were the formation of "amianthoid" fibers, multinucleated giant cells, and foci of metaplastic ossification

Immunohistochemistry of SFTs
Immunohistochemistry has assumed a prominent role in the diagnosis of SFT. Keratin and EMA are always negative; actin, desmin and S-100 are negative. CD 34 is positive in 80% of cases and bcl-2 is positive in almost all cases. CD99 often positive. These two stains are not, by any means, specific but do serve, in concert with other tests, to narrow the possibilities.

Management issues:
The clinical behavior of thoracic SFTs?
SFTs usually have a benign clinical course but 5-10% are clinically malignant. Many of these can be picked out using the features in the table below.

In England and colleagues series (England, 1989), of the 169 tumors where follow-up was available, all of the morphologically benign and 45% of the morphologically malignant tumors were cured by simple excision. Patients surgically cured of a histologically malignant neoplasm had pedunculated or well-circumscribed lesions. However, 55% of patients with malignant tumors succumbed to their disease secondary to invasion, recurrence, or metastasis. They concluded that respectability was the single most important indicator of clinical outcome.

Features associated with malignancy in solitary fibrous tumors (England, 1989)

<table>
<thead>
<tr>
<th>Histologic features:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased cellularity</td>
</tr>
<tr>
<td>Pleomorphism</td>
</tr>
<tr>
<td>MI &gt; 4/10 hpf</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical/Gross features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pedunculated</td>
</tr>
<tr>
<td>Atypical location (parietal pleura, parenchyma)</td>
</tr>
<tr>
<td>Size &gt; 10 cm.</td>
</tr>
<tr>
<td>Necrosis &amp; hemorrhage</td>
</tr>
</tbody>
</table>

The clinical behavior of extra-pulmonary SFTs
The clinicopathologic story is much the same for extra-pulmonary SFTs. Vallat-Decouvelaere et al reviewed their experience with 92 cases of extrathoracic SFT and concluded that nuclear atypia, hypercellularity, greater than 4 mitoses/10 HPFs, and necrosis may be seen in up to 10% of extrathoracic SFTs, and are associated with aggressive clinical behavior.
REFERENCES:

General sources


Mediastinal SFTs


Differential diagnosis for pleural SFTs


CD 34, bcl-2 in solitary fibrous tumor and other neoplasms


Extra-pulmonary SFTs


**SFT morphologic variants**


CASE 12

Presented by Dr. Hendrickson

HISTORY:
This 55-year-old woman complained of abdominal fullness and post-prandial pain. CT revealed a 17 cm tumor in the stomach. A partial gastrectomy was performed and at gross examination the mass was found within the gastric muscularis.

HISTOLOGIC FINDINGS:
Low power: Highly cellular spindled proliferation interrupted by eosinophilic, acellular regions
Medium power: Acellular regions do not appear to be necrosis, rather, zones of fibrosis
High power: Syncytial-appearing eosinophilic cytoplasm; only rare mitotic figures

IMMUNOHISTOCHEMISTRY:

<table>
<thead>
<tr>
<th></th>
<th>Desmin</th>
<th>Actin</th>
<th>S100</th>
<th>CD 34</th>
<th>CD 117</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT (CD117)</td>
<td>+</td>
<td></td>
<td></td>
<td>++++</td>
<td>++++</td>
</tr>
</tbody>
</table>

DIAGNOSIS: STOMACH: Gastrointestinal Stromal Tumor (GIST), high risk in virtue of size (> 10 cm)

DIFFERENTIAL DIAGNOSIS:
The differential diagnosis of monomorphous spindle-cell neoplasms involving the muscularis propria of the stomach include GIST, a smooth muscle neoplasm, schwannoma and fibromatosis. Additionally, some thought should be given to metastatic spindle-cell melanoma. The location of the tumor (gastric wall rather than mesentery) and its high cellularity eliminate fibromatosis. The pattern doesn’t particularly suggest a nerve sheath tumor but would still be in the differential. The IPOX profile establishes the diagnosis of GIST (see table below). Having established the phenotype, we are left with the problem of assessing the clinical risk level posed by this tumor. Applying the Consensus criteria, this would be regarded as a high risk lesion in virtue of its size. The mitotic index is <5/50 hpf although the size of 17.0 cm makes mitotic index irrelevant.

<table>
<thead>
<tr>
<th></th>
<th>KIT (CD117)</th>
<th>CD34</th>
<th>SMA</th>
<th>Desmin</th>
<th>S-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIST</td>
<td>+</td>
<td>+ (60% to 70%)</td>
<td>+ (30% to 40%)</td>
<td>Very rare</td>
<td>5%+</td>
</tr>
<tr>
<td>Smooth muscle tumor</td>
<td>-</td>
<td>+ (10% to 15%)</td>
<td>+</td>
<td>-</td>
<td>Rare</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>+ (usually Antoni B)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fibromatosis</td>
<td>Disputed*</td>
<td>Rare</td>
<td>+</td>
<td>Rare cells</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviation: SMA, smooth muscle actin.
*Most, but not all authors report that fibromatoses are negative for KIT.
DISCUSSION:
Introduction
Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract. There is a huge literature about these neoplasms which is summarized, among other places, in the AFIP Fascicle on Gastric and esophageal neoplasms. These neoplasms have long been a source of confusion and controversy with regard to classification, line(s) of differentiation, and prognostication. The field has been transformed recently by the serendipitous discovery that, like the gastrointestinal pacemaker cells, the cells of Cajal, most of these problematic neoplasms are c-kit positive. This, of course, is of more than academic interest since there is a targeted therapy for neoplasms that have this abnormality. Since this observation, things have been moving swiftly both in establishing clinical trials to assess the efficacy of Gleevec for c-kit positive tumors and in bringing taxonomic order to this group of neoplasms.

The National Institutes of Health convened a GIST workshop in April 2001 with the goal of developing a consensus approach to diagnosis and morphologic prognostication. The Consensus group moved in the direction of essentially defining GISTs as those gastrointestinal neoplasms that are CD117 positive. They allowed for only a few exceptions which are detailed in their report. The second move they made was to swap out the traditional categories of ‘benign’ and ‘malignant’ for 4 levels of clinical risk. This has occasioned some controversy (Trupiano et al, 2002).

This case and the changing taxonomy of GISTs raises some interesting issues in classification.

Classification issues:

Molecular cancer types. Defining cancer kinds by a shared molecular abnormality; the wave of the future?
GIST tumors would seem to have the essential feature of having an activating KIT mutation. The net result is a ligand-independent activation of the KIT receptor tyrosine kinase and an unopposed stimulus for cell growth. STI-571 is a small molecule that selectively inhibits the enzymatic activity of the ABL, platelet-derived growth factor receptor, and KIT tyrosine kinases and the BCR-ABL fusion protein. In keeping with this observation, these tumors are particularly responsive to STI-571 (Gleevec). This exposure of the molecular mechanism responsible for GISTs is seen as analogous to the earlier discovery of the HbS mutation responsible for sickle cell anemia (Pauling’s celebrated ‘molecular disease’) and a paradigm-making breakthrough in cancer typing and therapy. It is taken to be proof of the principle that a specific molecular inhibitor can drastically and selectively alter the survival of a neoplastic cell with a particular genetic aberration.

Complications: Two types of KIT mutations: A more complicated story is told by Longley and colleagues (Longley et al, 2001) who divide c-kit activating mutation into two types - 'regulatory type' mutations, which affect regulation of the kinase molecule, and 'enzymatic pocket type' mutations, which alter the amino acid sequence directly forming the enzymatic site. They go onto to point out that KIT inhibitors have been suggested as therapeutic drugs for these conditions, but different types of activating mutations respond differentially to KIT inhibitors. They conclude that the classification of individuals on the basis of specific mutations is necessary to guide therapy.
Complications: More than one molecular way to get on the GIST boat: PDGFRA troubles: Heinrich and colleagues (Heinrich et al, 2003) report that in the approximately 35% (14 of 40) of GISTs lacking KIT mutations there are intragenic activation mutations in the related receptor tyrosine kinase, platelet-derived growth factor receptor alpha (PDGFRA). They found that tumors expressing KIT or PDGFRA oncoproteins were indistinguishable with respect to activation of downstream signaling intermediates and cytogenetic changes associated with tumor progression. Thus, KIT and PDGFRA mutations appear to be alternative and mutually exclusive oncogenic mechanisms in GISTs.

The emerging character of managerial categories

Beyond benign and malignant: Numbered clinical diseases.

The Consensus Group has moved away from the ancient dichotomy: 'benign / malignant' and this is to be applauded. It is in the spirit of recent sea changes in managerial classifications in the world of gynecologic pathology (Borderline, LMP etc.) and in the world of soft tissue tumors (Kempson et al, 2001).

TABLE 2. Proposed Approach for Defining Risk of Aggressive Behavior in GISTs

<table>
<thead>
<tr>
<th></th>
<th>Size*</th>
<th>Mitotic Count†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt;2 cm</td>
<td>&lt;5/50 HPF</td>
</tr>
<tr>
<td>Low risk</td>
<td>2-5 cm</td>
<td>&lt;5/50 HPF</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>&lt;5 cm</td>
<td>6-10/50 HPF</td>
</tr>
<tr>
<td></td>
<td>5-10 cm</td>
<td>&lt;5/50 HPF</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;5 cm</td>
<td>&gt;5/50 HPF</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm</td>
<td>Any mitotic rate</td>
</tr>
<tr>
<td></td>
<td>Any size</td>
<td>&gt;10/50 HPF</td>
</tr>
</tbody>
</table>

Abbreviation: HPF, high-power field.

*Size represents the single largest dimension. Admittedly this may vary somewhat between prefixation and postfixation and between observers. There is a general but poorly defined sense that perhaps the size threshold for aggressive behavior should be 1 to 2 cm less in the small bowel than elsewhere.

†Ideally, mitotic count should be standardized according to surface area examined (based on size of high-power fields), but there are no agreed-on definitions in this regard. Despite inevitable subjectivity in recognition of mitoses and variability in the area of high power fields, such mitotic counts still prove useful.
Managerial categories as lotteries: Risk groups are best thought of as lotteries. Given that your tumor satisfies the criteria for the ‘high risk’ category, you are in a clinical outcome lottery where the tickets drawn are labeled ‘relapse’ or ‘no relapse.’ There are, say 80 tickets marked ‘relapse’ and 20 marked ‘no relapse.’ Trivially, just as in the case of a fair coin toss, there is no dogmatic statement that can be made about the result of the next coin toss. But, the knowledge of the fairness of the coin allows you to make certain individual decisions. For example, agreeing to submit to the result in choosing who goes first in a game.

“All GISTS are STUMPs”. As near as I can tell, the obsessing over the use of ‘benign’ in the context of GISTS is about never being able to guarantee a probability of zero for an unfavorable outcome. But, managerial categories are designed for real world decision-making and in the real world there are very few things that are guaranteed with a probability of one. The issue is whether the probability is so close to one as to make no difference in one’s decision making. Driving the highways to work is not ‘benign’ in the sense that I’m guaranteed that I will not be a roadkill, but I still dutifully launch myself on the freeway each day.

REFERENCES:
General

Definition of GISTS

Trupiano JK, Stewart RE, Misick C, Appelman HD, Goldblum JR. Gastric stromal tumors: a clinicopathologic study of 77 cases with correlation of features with nonaggressive and aggressive clinical behaviors. *Am J Surg Pathol* 2002;26:705-14. This is an alternative view to the Consensus risk categories.

The clinicopathology of GISTS


The molecular pathology of c-kit


Recent studies of c-kit negative tumors


Most gastrointestinal stromal tumors (GISTs) have activating mutations in the KIT receptor tyrosine kinase, and most patients with GISTs respond well to Gleevec, which inhibits KIT kinase activity. Here we show that approximately 35% (14 of 40) of GISTs lacking KIT mutations have intragenic activation mutations in the related receptor tyrosine kinase, platelet-derived growth factor receptor alpha (PDGFRA). Tumors expressing KIT or PDGFRA oncogenes were indistinguishable with respect to activation of downstream signaling intermediates and cytogenetic changes associated with tumor progression. Thus, KIT and PDGFRA mutations appear to be alternative and mutually exclusive oncogenic mechanisms in GISTs.

Managerial classifications


CASE 13

Presented by Dr. Kempson

HISTORY (CTTR 25060): This 36 year old woman discovered a mass in her breast. This was excised.

HISTOLOGIC FINDINGS: Almost every acinus and almost all the lobular units in this biopsy are filled with cells with round uniform nuclei, which feature fine chromatin. The cytoplasm of the cells is lightly eosinophilic or vacuolated. Focally the cells become discohesive, but in most areas cell membranes can be identified. Mitotic figures are not identified. Most of the acini are filled, but focally they become expanded and in a rare lobular unit over half of the acini are expanded. The neoplastic cells are also proliferating in ducts producing a pagetoid pattern.

IMMUNOHISTOCHEMICAL FINDINGS: An E-cadherin stain was negative.

DIFFERENTIAL DIAGNOSIS: The differential diagnosis in this case is atypical lobular hyperplasia vs. lobular carcinoma in situ and a lobular lesion vs. a ductal proliferation.

DIAGNOSIS: Lobular carcinoma in situ (the lobular carcinoma in situ is very focal, the vast majority of lobular units are involved by atypical lobular hyperplasia).

DISCUSSION: Lobular lesions of the breast are recognized both by their cytologic features and the architectural arrangement of the constituent cells. Important clinical decisions hinge on whether in situ carcinomas are lobular or ductal because patients with untreated ductal carcinoma in situ have a risk of developing a subsequent invasive carcinoma mainly in the ipsilateral breast in the area of the in situ carcinoma whereas patients with lobular carcinoma in situ have an increased risk of developing invasive carcinoma in all areas of both breasts and the level of risk is nearly the same for both breasts. Patients with DCIS are usually treated by complete excision and sometimes radiation whereas most patients with LCIS are followed with regularly performed imaging studies. Thus it is critical to distinguish in situ lobular from in situ ductal lesions. This means that all pathologists must be using the same morphologic definitions of DCIS and LCIS in order for patients to receive appropriate therapy.

The distinction between infiltrating lobular carcinoma and infiltrating ductal carcinoma is less critical as is discussed in the section on infiltrating ductal carcinoma.

Morphologic Definitions
Atypical Lobular Hyperplasia and Lobular Carcinoma In Situ

Because the constituent cells of ALH and classic LCIS are not high grade both cytologic and architectural features are used to define these lesions. ALH is defined as having some but not all of the features of LCIS and hence its definition is based on the features of LCIS.
Lobular Carcinoma In Situ

Cytologically LCIS is composed of one of two types of cells. Classic or type A LCIS features cells with small, uniform, round to oval nuclei that have fine chromatin, smooth nuclear outlines, and inconspicuous to absent nucleoli. The cytoplasm is scant and often lightly eosinophilic, although many cells have clear or vacuolated cytoplasm and signet ring cells are not uncommon. Cellular discohesion is usually present; this is one of the hallmarks of lobular carcinoma in situ. Mitotic figures are difficult to find. Pleomorphic or type B LCIS is composed of cells that have more abundant cytoplasm, larger nuclei with more coarse chromatin and often prominent nucleoli. Nuclear membranes may be irregular and there is mild to moderate pleomorphism. However, the cytoplasm is still lightly eosinophilic to clear and discohesion is usually prominent. In pleomorphic LCIS mitotic figures are not uncommon. Of course these two types of cells exist in a continuum so the constituent cells of some examples of LCIS will have features intermediate between Type A and Type B cells.

Architecturally LCIS, whether composed of classic or pleomorphic cells, involves the acini of the lobular units. To qualify as LCIS all the acini in a lobular unit must be completely filled with the required cells and half of the acini must be expanded enough by the proliferating cells to be easily noticed as balloon-like and enlarged at low magnification. Lobular cells may form tiny acini, but cribriform spaces and micropapillary growth are not allowed. Rarely central necrosis is present in classic LCIS, most often in extensive lesions, but is more commonly present in pleomorphic LCIS.

LCIS cells may involve ducts either by growing under pre-existing ductal epithelium (Pagetoid growth) or, less commonly, by completely replacing the ductal cells. Pagetoid growth is unusual in DCIS so it serves as a useful marker of LCIS. Most frequently the lobules also contain LCIS when the ducts are involved but occasionally only ductal lesions will be present, particularly in core needle biopsies. LCIS may also involve sclerosing adenosis.

The cells in classic LCIS are almost always ER receptor positive and practically never express Her2/neu or p53. Pleomorphic lobular cells more frequently express Her2/neu and p53. Lobular cells typically lose expression of E-cadherin, an adhesion molecule, and this is probably the molecular basis for the discohesion seen histologically. Antibodies against E-cadherin are available and have some diagnostic use (see below).

Atypical Lobular Hyperplasia

Atypical lobular hyperplasia is composed of the same two cell types as LCIS although lesions composed of classic or Type A cells are more common. Distinction from LCIS depends on the extent of the proliferation of neoplastic cells. In ALH only some of the acini in a lobular unit may be filled with the required cells and, even if all of the acini are filled, less than 50% are expanded.
Summary

The morphologic features we find most useful in recognizing classic lobular proliferations are:

1. The population of small uniform cells with lightly eosinophilic to vacuolated cytoplasm.
2. Cellular discohesions.
3. Lobular growth pattern and Pagetoid spread within ducts.

In pleomorphic lobular proliferations the nuclei are larger, have more chromatin, may have prominent nucleoli and are often pleomorphic. However, they still have lightly eosinophilic to vacuolated cytoplasm and are discohesive. Pagetoid growth may be present.

DIFFERENTIAL DIAGNOSIS:

I. Normal acini vs. ALH. There is No Category of Lobular Hyperplasia.

There is no generally agreed upon category of lobular hyperplasia. The nomenclature for lobular lesions allows only ALH and LCIS, not lobular hyperplasia because lobular hyperplasia has not been defined as a clinically useful category. Thus the differential diagnostic problem is distinguishing between normal acini, which may contain a few lobular type cells and atypical lobular hyperplasia. Unfortunately, a crisp definition of this threshold is lacking in the literature. We follow the guidelines suggested by Page and associates and insist that the least developed examples of ALH must have at least one acinus filled by the characteristic lobular cells or that the characteristic lobular cells be present beneath normal acinar cells in several acini of a lobule. Most examples of ALH are fully developed and have many acini filled or partially filled by lobular cells. When we are faced with a borderline lesion that may or may not be ALH we do not diagnose ALH because the available evidence about risk is based on fully developed lesions of ALH.

II. Atypical Lobular Hyperplasia vs. Lobular Carcinoma In Situ

The morphologic features that allow this distinction to be made have been presented above. There is little of therapeutic importance at stake in this decision because almost all patients with either ALH or LCIS are managed by followup imaging studies. Exceptions to this are women who have LCIS and a family history of breast carcinoma in primary relatives. These individuals may opt for bilateral mastectomies. Also NASBP data suggests that large foci of LCIS with massively distended acini in almost every lobular unit have a significant enough risk for invasive carcinoma in the same area that such lesions should be treated as DCIS, i.e. by complete excision. Such lesions are very rare and probably warrant consultation.

III. LCIS vs. DCIS

This is one of the most important distinctions in breast pathology because the usual patient with LCIS is followed while patients with DCIS are treated by complete excision with tumor free margins and, in the case of high grade DCIS, with radiation and sometimes lymph node sampling or mastectomy if the lesion is large. The diagnostic problem arises mainly in distinguishing low grade DCIS from LCIS but occasionally pleomorphic LCIS can mimic intermediate or high
grade DCIS. Several differential diagnostic problems occur: (1) LCIS vs. cancerization of the lobules by DCIS; (2) LCIS vs. the solid type of DCIS; (3) LCIS with necrosis and microacini vs. DCIS; (4) Pleomorphic LCIS vs. DCIS.

The feature we find most helpful in recognizing cancerization of the lobules by DCIS include cellular cohesion, irregular and partial involvement of acini within the lobular units instead of the more uniform involvement of acini typical of LCIS, and residual lumens in involved acini. Cribriform and micropapillary architecture are not allowed in LCIS. Grade III nuclei have been reported in pleomorphic LCIS but this is very rare and pleomorphic LCIS is rarely more than Grade II. Therefore, a lesion composed of cells with grade III nuclei is most likely to be DCIS. More recently E-cadherin has been brought to bear on this problem. There is no doubt the constituent cells of lesions pathologists interpret as classic examples of LCIS lack E-cadherin staining as do the cells in pleomorphic LCIS and LCIS with comedo necrosis while those lesions considered to be classic DCIS are composed of cells that demonstrate positive membrane staining with this antibody. However, in the literature histologically indeterminate cases characterized by discohesive cells with microacini or cohesive cells with cytoplasmic vacuoles showed lack of E-cadherin staining in about 20%, positive staining in another 20%, while the rest contain both E-cadherin positive and E-cadherin negative cells.

While it is not clear is the significance of the E-cadherin staining pattern in a lesion that is indeterminate by H&E morphology. We think that if there is any possibility that the lesions may be ductal the patient should be managed as having a ductal carcinoma in situ and a positive E-cadherin stain may be supportive. Even if the E-cadherin is negative and the lesion has ductal features morphologically we suggest managing the patient as if she has DCIS. The significance of lobular and ductal lesions that contain both E-cadherin positive and E-cadherin negative cells is unknown. In general we think patients with such lesions also should be managed as if they have DCIS.

These same considerations apply to distinguishing solid DCIS, an unusual lesion from LCIS. The problem arises because solid DCIS can present as spherical masses of cells that mimic the acinar pattern seen in LCIS. Distinguishing pleomorphic LCIS from DCIS can be problematic because there is no agreement about the definitions of pleomorphic LCIS. There is no doubt that lobular lesions can be composed of cells with nuclei that demonstrate greater than grade I atypia because they meet the definition of lobular neoplasia on grounds of discohesion, lobular architecture and Pagetoid growth. They are also almost always E-cadherin negative. However, lesions with grade III nuclear features can mimic the lobular pattern of growth of lobular carcinoma in situ. The clinical significance of such lesions is unknown but we think it prudent to manage the patients as if they had DCIS. Fortunately grade III lobular lesions without an infiltrating component are very rare. In summary we recognize two types of nuclei in LCIS and ALH: Type A or classic and Type B or pleomorphic. The latter should have no greater than grade II nuclei. However, in the literature in situ lesions with grade III nuclei and the architectural pattern of lobular carcinoma in situ, have been classified by some investigators as pleomorphic lobular. These probably warrant consultation.
LCIS and ALH in Core Needle Biopsies

Atypical ductal hyperplasia in a core needle biopsy is generally regarded as an indication for an excisional biopsy because many investigators report a significant incidence of DCIS and invasive carcinoma in the subsequent excision. Whether this applies to LCIS and ALH is uncertain because of contradictory reports about the incidence of lesions that require further therapy and the number of patients is small. Until more information is available we think it prudent to have the patient who has LCIS or ALH in her core needle biopsy undergo excision if (1) there is discordance between mammographic and pathologic findings suggesting the targeted lesion is not in the core (2) if another lesion that is an indication for excision e.g. ADH is also present (3) if it is difficult to be sure whether the lesion is ALH/LCIS or DCIS. Even if the e-cadherin is negative but the histologic features are ambiguous we think an excision should be performed and (4) the ALH/LCIS is extensive.

Infiltrating Lobular Carcinoma

Classic infiltrating lobular carcinoma is composed of the same small discohesive cells with uniform nuclei and lightly eosinophilic cytoplasm that comprise classic LCIS. These are most often arranged in the well known linear cords usually no more than 2 cells thick although some tumors feature a sheet-like pattern or rounded aggregates of tumor cells. Rarely the bland tumor cells form tubules in which case the tumor is classified as tubulo-lobular. Infiltrating tumors composed of cells with larger more pleomorphic nuclei that infiltrate in this classic linear pattern are considered to be examples of pleomorphic lobular carcinoma. Most reports indicate the cells of such tumors are e-cadherin negative. However, tumors composed of discohesive pleomorphic cells grouped in aggregates or arranged in sheets are more problematic because the dividing line between pleomorphic lobular carcinoma and infiltrating ductal carcinoma has not been sharply defined except that duct formation is allowed only in ductal carcinoma. This said, infiltrating pleomorphic carcinomas with features of both ductal and lobular carcinoma are not uncommon.

Does it make any difference whether an infiltrating carcinoma is lobular or ductal? Probably not because the literature suggests that the essential information needed to treat patients can be captured by size, grade, and stage. Classic infiltrating lobular carcinoma is a grade I neoplasm (tubules =3, mitotic figures=1, nuclei=1) and the outcome of patients with classic infiltrating lobular carcinoma stage for stage is similar to patients with grade I ductal carcinoma. Pleomorphic lobular carcinomas are at least grade II. A few reports available indicate that patients with pleomorphic infiltrating lobular carcinoma have a similar outcome as patients with infiltrating ductal carcinoma of the same stage and grade. Unlike the cells of classic LCIS, the cells of pleomorphic infiltrating lobular carcinoma frequently express Her2/neu and p53.

We classify infiltrating lobular carcinoma by type (classic, pleomorphic, and mixed ductal-lobular) and also grade the tumors. If it is unclear whether the infiltrating carcinoma is lobular or ductal we so state and provide the grade.
REFERENCES:
CASE 14

Presented by Dr. Kempson

HISTORY (CTTR 29865): A mammogram performed on this 44 year-old woman revealed calcifications suspicious for carcinoma. A biopsy was performed.

HISTOLOGIC FINDINGS: Low power magnification reveals a lesion which has a stellate architecture in which ducts demonstrating sclerosing adenosis and marked expansion by proliferating cells seem to explode out from a center. The stroma is collagenous. Within the expanded ducts, the cells vary from those with elongate streaming nuclei to those with round regular enlarged nuclei which form cribriform spaces. Some ducts show partial involvement by cells with elongate streaming nuclei and cells with round regular enlarged nuclei. Mitotic figures can be found in the latter areas. In some areas, irregular cords and columns of cells are embedded in the fibrous stroma which focally becomes edematous and inflamed. Intraductal tumor cell necrosis is identified but is focal. A papilloma is noted in a cystically dilated space.

IMMUNOHISTOCHEMISTRY: An E-cadherin stain demonstrated strong diffuse membrane staining of the proliferating intraductal cells. Calponin and p63 stains identify the myoepithelial cells around the nests of tumor cells.

DIFFERENTIAL DIAGNOSIS: The main differential diagnostic considerations in this case are florid hyperplasia vs. atypical ductal hyperplasia vs. ductal carcinoma in situ vs. invasive carcinoma. The proliferation is ductal and not lobular and is within a radial scar. Many of the ducts are filled with cells with enlarged, rounded nuclei and in some of these the cells are growing in a cribriform pattern. Small amounts of necrosis are present in some of the spaces. The changes are those of ductal carcinoma in situ although ADH is present in other ducts. Florid hyperplasia is present in some ducts. The areas of questionable invasion have the histologic features of cancerization of ducts by in situ carcinoma cells and definite invasion is not identified. This is supported by calponin and P63 stains which identify myoepithelial cells around the ducts (see also ADH section below).

DIAGNOSIS: Intermediate grade ductal carcinoma in situ within a radial scar.

DISCUSSION:

Ductal Carcinoma In Situ (Intraductal Carcinoma)

Ductal carcinoma in situ (DCIS) does not represent a single, uniform morphologic entity but rather a group of lesions that can be divided into (1) usual types of low grade, intermediate grade, high grade (comedo), and (2) special types. In recent years it has become apparent that applying a grade to the usual types of DCIS has distinct advantages over classifying them into architectural types such as cribriform, micropapillary, solid comedo, etc. The features most commonly used to define the grade of the usual DCIS are nuclear size and shape, type of chromatin, prominence of nucleoli, and, the presence or absence of necrosis. There is no
generally accepted grading scheme for DCIS, but the one most commonly used in the United States is a modification of the grading criteria originally proposed by Lagios. This scheme is as follows:

**Low grade DCIS** = Nuclei 2x the size of a RBC (10-12μ), oval to round regular with evenly dispersed chromatin. Nucleoli, if present, are small and indistinct. Necrosis is almost always absent and, if present, is focal.

**Intermediate grade DCIS** = Nuclei 2-3x the size of a RBC (12-15μ), mildly irregular, and minimally pleomorphic. Nucleoli are visible, but usually not enlarged. Necrosis is variable but is required in the Van Nuys grading scheme as noted immediately below.

**High grade DCIS** = Nuclei > 3x the size of a RBC (>15μ), with irregular shapes often pleomorphic with clumped chromatin and almost always prominent enlarged nucleoli. Luminal necrosis is almost universal.

Silverstein, Lagios and associates have presented grading criteria that take into account the presence or absence of necrosis. (Van Nuys grading scheme). The nuclear grading criteria are the same as for the Lagios modification above.

**High grade** (score III) = any DCIS with grade III nuclei with or without necrosis.

**Intermediate grade** (score II) = DCIS with grade I or II nuclei with substantial tumor cell (comedo) necrosis.

**Low grade** (score 1) DCIS with grade I or II nuclei without substantial tumor cell (comedo) necrosis.

Many studies indicate that high grade lesions, whatever the grading scheme, have a significantly higher risk of a subsequent adverse event (recurrent DCIS or invasive carcinoma, occult invasion, and occult lymph node metastases) than low grade lesions so all DCIS should be graded. We use the Van Nuys system.

In addition to these more common or usual types of DCIS there are less frequent types that are usually referred to as special types of DCIS. These are (1) pure micropapillary, (2) apocrine, (3) mucinous, (4) endocrine, (5) associated with mucocele-like lesion, (6) cystic hypersecretory, and (7) papillary. The significance of some of these special types of DCIS is known but for others it is not fully understood. In spite of that, the presence of special types should be recorded in the surgical pathology report. It is very common for low grade cribriform DCIS to be mixed with low grade micropapillary DCIS and the significance is the same as for low grade cribriform DCIS. However, pure micropapillary is commonly multifocal or even multicentric so it should be distinguished from the mixed type.
Low Grade Ductal Carcinoma In Situ
(Cribiform, Micropapillary, Solid Acinar Architectural Patterns)

Because the constituent cells of low grade DCIS are not cytologically malignant, it is required that both the architectural and cytologic features described in the next paragraph be present before making a diagnosis of this type of intraductal carcinoma.

Low grade (cribiform/micropapillary) DCIS is histologically defined as dilated ducts filled, with or lined by, a stratified population of monotonous cells, all with the same appearance, arranged around cleanly punched out spaces or arranged in small finger-like or club shaped protuberances with bulbous ends which extend into the dilated lumen. The spaces have also been described as supported by rigid bars of cells giving rise to a "crisp" punched out appearance. The cells all must have identical round regular nuclei that are approximately 2 times the size of a RBC. Chromatin, which may be dense and smudged or vesicular, is fine and evenly distributed. Nucleoli are inconspicuous and small or not visible. Necrosis is usually absent (is absent by definition if one uses the Van Nuys grading scheme) and if present is focal and small in amount. Mitotic figures are usually sparse to absent and abnormal forms are rare. Cytoplasm may be sparse and difficult to see but it is usually more abundant. The constituent cells of low grade DCIS are in sharp contrast to the elongate randomly arranged, often steaming cells, with evenly distributed chromatin found in hyperplasia and the larger cytologically malignant cells that characterize high grade DCIS.

Solid low grade DCIS is entirely composed of cells with the same nuclear features as those in cribiform/micropapillary DCIS but these cells fill in small round ducts in a pattern that mimics LCIS. Solid low grade DCIS is most often found in association with the cribiform/micropapillary type.

The minimal criteria for the diagnosis of low grade DCIS are: at least two dilated duct spaces (Page et al) filled by a uniform population of the cell types described above arranged in the required architectural patterns and the lesion is greater than 2-3mm (Tavassoli and Norris). Ducts in which only some of the cells meet the requirement for low grade DCIS represent atypical ductal hyperplasia. Lesions, which have the cytologic features of cribiform DCIS but not the architectural features, required for the diagnosis are also placed in the category of atypical ductal hyperplasia. We think the quantity requirements of Page et al and Tavassoli and Norris are very important and should be observed because according to their data only those lesions that fulfill the quantity requirements have the risk associated with low-grade ductal carcinoma in situ. Cribiform, solid and micropapillary lesions which otherwise morphologically qualify for low grade in situ carcinoma but are less than 2 mm in aggregate dimension are classified as atypical ductal hyperplasia.

High Grade Ductal Carcinoma In Situ (Comedo DCIS)

The definition of high grade DCIS has changed. Formerly, necrosis was the defining feature; now it is defined by high grade nuclear features. High Grade DCIS features dilated ducts lined by large cells with nuclei >3x the size of a RBC (>15μ). Nuclear chromatin is coarse and
irregular and the nuclei are irregular and pleomorphic. Nucleoli are prominent and often strikingly enlarged. Mitotic figures, including abnormal forms, are typically numerous. Central luminal tumor cell necrosis is practically always present. The constituent cells may be in any architectural arrangement. In other words, unlike low-grade DCIS, there is no architectural requirement for high grade DCIS.

Because the constituent cells of high grade DCIS are cytologically malignant and because necrosis is almost always extensive, there is seldom difficulty in diagnosing this type of intraductal carcinoma. The most frequent of diagnostic problem is determining whether early stromal invasion is present or not. This problem arises because high grade DCIS often extends as an in situ process into ramifying small ducts and lobular acini (cancerization of the lobules) and this growth pattern may be associated with a granulation tissue reaction of the type often seen in invasive carcinoma. We insist on finding jagged infiltration of cords and ducts formed by carcinoma cells extending beyond the lobules before interpreting suspicious areas as definite evidence of stromal invasion. Sometimes one cannot be certain whether invasion is present or not; in such cases, we think this uncertainty should be expressed in the surgical pathology report using such terms as "suspicious for invasion" or "early microinvasion cannot be excluded" and providing the maximum size of the possibly invasive foci. If myoepithelial cells are present around the focus in question it is not invasive and these can be detected by a panel of calponin and p63 stains. On the other hand, a duct involved by DCIS may lose its myoepithelial cells so negative stains should be interpreted cautiously.

Investigators have reported on various biologic and clinical characteristics of high grade DCIS that contrast to other DCIS types. High grade DCIS has been found most often to be composed of cells with an aneuploid DNA content, a not unexpected finding given the cytologic appearance of the cells, which constitute the lesion. The high grade lesion has a proliferation rate which is significantly higher than other types of in situ carcinoma and which in fact is similar to that observed in intermediate and high grade invasive carcinoma. The cells in high grade DCIS usually express the Neu oncogene, a feature that has been associated with aggressive breast carcinomas. High grade DCIS is by far the one most frequently associated with foci of microinvasion in which jagged nests of malignant epithelial cells extend from the duct or ductule into the surrounding stroma. High grade DCIS is associated with a higher rate of recurrence after local excision in many series and is the type of in situ carcinoma most often associated with lymph node metastasis. The latter is most often associated with high grade DCIS that is over 2 cm.

Intermediate Grade Ductal Carcinoma In Situ

Intermediate grade DCIS is defined above. Whether this lesion reflects greater risk of recurrence than low grade is uncertain.

Mixtures

It is not uncommon for cribriform, micropapillary and solid patterns of intraductal carcinoma to be mixed in the same lesion. It is also not uncommon for atypical ductal hyperplasia to be intermixed with low grade intraductal carcinoma. Page and associates found that when ADH
and low grade DCIS were mixed in the same lesion, the in situ carcinoma tended to be in the center and ducts containing ADH at the periphery. They concluded that these observations support the hypothesis that DCIS begins in a central focus and spreads peripherally. Much less commonly, low grade and high grade in situ carcinomas may be mixed together. The area of highest grade is used for the ultimate grade.

**Atypical Ductal Hyperplasia**

Atypical ductal hyperplasia (ADH) is distinguished from florid epithelial hyperplasia by the presence of cells that have the features of the cells that constitute low grade ductal carcinoma in situ. Classically a duct space is partially involved with cells of low grade DCIS arranged in the required pattern while the rest of the duct space is lined by normal ductal cells or hyperplastic ductal cells. In addition ADH is also diagnosed when the cytologic changes of low grade cribriform/ micropapillary DCIS are present in ducts but the required architectural features of DCIS are absent or incomplete. The cells in atypical hyperplasia are never as severely atypical as the carcinomatous changes seen in the cells that constitute high grade DCIS. In other words it is low grade DCIS that is the differential diagnostic partner of atypical ductal hyperplasia. The diagnosis of atypical ductal hyperplasia rather than DCIS is also made when there is involvement of less than 2 duct spaces by the characteristic cytologic and architectural changes of low grade DCIS or all the features of low grade cribriform/micropapillary/solid DCIS are present in ducts but the involved ducts measure less than 2 mm in aggregate dimension. ADH reflects an approximately 5 times increased relative risk of developing invasive carcinoma and Page and associates report that the risk is the same for both breasts.

**REFERENCES:**


Clinical Implications of DCIS, Special Types of DCIS

Intraductal Papillary Carcinoma

Clinical Implications of Low Grade DCIS

While it has not been possible to study the "true" natural history of low grade DCIS (since the procedure required for diagnosis can alter the natural history of the disease), there are published studies with long-term outcome data that have examined the clinical implications of low grade DCIS found in breast biopsies after which there is no further therapy. The most widely known study, and the one from which currently used risk statistics have been derived, is that of Page et al who reviewed 11,760 "benign" breast biopsies and identified 28 cases which fulfill the current criteria for low grade cribriform/micropapillary DCIS. The lesions were small but the report does not indicate the status of the biopsy margins. Follow-up data (average 15 years) was available on 25 women of which seven (28%) developed subsequent invasive carcinomas between three and ten years after biopsy. All invasive carcinomas occurred in the same quadrant of the same breast as the initial biopsy. These results indicate that a woman with low grade DCIS treated only by biopsy has a 25% chance of developing invasive carcinoma over the following 15 years or, looked at another way, she has a relative risk of 11, i.e. such a woman is 11 times more likely to develop invasive carcinoma than age-matched controls. This relative risk is not per year; it is the risk over the entire follow up period and that was 15 years in the study by Page et al. The other side of the "coin" should also be considered: 75% of women with low grade DCIS treated by biopsy alone do not develop invasive carcinoma. In 1995, Page and associates reported the outcome of these same 28 women with almost 30 years of follow-up. Two additional women have developed invasive carcinoma between 20 and 30 years and another developed extensive low grade DCIS at 25 years. The relative risk for invasive carcinoma at 30 years is 9 times that of the general population which is similar to the 11 times risk at 15 years of follow-up.

Clinical Implications of High Grade DCIS

An early study that examined the clinical significance of high grade DCIS in patients treated by excision only was that of Lewis and Geschickter in 1938. In their study of 47 patients, there...
were eight patients who were initially treated by local excision alone. Six of the eight patients developed local recurrence, five within eighteen months and the other after four years. In three of the patients, axillary metastases were found at the second operation. It should be noted that the patients in this study clinically presented with a palpable breast mass and most had, by today's standards, relatively extensive disease (the size of the eight lesions were as follows: 0.5 cm, 1 cm, 2 cm, 3 cm, 6 cm, 9 cm, "grapefruit"). Although this data may not be applicable to mammographically detected lesions, it is generally accepted that high grade DCIS results in a relative risk for developing invasive carcinoma greater than the risk which results from the low grade DCIS lesions and this risk increases with increasing size of the lesion. Also the risk of occult invasion and lymph node metastases is significantly higher for high grade DCIS and the larger the high grade DCIS the higher the risk for occult invasion and lymph node metastases.

**Significance of Size, Margins, and Grade of DCIS**

In addressing the question of occult invasion, multicentricity and occult lymph node metastases, Lagios examined mastectomy specimens using a serial subgross method following an initial biopsy diagnosis of DCIS. He found that the incidence of multicentricity was rare and that occult invasion was absent in women whose initial biopsy showed the DCIS lesion to be less than 2.5 cm in size. In contrast, patients with lesions larger than 4.0 cm had a significant risk of multicentricity (14 of 17) and occult invasion (10 of 17). Their study of 115 cases showed that approximately 40% of the 31 biopsies with DCIS lesions greater than 4.5 cm were associated with occult invasion when the mastectomy specimens were examined by the serial subgross technique; this finding did not occur in the 84 biopsies with DCIS lesions less than 4.5 cm. These studies document that small DCIS lesions are very rarely associated with occult invasive carcinoma and that as the size of the lesions increases, (particularly nearing 4 or 5 cm), so does the probability of finding associated invasive carcinoma elsewhere in the breast. This is particularly true for high grade DCIS.

Lagios *et al* have also reported on the significance of the histologic grade of DCIS on recurrence in non-randomized patients treated by excision only who had small (< 2.5 cm), mammographically detected DCIS lesions nearly all of which were completely excised. Their study group of 79 cases was divided into “types” or grades based on architecture, nuclear morphology and necrosis resulting in categories similar to high grade DCIS, intermediate grade lesions, and low grade DCIS categories currently in use. In that study, 19% (seven of 36) of patients who had high grade nuclear morphology and comedo type necrosis developed recurrence; only one of ten patients with intermediate grade histology developed a recurrence, and none of the 33 patients with DCIS of the micropapillary/non-necrotic cribriform type and low grade nuclear morphology developed a local recurrence. Most recent studies although non-randomized have confirmed that women with low grade DCIS have a significantly lower rate of recurrence than do women with high grade DCIS after therapy.

Several groups have reported that the closer the DCIS to the margin, the greater the risk for recurrence of DCIS or invasive carcinoma. In fact, in several studies distance from margin was the most significant predictor of outcome. ECOG currently has a randomized trial underway to test the incidence of recurrence when margins are free of tumor with or without post-operative radiation.
DCIS: Content of the Surgical Pathology Report

Once a diagnosis of DCIS is made, the surgical pathology report should indicate the type and grade of the DCIS lesion, the size (extent) of the lesion and the status of the excision margins whenever possible. Determining the size (extent) of the DCIS lesion may be difficult because DCIS is not usually identified grossly. We think the most practical way to determine the size or extent of DCIS is by measuring it on the first section it appears and then adding the thicknesses of each subsequent block in which it appears. This presumes that tissue blocks are labeled and submitted sequentially (which we think should be done). The entire area involved by DCIS on a slide is measured even if normal lobules intervene. If blocks, which contain DCIS, are followed by ones that do not and then by subsequent blocks that do, we add the areas of involvement together. The distance of the lesion from the nearest margin should be measured and recorded. We do not report margins as involved unless the abnormal process has been cut through. We do not use the “peel” technique to determine margins; rather we submit the entire area(s) of DCIS and measure from the DCIS to the margin. If the specimen was removed for microcalcifications, these should be sought and their presence or absence recorded and the tissue findings correlated with the specimen mammogram.

Ductal Carcinoma In Situ: Special Types

In addition to the usual types of DCIS other morphologic types usually referred to as special types, may be encountered. The clinical implications of some but not all of these is known.

*Pure Micropapillary:* When a lesion is entirely micropapillary it frequently is multifocal and multicentric. What the effect is on the success of conservative therapy is largely unknown but patients whose excisions do not have free margins may wish to consider further therapy. In any case clinicians need to be alerted and special attention paid to margins. Micropapillary DCIS is usually low grade but can be high grade.

*Apocrine DCIS:* The cells in apocrine metaplasia have large nuclei so an estimation of nuclear size based on red cell diameter cannot be used to distinguish apocrine hyperplasia from apocrine DCIS or to grade the lesions. Instead size is based on the nuclei in apocrine metaplasia as follows: Grade I apocrine DCIS features nuclei 2x the size of those in apocrine metaplasia and these may be slightly pleomorphic. Grade II has nuclei 3-4x as large and high-grade apocrine DCIS has nuclei >5x the size of nuclei in apocrine metaplasia as well as necrosis and pleomorphism. All low-grade apocrine DCIS should have the architectural features of the usual low-grade DCIS but they may be less well developed. The significance of apocrine DCIS is, as far as is known, the same as the usual DCIS of the same grade so patients with apocrine DCIS lesions are treated like those with non-apocrine DCIS.

*Mucinous DCIS:* In this type of DCIS extracellular mucin is present in a duct involved by DCIS. It is easy to confuse mucinous DCIS with invasive mucinous carcinoma in which the mucin pools contain large numbers of cells. In the former epithelium lines all the spaces; in the latter mucin is free in the stroma *i.e.*, epithelial cells do not line spaces separating the mucin from the stroma.
**Endocrine DCIS:** The architectural pattern is papillary or solid with or without acini and definitionaly, over half the cells must be chromogranin or synaptophysin positive. The cells have neuroendocrine features by light microscopy and extracellular mucin is commonly present. Twenty of the 34 in situ lesions in one series were associated with invasive carcinoma. The invasive component was mucinous in 12, carcinoid in 3, mixed carcinoid and mucinous in 4, and small cell undifferentiated in 1. Maluf and Koerner have reported identical lesions as solid papillary carcinoma of the breast.

**DCIS Associated with Mucocèle-like Lesion:** Cells with the pattern of DCIS line spaces that have ruptured and spilled mucin into the stroma. The significance is the same as the usual DCIS except that it may be difficult to exclude mucinous carcinoma.

**Cystic Hypersecretory DCIS:** cells in the pattern of low grade DCIS line large dilated ducts filled with eosinophilic secretion.

**Intraductal (Intracystic) Papillary Carcinoma:** Intraductal (intracystic) papillary carcinoma is a non-invasive papillary epithelial proliferation occurring within a large dilated duct, which is designated as carcinoma on the basis of a combination of architectural and cytologic features. It is considered apart from the other lesions in DCIS category because of its distinctive histologic appearance but many examples overlap considerably with low grade cribriform DCIS.

Intraductal papillary carcinoma is usually a solitary lesion. Architecturally, the defining feature is a large dilated duct or cystic space containing complex and arborizing generally thin, delicate fibrovascular stalks on which is found a single population of epithelial cells. Four main patterns are recognized. In one, the pattern is that of cribriform DCIS extending from the usually thin delicate fibrovascular stalks. Atypical ductal hyperplasia may be present in a papilloma, however diagnostic areas of DCIS should be identified before the lesion is classified as papillary carcinoma of the cribriform type. Cribriform/micropapillary DCIS may be present in adjacent smaller duct spaces. In the second type (the “tall-hyperchromatic cell or stratified spindle cell type”), the stalks are lined by a single population of tall cells with elongate, hyperchromatic stratified or pseudostratified nuclei arranged perpendicularly to the stalks. The cells are closely packed together and they may have nuclear clearing. A third pattern (the “compact columnar”) is characterized by enlarged uniform, often columnar cells, with fine evenly distributed chromatin arranged on delicate fibrovascular stalks. In the fourth, the cells resemble those of low grade transitional cell carcinoma of the bladder. Combinations of these patterns are not infrequently encountered. In all four types, mitotic figures may be present and are a very useful feature because mitotic figures are rare or absent in papillomas in women over 40. In addition, focal necrosis is much more common in carcinoma that in papillomas in women over 40 years of age. Only occasionally the cells cytologically malignant in any of the four types, i.e., in most instances they do not resemble the cells in high grade in situ carcinoma. Some intraductal papillary carcinomas are associated with extracellular mucin. Care must be taken to see such lesions are not invasive because invasive mucinous carcinoma may contain papillary fragments in the mucin. In in situ carcinoma epithelium should be anchored at the periphery of the
involved ducts, in invasive mucinous carcinoma the epithelium is at least partially detached and floating in the mucin.

The main differential diagnostic consideration, of course is intraductal papilloma which is usually characterized by broad, hyalinized stalks, two distinct cell types (epithelial and myoepithelial) and a complex, adenosis-like ductal proliferation within the hyalinized stroma. Stratification is most often absent. When cellular stratification is present in a papilloma it may be in the pattern of hyperplasia (papilloma with florid hyperplasia) or atypical ductal hyperplasia (papilloma with atypical hyperplasia). Calponin and p63 stains may be useful in highlighting the myoepithelial cells in a papilloma. Care must be taken not to interpret the smooth muscle cells of vessels or fibrocytes in the stroma as myoepithelial cells. A few myoepithelial cells may be found in the fibrous stalks of papillary carcinoma but they are not present in the sheets of stratified cells arranged in cribriform patterns. They are also usually absent in areas of florid hyperplasia or atypical ductal hyperplasia in a papilloma. Necrosis is unusual and mitoses are rare in papillomas. Any papillary lesion that features necrosis and large numbers of mitotic figures should be interpreted very carefully because it may be carcinoma particularly if the patient is over 40 years of age. However it is important to remember that considerable atypia, mitotic activity and even necrosis are allowed in papillomas in younger individuals and in subareolar papillomas (also called papillomas of the nipple). Papillary lesions with features intermediate between carcinoma and papilloma are usually termed atypical papillomas or papillomas with atypical hyperplasia.

Clinical Implications:
Lefkowitz and colleagues report a recurrence-free rate of 91% and the recurrence rate in their series was related to nuclear grade, i.e., none of their low grade lesions recurred.

REFERENCES: DCIS


CASE 15

Presented by Dr. Kempson

HISTORY (CTTR 27493): This 57 year old woman presented to her physician because she discovered a mass in her breast. This was excised and measured 3.0 cm.

HISTOLOGIC FINDINGS: At low magnification this mass appears to be predominantly a spindled fibroblastic proliferation in which the constituent cells are focally arranged in a whorling pattern. Within this fibrous stroma, there are ducts lined by stratified cells with enlarged nuclei. As one looks more closely in the stroma particularly around the ducts, the stromal cells have round instead of elongate nuclei and similar cells can be seen focally within the stroma. Thus, it appears that there is a condensation of epithelioid around the ducts and focally within the stroma. The stratified epithelial cells lining the ducts have enlarged nuclei over three times the size of a red blood cell. In some areas these are associated with hyalinized connective tissue cores.

IMMUNOHISTOCHEMISTRY: The ductal cells stain strongly and diffusely for AEI Keratin/CAM 5.2. However, some of the elongated fibroblastic appearing stromal cells are also Keratin positive as are the epithelioid cells condensing around the ducts.

DIAGNOSIS: Spindle cell carcinoma.

DIFFERENTIAL DIAGNOSIS: The differential considerations in this case include spindle cell carcinoma vs. fibromatosis vs. phyllodes tumor with stromal overgrowth vs. myofibroblastoma vs. a pure sarcoma. The ducts containing stratified atypical cells and the keratin positive cells in the stroma indicate this is spindle cell carcinoma. The epithelial elements do not have the architectural features of phyllodes tumor and fibromatosis does not contain keratin positive cells in the stroma. Similar considerations apply to myofibroblastoma.

DISCUSSION: The term metaplastic carcinoma has been used in at least two different ways: 1) To refer to neoplasms composed of ductal carcinoma or squamous cell carcinoma mixed with a mesenchymal appearing component. The mesenchymal component may resemble pleomorphic MFH or fibrosarcoma, or it may contain heterologous elements such as cartilage and bone. This type of metaplastic carcinoma has been variously labeled as carcinosarcoma, metaplastic carcinoma with heterologous elements and as matrix producing carcinoma. Alternatively, the mesenchymal element may be less cellular resembling fibromatosis or nodular fasciitis and this lesion is most often referred to as spindle cell carcinoma. 2) The term metaplastic carcinoma has also been used to refer to pure carcinomas with metaplastic squamous elements, either mixed with ductal carcinoma or as pure squamous cell carcinoma.

Most studies support the concept that the apparently mixed mesenchymal-epithelial neoplasms behave as carcinoma because they metastasize to axillary lymph nodes, whereas pure sarcomas almost never do so. Moreover, the metastases are usually pure carcinoma. These observations suggest that mixed neoplasms in which both the mesenchymal and epithelial elements are malignant should be considered as carcinomas with metaplasia for purposes of management and
therapy. As a consequence we designate all carcinomas with mesenchymal elements and all carcinomas with squamous elements as metaplastic carcinoma, and we separate the pure sarcomas from this group. Recently Page and associates have reported that bland fibromatosi-like spindle cell metaplastic carcinomas are capable of local recurrence but do not spread beyond the breast.

As pointed out above it is important to make a distinction between metaplastic carcinoma and pure sarcoma. Unfortunately this distinction is not always easy because the mesenchymal component in mixed carcinomas is identical by light microscopy to that found in pure sarcoma or to that found in bland fibrous proliferations such as fibromatosis or nodular fasciitis. The histologic distinction of metaplastic carcinoma from sarcoma rests with the identification of cohesive nests of tumor cells that have the morphologic features of carcinoma or immunohistochemical evidence of keratin expression by tumor cells. Consequently, all apparently pure mesenchymal tumors of the breast should be thoroughly examined to exclude focal areas of epithelial differentiation. Immunoreactivity with antibodies to epithelial antigens by tumor cells is taken as evidence that an apparently pure mesenchymal tumor is a carcinoma with extensive mesenchymal differentiation at least for management purposes. High molecular weight Keratins such as 34 Beta E 12 are more often positive in spindle cell carcinoma than AE1 and CAM 5.2.

**DIAGNOSTIC CRITERIA:**
Metaplastic carcinoma is recognized on the basis of a mixture of carcinoma and sarcoma or because the carcinoma is composed partially or completely by squamous cells. Consequently any breast neoplasm, which appears mesenchymal should be thoroughly sectioned to exclude a carcinomatous component. The subcategories of metaplastic carcinoma that we recognize are:

1. **Ductal and/or squamous carcinoma with obviously malignant stroma.** The sarcoma most often has the histologic appearance of malignant fibrous histiocytoma or fibrosarcoma and heterologous elements may be present.

2. **Spindle cell carcinoma** in which the mesenchymal element is composed of cells that resemble fibroblasts. The tumor cells may be as bland as those found in fibromatosis or nodular fasciitis. The recognizable epithelial element may be ductal or squamous and it may be sparse. Consequently, the possibility of spindle cell carcinoma should be considered whenever a fibrous appearing proliferative process is encountered in the breast. Sometimes the squamous component is cystic.

3. **Pure carcinomas with squamous elements:** Pure squamous cell carcinomas of the breast are rare, whereas squamous metaplasia in the usual duct carcinoma is somewhat more common. Adenosquamous carcinomas are rare and resemble the syringomatous tumor of the nipple except they occur elsewhere in the breast and they recur. They are however, low grade and rarely metastasize. The problem often arises as to what counts as squamous differentiation because ductal carcinoma cells may have “squamoid” features. We require intercellular bridges and/or keratinization.

**DIFFERENTIAL DIAGNOSIS:**

1. **Pure sarcoma:** Carcinoma is not identified after thorough sectioning and the tumor cells are keratin negative. Use high molecular weight keratin stains.
2 Phyllodes tumors with stromal overgrowth: In this neoplasm, the epithelium has the architectural features of a fibroadenomatous tumor. The stroma may be either bland or have obvious sarcomatous features. Stromal overgrowth in a phyllodes tumor is always a consideration when contemplating a diagnosis of spindle cell carcinoma. Cutting many sections to find characteristic areas is always warranted.

3. Fibromatosis: These are very rare lesions and should be diagnosed only after thorough sampling of the lesion fails to turn up carcinoma. Immunohistochemical reaction for keratin can also be helpful. Spindle cell carcinoma often bears a close resemblance to nodular fasciitis and fibromatosis so great care should be exercised before making a diagnosis of fasciitis or fibromatosis in the breast. Characteristically fibromatosis traps normal lobules within the tumor, a feature practically never observed in spindle cell carcinoma.

4. Myofibroblastoma: This lesion is characterized by irregularly arranged fibroblasts separated by long thin linear strips of collagen. In other words the histology is similar, and often identical, to solitary fibrous tumors. The tumor cells are CD34 positive and may be desmin or actin positive.

REFERENCES:
CASE 16

Presented by Dr. Kempson

HISTORY (CTTR 25581): This 55 year old woman sought treatment because she discovered a mass in her breast. A biopsy was performed.

HISTOLOGIC FINDINGS: This vascular lesion features channels lined by flattened bland cells. Many of the vascular channels are round but focally they become elongate and some feature interanastomosing channels. Papillae are present, but only focally. The striking feature of this lesion, however, is the infiltration of lobular units and fat.

IMMUNOHISTOCHEMISTRY: Not surprisingly the tumor cells are CD31 positive.

DIFFERENTIAL DIAGNOSIS: Angiosarcoma vs. hemangioma vs. pseudoangiomatous hyperplasia vs. atypical vascular proliferation. The pattern of infiltration, the complex interanastomosing channels and the papillae formation indicate this is angiosarcoma (see also differential diagnosis below).

DIAGNOSIS: Grade I angiosarcoma

DISCUSSION: Angiosarcomas are almost always palpable masses with an average diameter of 5 cm. It is rare for them to be less than 2 cm, and they are most frequently hemorrhagic on cut surface. The age at diagnosis ranges from the teens to the nineties with a mean of 35 years. Younger women tend to have high grade tumors. Histologically angiosarcomas are composed at least in part of anastomosing interconnecting, often complex vascular channels lined by neoplastic endothelial cells that often stratify sometimes into tufts. Angiosarcomas infiltrate without regard to lobular architecture. In the characteristic high grade angiosarcoma, the tumor cell nuclei lining the vascular spaces are enlarged, and have prominent nucleoli and mitotic figures can be easily found. Focally the tumor cells stratify and form tufts. Solid areas of undifferentiated malignant cells and solid spindle cell areas are common. On the other hand, low grade angiosarcomas of the breast are composed of non-stratified endothelial cells with deceptively bland histology. These are recognized on the basis of anastomosing channels infiltrating breast stroma and fat, the minimally enlarged and often hyperchromatic cells lining the tumor vascular spaces and the fact that the patient has a hemorrhagic mass.

Rosen and associates have presented data to show that cytologic features and the degree of differentiation of angiosarcoma are independent variables predicting outcome. These authors define 3 morphologic categories they label as Type I, II, and III. Type I is characterized by well formed vascular channels lined by flattened cells with focally hyperchromatic nuclei and essentially no stratification. Type II tumors are similar to Type I except that focally they feature cellular stratification that may result in tufting. Spindle cell areas may be present. In type III, solid spindled or undifferentiated sarcoma patterns are usually present and sometime predominate. Tumor cell necrosis and hemorrhage in the form of blood lakes may be found. Tumor cell necrosis and blood lakes are not found in low and intermediate grade tumors. The tumor cells in Type III are enlarged with prominent nucleoli and mitotic figures are easily found.
The outcome for patients with Types I and II angiosarcoma is similar (approximately 75% survival) while patients with Type III angiosarcoma have only a 15% survival.

**DIFFERENTIAL DIAGNOSIS:**
The differential diagnosis of angiosarcoma includes hemangioma and diffuse angiomatosis. In the past, it has been pathologic dogma that all angiomatous lesions of the breast are malignant. This is erroneous because hemangiomas do occur in the breast. However, they are usually incidental histologic findings limited to lobules and they do not infiltrate. With rare exceptions, hemangiomas of the breast are smaller than 2 cm while angiosarcomas almost always present as a mass and are almost always larger than 2 cm. The vascular channels in hemangiomas are not as complex as those in angiosarcomas and hemangiomas may be associated with normal large arteries and veins, a feature not seen in angiosarcoma. Hemangiomas may have atypical histologic features such as nuclear enlargement and nuclear hyperchromasia however, such tumors are <2.0 and circumscribed. They do not destructively infiltrate or form solid masses and hemorrhage and necrosis are absent. Diffuse angiomatosis is characterized by vessels lined by flattened bland cells growing diffusely in breast parenchyma. Confusion with angiosarcoma is possible because a mass lesion may be present and because of apparent infiltration. Bland flattened endometrial cells line simple round vessels rather than complex channels. Complete excision of angiomatosis is necessary to be sure changes characteristic of angiosarcoma are not present elsewhere because angiosarcomas may contain focal areas that closely resemble angiomatosis. It is worth remembering that angiomatosis is very rare and only a few cases have been reported.

Pseudoangiomatous hyperplasia of the mammary stroma is characterized by numerous slit-like spaces in dense hyalinized connective tissue. Because the spaces vaguely resemble blood vessels it is conceivable these could be confused with angiosarcoma, particularly if the fibrous stroma forms a mass. However, the spaces are not lined by endothelial cells and immunohistochemistry should immediately sort out those few cases where pseudoangiomatous hyperplasia mimics a vascular neoplasm.

Angiosarcoma arising in the irradiated breast after breast conserving therapy is being reported with increasing frequency and increasing numbers of an atypical vascular proliferation are also being found in the skin of the breast of women who have received radiation for carcinoma of the breast. Almost all of the latter have been in the dermis, but a few are in the mammary parenchyma. Microscopically they bear considerable resemblance to angiosarcoma, but differ in some ways. Atypical vascular lesions are usually very small, single and discreet. Rarely they can be multifocal. They are pink rather than blue or hemorrhagic. On the other hand angiosarcomas usually present with diffuse or multifocal involvement with thickening of the skin and typically the result is ecchymosis or a hemorrhagic appearance. Histological features characteristic of atypical vascular lesion not seen in angiosarcoma include relative circumscription, bloodless spaces, and delicate projections of endothelial lined stroma into vessel lumens. The constituent cells are not stratified and are not significantly atypical. Features of angiosarcoma not seen in atypical vascular lesions include infiltration into the subcutaneous tissue, prominent dissection of dermal collagen, hemorrhage, extravasated red blood cells, blood lakes, tufting, and diffuse stratification of endothelial cells, prominent nucleoli, mitotic figures and considerable cytologic atypia. It is not known whether atypical vascular lesion is
premalignant but it must be distinguished from angiosarcoma because so far they have had a clinically benign, although occasionally recurring, course.

REFERENCES:
LEGENDS

Case 1: Ovary: Mucinous LMP with IEC
Figure A: Cysts lined by mucinous epithelium
Figure B: Stratified mucinous cell
Figure C: Cytologic atypia
Figure D: Cytologic atypia

Case 2: Ovary: Clear cell Carcinoma
Figure A: Prominent fibrous matrix surrounds glands of varying sizes into which papillae insert.
Figure B: Tubulo-papillary architectural pattern with hobnail epithelium
Figure C: Hobnail cells with prominent nucleoli; hyaline matrix

Case 3: Endometrial Metaplasia
Figure A: Expanded endometrial glands with papillary infoldings set within a cellular stroma.
Figure B: Squamous metaplasia
Figure C: Mucinous metaplasia
Figure D: Ciliated and mucinous metaplasia

Case 4: Epithelioid Smooth muscle with vacuolization (?lipoblasts)
Figure A: Sheets of spindled and rounded cells merging that acquire increasingly large vacuoles.
Figure B: Mixture of vacuolated cells and some cells that begin to look like adipocytes.
Figure C: Most of the field is occupied by cells that look like lipoblasts.

Case 5: Pelvis: Leiomyosarcoma
Figure A: Highly cellular neoplasms composed of Interdigitating fascicles of spindled cells
Figure B: Coagulative tumor cell necrosis
Figure C: Higher power view showing the abrupt transition from viable cells to necrotic cells
Figure D: Nuclear hyperchromasia and large numbers of mitotic figures

Case 6: Pelvic Smooth muscle with stromal elements
Figure A: Dense, osteoid-like collagen separates rows of uniform blunt spindled cells.
Figure B: Interface of endometrial stromal type areas with collagen
Figure C: Interface of smooth muscle and endometrial stromal areas.
Figure D: 

Case 7: Angiomyolipoma (PEComa)
Figure A: Large abnormal vessels associated with epithelioid cells are features of angiomyolipoma.
Figure B: Fat is present in part of the tumor.
Figure C: Large cells with eosinophilic cytoplasm were scattered through the tumor.
Figure D: The abnormal vessel seen here is characteristic of those found in angiomyolipoma and may be see in other types of PE Comas.

Case 8: Atypical lipomatous tumor
Figures A and B: The striking features of this tumor are the large cells with irregular hyperchromatic nuclei set in a fibrillar to fatty stroma.
Figure C: Cells with large irregular hyperchromatic nuclei are needed to diagnose atypical lipomatous tumor (except in the retroperitoneum – see discussion).
Case 9: *Myxofibrosarcoma, intermediate grade (Myxoid variant of MFH)*

Figures A and B: Portions of the tumor are composed of pauci myxoid tissue with arching capillaries – the tumor becomes more cellular at the edge in B.

Figure C: Hypercellular areas in the tumor – note the loss of the myxoid stroma and the vascular pattern seen in A and B.

Figure D: Focally cells with large nuclei are present.

Case 10: *Undifferentiated malignant neoplasm*

Figures A and B: This malignant neoplasm is composed of undifferentiated epithelioid cells, which focally become discohesive.

Case 11: *SFT*

Figure A: Collagenized, paucicellular proliferation

Figure B: Bland spindled cells arranged in rows alternate with layered collagen

Figure C: Wavy collagen and bland spindled cells

Case 12: *GIST*

Figure A: Highly cellular fusiform spindled cells

Figure B: Vacuolated cytoplasm; bland nuclei; no mitotic figures

Case 13: *Lobular carcinoma in situ*

Figures A and B: The acini of several lobular units are filled with cells with uniform nuclei and pale eosinophilic cytoplasm. Note that the acini in one lobular unit of A are expanded.

Figure C: Some of the constituent cells have vacuolated cytoplasm and the cells are discohesive.

Case 14: *Intermediate grade ductal carcinoma in situ within a radial scar*

Figure A: The lesion has a stellate architecture with rays of fibrous tissue containing ducts radiating from the center.

Figure B: Some ducts contain low grade DCIS.

Figures C and D: In other areas there is a host reaction and irregular nests of epithelial cells raising the question of stromal invasion. Calponin and p63 stains identify myoepithelial cells around the nests of cells.

Case 15: *Spindle cell carcinoma*

Figures A and B: This lesion appears to be a fibrous proliferation, which has trapped ducts.

Figures C and D: Focally the stromal cells take on an epithelial appearance and these are keratin positive.

Case 16: *Grade I angiosarcoma*

Figures A and B: This vascular lesion infiltrates the lobular units and fat.

Figure C: Focally papillae are present and the channels become somewhat complex.
California Tumor Tissue Registry

Department of Pathology
11021 Campus Avenue, AH 335
Loma Linda, California 92350

Voice (909) 558-4788
Fax (909) 558-0188

Email: cttr@linkline.com

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Dr. Richard Kempson is Co-Director of Surgical Pathology at Stanford University Medical Center, and Professor of Pathology at Stanford University School of Medicine, Stanford, California. He is a graduate of Tulane University School of Medicine, and did his internship at Philadelphia General Hospital, and fellowships at Tulane University School of Medicine and Washington University School of Medicine. Long recognized as an authority in all aspects of surgical pathology, Dr. Kempson has published over 100 articles, while authoring and co-authoring over 31 books and book chapters.

Dr. Michael Hendrickson, Co-Director of Surgical Pathology for Stanford University Medical Center, is Professor of Pathology at Stanford University School of Medicine. He is a graduate of Stanford University, where he also had his residency and fellowship. He is of international renown, and has published over 50 articles, and authored or co-authored over 28 books and/or book chapters.

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Westin Hotel
South Coast Plaza
686 Anton Boulevard
Costa Mesa, CA 92626
(714) 540-2500; FAX (714) 662-6695

The Westin South Coast Plaza is located within minutes from the Orange County John Wayne Airport, and provides a complimentary shuttle service between the hotel and airport. From its stately interiors to its gracious rooms, the Westin sets the standard of world-class luxury accommodations. The hotel offers a myriad of entertainment opportunities, including recreational and cultural activities. Immediately adjacent to the hotel are the highly acclaimed South Coast Plaza Retail Center, and Orange County’s celebrated Performing Arts Center. Past attendees of the Registry’s seminars have expressed their delight with the accommodations and meeting facilities.

Seminar Objectives:

"The object of the seminar is to present a wide range of tumor types and recent advances made in diagnostic techniques. The session will stress a current understanding of the nature of these processes, the method of arriving at a diagnosis, differential diagnoses, and of course, natural history as morphology relates to clinical outcome.

At the conclusion of this seminar, attendees will have up-to-date criteria for diagnosing tumors and tumor-like conditions, and will be able to formulate appropriate differential diagnoses for common and uncommon neoplasms. The participant will also be able to better distinguish cellular atypias, especially in pre-neoplastic conditions, and will be able to confidently interpret immunohistochemical and molecular tools in the diagnosis of neoplasms."