A practical diagnostic approach to the non-neoplastic endometrial biopsy

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Session Overview

• This is intended to be a basic overview of non-neoplastic endometrial pathology as seen in biopsies/curettages, and would essentially be a refresher course for practicing pathologists and residents.
• A diagnostic approach that ensures that the optimal amount of information is conveyed to the clinician will be presented.
• There will be an emphasis on differential diagnosis and diagnostic pitfalls that could potentially result in misinterpretation.

Topics to be covered:
• Pathology of dysfunctional uterine bleeding
• Endometrial “metaplasias”
• Endometrial polyp
• Endometritis
• Evaluation of hyperplasias in the post treatment setting
• Reporting approaches and differential diagnostic considerations in all of the above.
• Other selected artifacts of the endometrial biopsy

Course Objectives
• Accurately interpret the pathologic findings in an endometrial biopsy or curettage and avoid diagnostic pitfalls
• Present pathologic findings in a manner that optimizes communication with the clinician and which addresses the diagnostic questions being asked
• Knowledge update on selected aspects of non-neoplastic endometrial pathology
Why is an endometrial biopsy/curettage obtained?

• Analysis of 100 consecutive endometrial biopsies at Vanderbilt University Med Ctr
  – Abnormal uterine bleeding (96%)
  – Normal endometrial cells in a Pap test (2%)
  – Infertility work-up (1%)
  – Evacuation of possible POC (1%)
## Diagnostic Question #1:

### How old is the patient?

<table>
<thead>
<tr>
<th>Peri-pubertal and adolescence</th>
<th>Reproductive years</th>
<th>Perimenopausal</th>
<th>Post-menopausal</th>
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<tbody>
<tr>
<td>Dysfunctional uterine bleeding, especially anovulatory cycles</td>
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<td>Atrophy</td>
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<td>Pregnancy complications</td>
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<td>Intrinsic (organic) lesions: neoplasia, hyperplasia, polyps, endometritis</td>
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Clinical Questions *a priori*:

- How old is the patient?
- Indication for biopsy?
- Pipelle or other biopsy versus curettage?
- Recent prior sampling in the endometrium?
- Prior hormonal use?
- Last menstrual period
Is the biopsy adequate for diagnosis?

- There are no universal standards
- Is ultimately an individual judgment regarding how representative of the patient’s entire endometrium the sample is
- Biopsies with a diagnosable neoplastic process are “adequate”, by definition
Adequacy issues

- Atrophic endometrium is often very scant in a biopsy and such biopsies are still “adequate”
- A mucus-rich, apparently purely endocervical sample has to be reviewed in detail to exclude rare endometrial fragments
- Lower uterine segment or basalis endometrium are inappropriate for endometrial dating
- *In general, descriptions of sample limitations are preferable to blanket declarations of specimen inadequacy*
The Abnormal Uterine Bleeding (AUB) biopsy

Clinical questions

• Is there any evidence of endometrial hyperplasia, carcinoma or other neoplasia?

• Are there any other organic lesions that would explain the bleeding, e.g. gestation, endometrial polyps, inflammation?

• Are the findings suggestive of dysfunctional uterine bleeding?; Is there breakdown?
Topics to be covered

• Pathology of dysfunctional uterine bleeding
• Endometrial “metaplasias”
• Endometrial polyps
• Endometritis
• Evaluation of hyperplasias in the post treatment setting
• Reporting approaches and differential diagnostic considerations in all of the above.
• Other selected artifacts
Pathology of dysfunctional uterine bleeding

– Breakdown changes
– Proliferative endometrium with glandular and stromal breakdown
– Persistent proliferative phase/Disordered proliferative endometrium
– Abnormal secretory phase
  • Luteal Phase defects
  • Irregular shedding
  • Abnormal secretory phase not otherwise specified
Dysfunctional Uterine Bleeding

- Uterine bleeding related to derangements in the normal cycling hormones that control endometrium, and which, by definition, cannot be attributed to any organic uterine disorder
- Clinically, DUB is thought of as being essentially synonymous with ovarian hormonal dysfunction
- DUB is most commonly due to anovulatory or oligo-ovulatory cycles; less commonly luteal phase anomalies
- DUB-related abnormalities are a common cause of bleeding in perimenopausal women
Glandular and Stromal Breakdown

- A non-specific manifestation of bleeding that can be seen in:
  - Menstrual endometrium
  - Anovulatory or Oligo-ovulatory cycles (persistent follicles or precipitous follicle regression)
  - Endometrial polyps, endometritis, neoplasia
  - Gestation-related bleeding (pregnancy, post-pregnancy, retained products of conception)
  - Status post progestin therapy
  - Abnormal luteal phase
Crush artifact may superficially mimic breakdown at low power
Breakdown: variation in associated glandular components
Diagnostic Approach

Evidence of Breakdown

- Is there an underlying organic lesion? (polyps, neoplasia, hyperplasia, endometritis etc)
  - Yes: diagnose as such
  - No: see next
Diagnostic Approach

Breakdown with no evidence of underlying organic lesion

Are the glands secretory or proliferative?

secretory
- Look for evidence of menstrual or premenstrual pattern endometrium:
  - Necrotic predecidua, stromal polymorphs, diffuse breakdown,
  - Diffuse glandular apoptosis;
  - DDX: Post-pregnancy, abnormal secretory phase, functional polyp

proliferative
- Anovulatory cycle with persistent follicle:
  - Fibrin thrombi and dilated venules, subtly irregular
  - and cystic glands, glandular apoptotic bodies
- Anovulatory cycle with precipitously regressed follicle:
  - Intact functionalis, diffuse breakdown, glands remain coiled or tubular
- Hormone replacement therapy:
  - Spindled stroma, weakly proliferative tubular glands
Diagnostic Approach

Breakdown with no evidence of underlying organic lesion

Are the glands secretory or proliferative?

Look for evidence of menstrual or premenstrual pattern endometrium:
- Necrotic predecidua, stromal neutrophils and “granulated” lymphocytes, diffuse breakdown, diffuse glandular apoptosis;
- DDX: Post-pregnancy, abnormal secretory phase, Functional polyp

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Hormone replacement therapy:
- Spindled stroma, weakly proliferative tubular glands
What if endometrium is secretory, with breakdown, but non-menstrual?
Secretory Endometrium with Premature Breakdown
(Abnormal Secretory Phase)
Pathology of dysfunctional uterine bleeding

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Each follicle houses a primary oocyte arrested in the prophase of the first meiotic division. The most developed Graafian follicle releases its oocyte during ovulation. As that primary oocyte is being released, it finishes its first meiotic division, becomes a secondary oocyte, and is arrested in the metaphase stage of the second meiotic division. Subsequent to ovulation the Graafian follicle differentiates into the corpus luteum, which will eventually degenerate into the corpus albicans.
Bleeding in Anovulatory Cycles

Absence of Progesterone

Reduced endometrial stromal cell *Tissue Factor*, *Plasminogen activator inhibitor-1* production, increased *metalloproteinase* activity, increased angiogenic factor expression

Vascular Instability and Impaired hemostasis

Bleeding
Diagnostic Approach

**Breakdown with no evidence of underlying organic lesion**

- Are the glands secretory or proliferative?

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- Look for evidence of menstrual or premenstrual pattern endometrium:
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**Anovulatory cycle with persistent follicle:** Fibrin thrombi and dilated venules, subtly irregular and cystic glands, glandular apoptotic bodies
Diagnostic Approach

Anovulatory cycle with precipitously regressed follicle:
Intact functionalis, diffuse breakdown, glands remain coiled or tubular
“Proliferative Endometrium with Glandular and Stromal Breakdown; Negative for Hyperplasia or Malignancy”

Much preferred over “Endometrium with no significant pathologic change”
Proliferative Endometrium

Nuclear pseudostratification, mitotic activity
Early proliferative endometrium:
"reparative", edematous stroma, straight glands
Subepithelial venular ectasia and fibrin thrombi in a woman with DUB that was thought to be related to anovulatory cycles.
Breakdown associated with rare cystic proliferative glands
Pathology of dysfunctional uterine bleeding

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Persistent proliferative phase/Disordered proliferative endometrium

• **Focal** glandular disorganization and dilatation most likely related to chronic anovulation, interspersed within normal glands
Differential: Simple Hyperplasia without Atypia

irregular and cystically dilated glands diffusely distributed in sample
Differential: Cystic glands that may be seen in the basalis:

In a curettage, look for associated weakly proliferative basalis glands, associated thick-walled vessels, dense basalis stroma that may be distinct from background.
**Differential:** Cystic glands that may be seen in the basalis:

*In a curettage, look for associated weakly proliferative basalis glands, associated thick-walled vessels, dense basalis stroma that may be distinct from background.*
**Differential**: Cystic glands that may be seen in the basalis:

*In a biopsy, look for associated weakly proliferative basalis glands, associated thick-walled vessels, dense basalis stroma that may be distinct from background.*
**Differential**: Cystic and dilated glands of an endometrial polyp or endometrial atrophy
Pathology of dysfunctional uterine bleeding

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Menstrual-Pattern Endometrium
What if endometrium is secretory, with breakdown, but non-menstrual?

Secretory Endometrium with Premature Breakdown
(Abnormal Secretory Phase)
Progesterone-related bleeding

- Luteal phase defects
- Irregular shedding
- Abnormal secretory phase not otherwise specified
  - In all 3 categories, if infertility is not a consideration, descriptive diagnoses are preferable.
  - Overlapping morphologic features between biopsies obtained from patients with Luteal phase defect-related bleeding and those with abnormal secretory phase not otherwise specified.
  - All are descriptive, not diagnostic terms.
- Long-term progestin only OCPs (resulting in unrestrained angiogenesis, abnormally fragile vessels)
Luteal phase defects

- Ovulation occurs, but the corpus luteum is functionally inadequate, regressing too early or producing inadequate progesterone (or the endometrium fails to respond), causing either infertility or non-menstrual secretory bleeding.

- Pathology: In the infertility setting, histologic dating of the endometrium is required; LPD is a clinical diagnosis.

- In the AUB setting, glands appear secretory, but do not match any one date of the cycle in that they are straight or abnormally stellate; predecidualization is suboptimal; breakdown is variably present before menstrual phase.
Abnormal secretory phase
Irregular shedding

- Rare pattern.
- Persistent corpus luteum and abnormally long progesterone production
- Pathology: Mixed phase pattern of proliferative and secretory endometrium, at least 5 days after onset of bleeding; breakdown, if present, is usually focal
- Secretory endometrium with 4 days or more morphologic difference in different areas
- Mixed phase pattern may also be seen in delayed ovulation, anovulation with superimposed progestins, exogenous hormones with HRT or OCPs, and of course neoplasia
Mixed Phase Pattern: Irregular Shedding
Mixed Phase Pattern in which Proliferative Phase Component is Hyperplastic, possibly from delayed ovulation following a persistent follicle.

Day 17 secretory endometrium

Simple Hyperplasia without Atypia
Bottomline: Reporting pathology of DUB

- **Reporting Breakdown, at the very minimum, localizes the source of bleeding to the endometrium**
- **Why “phase” the biopsy in the report (SE vs PE)?**
  - PE with breakdown is consistent with DUB
  - SE argues against anovulation-based DUB
  - Stating morphologic subtleties that make the SE abnormal would be consistent with a progesterone-based bleeding
  - In real life practice, OCPs or progestins are often started before biopsy results come back (or before the patient is biopsied at all). Some patients, however, may have contraindications for standard treatments
Bottomline: Reporting pathology of DUB

- **For progesterone related bleeding:**
  - Descriptive diagnoses are preferable over meaningless generalizations or broad clinical diagnoses that overstate our understanding of the pathophysiology in a given patient, for example
  - “Secretory endometrium with premature breakdown” is better than “Secretory endometrium with breakdown” or “abnormal secretory phase NOS”
  - Mixed phase pattern with a description of both components is better than “irregular shedding”
  - Luteal Phase defect is a clinical, not pathologic diagnosis
Topics to be covered

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Endometrial Metaplasias

• May result in overdiagnosis of adenocarcinoma or the assignment of a wrong histotype when an adenocarcinoma has surface metaplastic changes
• Can be focal or diffuse
• Often have a hormonal basis
• Kaku et al (1992): carcinomas associated with metaplasia tend to be well differentiated and without myometrial invasion and pelvic lymph node metastases, and generally have a better prognosis*
• There are typically (82% of cases) 2 or more types of metaplasias in the same uterus**

### Frequency of Endometrial Metaplasias

<table>
<thead>
<tr>
<th>Metaplasia</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Ciliated (tubal) metaplasia</td>
<td>58%</td>
</tr>
<tr>
<td>Eosinophilic metaplasia</td>
<td>48%</td>
</tr>
<tr>
<td>Squamous metaplasia or morules</td>
<td>34%</td>
</tr>
<tr>
<td>Mucinous metaplasia</td>
<td>24%</td>
</tr>
<tr>
<td>Papillary metaplasia</td>
<td>12%</td>
</tr>
<tr>
<td>Hobnail metaplasia</td>
<td>6%</td>
</tr>
<tr>
<td>Clear cell metaplasia</td>
<td>4%</td>
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</tbody>
</table>

Ciliated “tubal” metaplasia

- Cilia is a normal finding in surface endometrium and superficial glands
- May show architectural and/or cytologic atypia
- Considered a manifestation of estrogen exposure when accompanied by abundance of “secretory” or “peg” cells and in glands
Atypical Ciliated “tubal” metaplasia

• Tubal metaplasia may display areas of cytologic atypia
• Simon et al: “Our study indicates that atypical tubal metaplasia displays an immunostaining pattern similar to otherwise typical tubal metaplasia of the endometrium, and distinct from uterine serous neoplasms. The presence of atypical tubal metaplasia in endometrial samplings does not increase the risk of developing endometrial hyperplasia or malignancy”.
• Tubal metaplasia express p16, PAX2 and bcl-2

Simon et al. Mod Pathol. 2011 Sep;24(9):1254-61.
Eosinophilic metaplasia

- Possibly related to mucinous metaplasia*
- Eosinophilic cell change was more frequently seen in endometrial hyperplasia and carcinoma than in benign non-hyperplastic endometrium
- DDx: Oxyphilic endometrioid adenocarcinoma

Focus showing eosinophilic metaplasia, ciliated (tubal) metaplasia, and cribriform formation

Complex tubal metaplasia: A precursor lesion of ciliated endometrioid carcinoma???
Hobnail metaplasia

- May be seen as a reactive or reparative phenomenon (e.g. after a recent curettage), in pregnancy, Arias-Stella reactions or other progestin-related changes, but is most often idiopathic; typically focal
Differential Diagnosis: Hobnail cells in endometrioid or clear cell adenocarcinoma
Papillary Syncytial Metaplasia
aka Eosinophilic syncytial change

- Regenerative epithelial change following bleeding, ovulatory or anovulatory
- Syncytium of cells, papillae without fibrovascular cores, degenerative nuclear atypia may be present, but commonly bland, rare and normal mitotic figures allowable; p16+; p53 focal+
- Differential diagnosis: serous carcinomas: more cytologic atypia, more mitotic figures, florid budding, psammoma bodies, diffusely p53+
- Endometrioid adenocarcinoma with surface papillary syncytial change; evaluate underlying lesion by conventional criteria
**Papillary Syncytial Metaplasia (Eosinophilic Syncytial Change)**
Surface process
Mild to moderate cytologic atypia
No psammoma bodies
Only patchy weak expression of p53**
May express p16
Rare, normal mitotic figures
Low Ki67 proliferative index

**Endometrial Serous Carcinoma (UPSC)**
Usually an invasive and/or mass-forming process, but when “minimal”, can be purely surface
Moderate to severe cytologic atypia
One-third have psammoma bodies
Diffuse expression of p53 protein
Diffuse expression of p16
Numerous mitotic figures; high ki67 index
Slit-like spaces, LVSI

Mucinous metaplasia

- May be seen in otherwise physiologic endometrium or in endometrial polyps
- Intestinal-type mucinous metaplasia (with goblet cells) is extremely rare*, rule out neoplasia when seen in a biopsy
- DDX: mucinous adenocarcinoma, primary or metastatic

Clear cell metaplasia

- Associated with pregnancy but may be idiopathic
- DDX: adenocarcinoma, putative clear cell precursor lesions
Differential diagnosis: Putative Precursor Lesions of Clear cell carcinoma
Clear cell and ciliated metaplasia
Differential diagnosis: Clear cells in clear cell, endometrioid or serous carcinoma
Squamous metaplasia

- **Morular form:**
intraglandular nodules of squamous epithelium; may be idiopathic or associated with estrogens and/or progestins (no intercellular bridges or keratinization (beta-catenin nuclear/cyto+, ER-, p63-, CD10+, CDX2+))

- **Plaque-like or keratinizing forms:**
sheets or foci of obvious keratinization, with intercellular bridges (ER-, p63-, CD10+, CDX2-, beta-catenin membrane+)
Squamous Morules

- When seen in association with premalignant lesions, squamous morules are functionally inert (low Ki67, negative ER/PR), but share the same PTEN mutation with the glandular components, suggestive of a shared lineage**
- Squamous morules are “immunonegative for epithelial antigens including involucrin, EMA, and cytokeratins, but (are) positive for neurone specific enolase”*

Squamous morules in hyperplasias or endometrioid neoplasia
• Viewpoint: “..Even isolated morules should be carefully followed, however, to exclude a coexisting undersampled, or occult, glandular lesion”**.

Differential: Squamous metaplasia in endocervical tissue or cervical microglandular hyperplasia in an endometrial biopsy/curettage
Ichthyosis Uteri

Entire Endometrial Surface Covered by Squamous Epithelium
Bottomline: reporting endometrial metaplasias

- **The significance of metaplasias**
  - Squamous morules seen in isolation should prompt recuts to identify an underlying glandular lesion
  - Clear cell, eosinophilic, hobnail, tubal, and papillary syncytial metaplasia bear their most significance in the fact that they may confused with malignant processes in a biopsy/curettage; they may or may not be mentioned in the pathologic report (We typically don’t)
  - All metaplasias may be seen in association with adenocarcinoma or atypical hyperplasia
  - Tubal metaplasia helps in the evaluation of endometrium in AUB, as it is most commonly an estrogenic manifestation when diffuse; Complex tubal metaplasia should be reported
Topics to be covered

• Pathology of dysfunctional uterine bleeding
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Endometrial polyps

- Common: Seen in 2 - 23% of biopsies for abnormal uterine bleeding*
- Most polyps are single (only 20% multiple); and typically are around 2.0 cm (range 0.3 to 12 cm in one study**)
- Up to a third of women on tamoxifen may get endometrial polyps, which tend to be larger and multiple

** Peterson and Novak. Obstet Gynecol 1956;8:40-9
Endometrial polyps

- May present with abnormal bleeding, but are often incidental
- The clinical significance of the diagnosis
  - Explains AUB and thus prevents erroneous patient management for DUB
  - May explain infertility
  - May harbor pathology with background endometrium correlates and/or malignant potential
  - Tamoxifen-related polyps may recur
Histopathology

• Altered, typically more fibrous stroma relative to background endometrium
• Glands may be cystic, inactive, metaplastic, secretory, proliferative; glands may be oriented parallel to surface epithelium
• Stromal clusters of thick walled vessels
• Stroma may be cellular, mitotically active, have atypical stromal cells
• Is commonly a polypoid fragment with epithelium on 3 to 4 sides
ENDOMETRIAL POLYP WITH INCREASED CELLULARITY, BREAKDOWN AND SURFACE PAPILLARY SYNCYTIAL METAPLASIA
FUNCTIONAL ENDOMETRIAL POLYP
ATYPICAL STROMAL CELLS IN A HYALINIZED ENDOMETRIAL POLYP

INFARCTED ENDOMETRIAL POLYP
Differential: Early proliferative endometrium: “reparative”, edematous stroma, straight glands
Differential: Secretory endometrium often come labeled "endometrial polyp"

Vascular Clusters in Normal Endometrium: Mid and Late Secretory Phase
Vascular Clusters in Normal Endometrium: Basalis & Superficial Myometrium
Vascular Clusters in Normal Endometrium: Nonspecific clusters in the functionalis:
In an endometrial biopsy or curettage

• Basalis vessels are accompanied by cellular stroma typically distinct from background; glands weakly proliferative or inactive; typically only in a few of many fragments

• Functional polyps, especially secretory phase ones, are diagnostically difficult in a biopsy, but often appear “out of phase” with the background endometrium and have a central core of fibrous or cellular stroma, thick-walled vessels and inactive or weakly proliferative glands
Irregular pattern of hormonal response in an endometrial polyp
**Differential:** Polypoid Adenomyoma or Adenomyomatous polyp

- Adenomyomas have diffuse myomatous stroma; at least focally, glands are surrounded by endometrial stroma
- Endometrial polyps may have smooth muscle metaplasia, but this is usually not diffuse and is centered around blood vessels
**Differential:** Atypical Polypoid Adenomyoma (APA)

- APA diagnosis may result in a hysterectomy: 8.8% risk of adenocarcinoma in subsequent resection, and 45% recurrence rate*
- Haphazard glands with mild to moderate cytologic in a myomatous or fibromatous stroma; squamous metaplasia typical; no periglandular stromal collarette

*Heatley MK. Histopathology 2006;48:609-10
**Differential: Atypical Polypoid Adenomyoma (APA)**

- **DDX: Myoinvasive endometrioid carcinoma** (free epithelial tumor fragments, may have severe atypia, non-lobulated or polypoid, stromal or myomatous cells tend to be long and sweeping, rather than short and interlacing in an APA)
- If there is a diagnostic question, best to state that and/or seek other opinions
Papillary Proliferation of Lehman & Hart

- Postmenopausal women presenting with bleeding
- 67% associated with endometrial polyps
- Papillae with fibrovascular cores, no more than mild atypia, occasional mitoses
- Metaplasias (decreasing order: mucinous, eosinophilic, ciliated, squamous, hobnail)
- Thought to be benign, but only 3 patients treated with less than a hysterectomy had significant follow-up

Neoplasia in Endometrial Polyps

- Hyperplasia is seen in 11-30% of polyps
- Carcinoma is seen in 0.5-3% of polyps (general population)
- Carcinoma is seen in 3-10.7% of polyps in tamoxifen-treated women
- Overall prevalence (premalignant/malignant): 5.42%
- Neoplasia prevalence, women presenting with AUB vs women without AUB: 4.15% versus 2.15%
- Complex hyperplasia within a polyp is predictive of hyperplasia (72%) or carcinoma (31%) in the non-polypoid endometrium in a significant proportion of cases

References:
Cohen I. Gynecol Oncol 2004;256-66
deCosta/Mittal. Mod Pathol 2006;19:175A
Shusan A. Gynecol Obstet Invest 2004;58:212-5
Neoplasia in Endometrial Polyps

- Cystic glands lined by proliferative endometrium is not an indication for a diagnosis of simple hyperplasia in a polyp (the diagnosis of simple hyperplasia should not be made in a polyp)
- A mild degree of glandular crowding and architectural complexity is also allowable without a diagnosis of complex hyperplasia
- Serous carcinomas may be a subtle finding in a polyp
Bottomline: reporting endometrial polyps

• Report:
  – Endometrial polyp
  – If tissue sample is suggestive of but not diagnostic of a polyp due to fragmentation, that can be stated
  – Simple hyperplasia is not reported in polyps; some degree of glandular crowding is allowed without a diagnosis of complex hyperplasia
  – As always, carefully evaluate for neoplasia.
Topics to be covered

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- Evaluation of hyperplasias in the post treatment setting
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- Other selected artifacts
Chronic Endometritis

- **Kitaya et al (2011):** Seen in 11.1% of samples assessed with a plasma cell IHC marker; 23.1% of women are asymptomatic.
- **Smith et al (2010):**
  - Low (4%) association rate with PID
  - Few patients (3%) received antibiotics or further clinical intervention after the diagnosis.
- **Gilmore et al (2007):** Plasma cells were identified in the majority of proliferative endometrium samples with breakdown (66%); Disordered PE also frequently showed plasma cells.

Chronic Endometritis: Histopathology

- Diagnosis depends on identification of plasma cells in the appropriate context (see below)
  - Plasma cell infiltration (syndecan-1 [CD138] and methyl green pyronin [MGP] may be useful)
    - Endometrial epithelium may be CD138+
  - Supportive evidence:
    - Neutrophil aggregates in epithelium.
    - Stromal spindled alteration, stromal edema, fibrin thrombi
    - Eosinophils, hemosiderin-laden and/or conventional macrophages, lymphoid aggregates

- Plasma cells may be seen in any breakdown endometrium (including from menstruation), upper endocervix, polyps or other mass-like pathologic processes in the uterus

Siddiqui MA et al. Mod Pathol 2006;19;196A
Gilmore et al. Hum Pathol. 2007;38:581-4
Chronic Endometritis
Chronic Endometritis
Chronic Endometritis: Luminal neutrophils with other stromal morphologic features
However, an isolated focus of luminal neutrophils in otherwise normal endometrium has no known significance.
Chronic Endometritis: Stromal spindled or “fibroblastic” alteration
Lymphoid aggregates

- Lymphoid aggregates, when in conjunction with plasma cells and other morphologic features, may be seen in chronic endometritis, but by themselves are devoid of significance.
- Lymphoid aggregates are a normal component of the basalis, and these have prominent admixtures of B (CD20+) and T (CD3+) cells.
- Lymphoid aggregates in the functionalis stroma are typically mostly T cells, with increased B cells seen in chronic endometritis.
Xanthogranulomatous endometritis with various epithelial metaplasias

- Postmenopausal women presenting with bleeding
- s/p radiation treatment
- Cervical stenosis and/or pyometra
- Foam cells and other inflammatory changes, often with reactive epithelial change
- DDX: Non-specific endometrial foam cells

“Focal Necrotizing Endometritis”

- Focal finding in mostly premenopausal women presenting with abnormal uterine bleeding; Has no known clinical significance
- No plasma cells; inflammation is focal or patchy; non-confluent
- Neutrophils, lymphocytes and macrophages
- May resemble a “crypt abscess” as seen in the colon
- We are descriptive on these rare cases to avoid confusion

Breakdown with neutrophils and plasma cells
**Differential**: Inflamed fragment of endocervical tissue in an endometrial biopsy
Bottomline: reporting endometritis

• The significance of the diagnosis
  – Explains *abnormal uterine bleeding*, may be managed with antimicrobials, and prevents erroneous management for *dysfunctional uterine bleeding*
  – May explain infertility

• Report: presence of endometritis, type of endometritis or specific infection (granulomatous, viral inclusions, e.t.c) if identifiable, whether some other identifiable cause can be identified, and the severity of inflammation

• Neutrophils and plasma cells associated with menstrual endometrium or in foci of breakdown, should not be reported as endometritis
Topics to be covered

- Pathology of dysfunctional uterine bleeding
- Endometrial “metaplasias”
- Endometrial polyps
- Endometritis
- Evaluation of hyperplasias in the post treatment setting
- Reporting approaches and differential diagnostic considerations in all of the above
- Other selected artifacts
Hormonally-treated endometria that the pathologist is most likely to encounter

– Oral contraceptives for the treatment of presumed dysfunctional uterine bleeding or general contraception
– Progestins for the treatment of hyperplasias or DUB
– Biopsies from post/peri-menopausal women on hormone-replacement therapy and AUB
– Less common: tamoxifen for breast cancer, hormonal treatments for endometriosis, hormonal treatments for assisted reproduction
– The changes may be progestin-related (the vast majority), estrogenic or androgenic
Progestin effects (most common)

• Mazur-Kurman Classification
  – Decidual (pregnancy like) pattern: abundant tissue, vascular ectasia, decidualized stroma with lymphoid infiltrate
  – Secretory pattern: moderate to sparse tissue, mildly tortuous glands, stromal cells predecidualized
  – Atrophic pattern: scant tissue, glands atrophic, stroma variable

**Note: This is a morphologic description that highlights the spectrum of changes that may be seen, and is not a diagnostic classification. The changes seen in a given case depend on the duration of use and potency of medication**

Mazur MT Kurman RJ 2nd Ed., Diagnosis of endometrial biopsies and curettings. Springer 2005
Tortuous secretory glands, stromal predecidualization, typically seen in early phase of use.
Stromal predecidualization
Small atrophic glands, stromal predecidualization, Lymphoid aggregates
Small glands, secretory

Small glands, atrophic
Rarely, progestin-like changes may be seen in a woman with no history of exogenous hormone use, and/or may be a manifestation of an occult functioning extrauterine neoplasm.
Bottomline

• At Vanderbilt, we report endometrial biopsies obtained with the advanced progestin changes as “Inactive endometrium with progestin-like effects” or similar variations.

• When the changes are in the overtly secretory stage, it is difficult to separate these changes from cyclic secretory phase in a premenopausal patient, but biopsies are typically not seen at this stage.
Evaluation of hyperplasias in the post-treatment setting

- Most patients with a biopsy/curettage diagnosis of simple hyperplasia without atypia or disordered proliferative endometrium, many patients with complex hyperplasia without atypia, and a minority of patients with complex atypical hyperplasia or well-differentiated adenocarcinoma, are managed with progesterone-based hormonal therapy.

- Endometrial biopsies are subsequently obtained every 3 months to monitor the response.
Patient X: Index Biopsy
• Squamous morules abridging glands: Complex hyperplasia
• Atypia difficult to evaluate in this setting, but nucleolar prominence and/or pleomorphism that is significantly above the background is diagnostic
• Complex hyperplasia, reduced in extent; cytologic atypia is not evident
• Complex hyperplasia or cytologic atypia no longer evident
• Scattered cystically dilated glands are present
• When the glands are embedded in predecidualized or edematous stroma, and are not lined by atrophic epithelium, this represents, in my opinion, evidence of background simple hyperplasia
Another patient, after 3 months of progestin treatments for complex hyperplasia without atypia
**Differential:** Basalis glands in progestin-treated patients tend to be cystically dilated.

In this scenario, glands are inactive, and are surrounded by cellular basalis stroma, rather than predecidualized stroma.
**Differential:** Basalis glands in progestin-treated patients tend to be cystically dilated
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- Reporting approaches and differential diagnostic considerations in all of the above.
- Other selected artifacts
Artifactual Papillary formation of Secretory Endometrium
Telescopering
Artifactual Crowding: Proliferative Endometrium
Artifactual Crowding: Secretory Endometrium
“Pseudo-Atypia”
Pseudoactinomycotic granules

Actinomyces
Topics to be covered

• Pathology of dysfunctional uterine bleeding
• Endometrial “metaplasias”
• Endometrial polyps
• Endometritis
• Evaluation of hyperplasias in the post treatment setting
• Reporting approaches and differential diagnostic considerations in all of the above.
• Other selected artifacts
Conclusions

• Incorporate specimen adequacy issues, patient age, any potential exogenous hormonal context, clinical presentation, and type of biopsy into diagnostic algorithm before interpretation.

• The first duty in AUB biopsies is to exclude hyperplasias and neoplasia; if these are absent, the second duty is to accurately classify the cause if possible.

• For DUB biopsies, avoid clinical terms; Descriptive interpretations are preferable.