Errors in Non-Gynecological Cytopathology and Pathology:
“There is More to Learn from System Failures than System Successes”

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Error reduction is an important aspect of continuous quality improvement. Error reduction and patient safety in healthcare has recently come to the forefront of medical practice. Follow-up is the great teacher in cytopathology. Cytopathology laboratories are required to perform cytology-histology correlation to improve their diagnostic practice and reduce errors in cytopathology. This seminar will review and discuss selected short and long cases that reveal errors at some stages prior to signing out or upon follow-up. Selected images from each case will be presented, followed by an interactive discussion between the instructors and the audience. The cases will highlight the diagnostic dilemmas and pitfalls including screening errors, interpretation errors, difficulties in well-differentiated neoplasms, benign entities the mimics malignancies, malignant entities with bland cytology, and coincident lesions and malignancies. Selected cases with errors in surgical pathology cases that were discovered through cytological diagnoses will also be presented.
Upon completion of this workshop you will be able to:
1. Identify the common types of errors in non-gynecological cytopathology and analyze root cause of cytopathology errors and how to reduce or prevent them.
2. Recognize the importance of cytology-histology correlation and that follow-up is the best teacher in cytopathology.
3. Understand that errors also occur in surgical pathology and that cytopathology can be QA for surgical pathology.
4. Experience practical examples of cases with errors in diagnoses and how we can develop a plan to deal with such cases in order to improve the overall quality of patient management.
• **Aspiration Cytology (FNA):**
  - By pathologist
  - By image-guidance

• **Exfoliative Cytology:**
  - Body Cavity Fluid Cytology
  - Washings

• **Touch Prep/Imprint Cytology**
  - Intraoperative or Bench top
  - Evaluation of Core Biopsies

• **Metastatic Disease:**
  - Lymph Node Metastases
  - Solid Organ Metastases: Liver FNA, Lung FNA
  - Body Cavity Fluids: Pleural, Peritoneal, CSF
Non-GYN Types of Cytology Errors: Overview

Pre-analytic Errors:
- Inexperienced aspirator/performer
- Poor Preparation
- Scant cellularity
- Inappropriate or Lack of triage (without ROSE)

Analytic Errors:
- Misleading immunostain (IHC) results
- Overinterpretation /FP
- Poor Sampling /FN
- Contamination vs. Lesional cells
Pitfalls of Contamination

- Lung
  - Reactive Bronchial Cells
  - Hepatocytes (RLL)
  - Mesothelial cells
  - Cartilage (from ribs)
- Lymph Node/Soft tissue
  - Seminal vesicle sampling (perirectal)
- Thyroid
  - Parathyroid sampling
  - Ciliated respiratory epithelium
  - Skeletal Muscle
  - Gel, platelets
Pitfalls of Respiratory Cytology

- Reactive/metaplastic changes
- Germinal center cells, large lymphocytes, and macrophages
- Granulomatous inflammation
- Lymphoid cells vs. SCLC
- SCLC vs. NSCLC
- Single, dyscohesive malignant cells
- Non-pulmonary metastases
- Bland neoplasms
- Lymphoma
• Inadequate sampling
• Bland appearing neoplasms in the lung
• Atypia of alveolar, bronchial, metaplastic or mesothelial cells
  – Examples: infarct, asthma, bronchitis, pneumonia, granulomas, therapy-related effects, etc
  – Reserve cell hyperplasia can mimic small cell carcinoma
• Mesothelioma versus Adenocarcinoma in pleural-based lesions

False Negatives

False Positives

Inaccurate Classification or Subtyping
DD/Pitfalls of Granulomatous Inflammation

• **Granulomatous Inflammation**
  – Necrotizing- infection (TB), other
  – Non-necrotizing- sarcoidosis, other
  – Granulomas associated with malignancy
    – Lymphoma, Seminoma, Metastatic Carcinoma

• Lymphohistiocytic aggregates in Reactive Lymphoid Hyperplasia

• Non-small cell carcinoma
  – Lung origin
  – Non-pulmonary origin- bland metastatic neoplasms
DD/Pitfalls of Met NSCLC in EBUS/EUS FNA

- Reactive epithelial cells (bronchial, squamous)
  - Treatment-related atypia (chemo/radiation)
- Other: Viral pneumonitis, Pulmonary infarct
- Features favoring **benign**:
  - Cilia, terminal bars, uniformity, absence of mitoses, no abnormal nucleoli
- Metaplastic cells
- Metastatic carcinoma
  - Pulmonary vs. Non-pulmonary origin
- Granulomatous inflammation
- Germinal center cells

Crapanzano JP & Saqi A, Diagn Cytopathol 2010
Monaco SE et al, Cytojournal 2010
Bland Neoplasms in the Lung

- **Primary Neoplasms**
  - Carcinoid
  - BAC- nonmucinous & mucinous
  - Signet-ring tumors

- **Metastatic Neoplasms**
  - RCC
  - Mesenchymal neoplasms
    - Giant cell tumor of bone
    - Benign Metastasizing Leiomyoma
• Benign Metaplastic Cells
• Signet ring adenocarcinoma
• Squamous cell carcinoma, keratinizing type
• Seminoma
• Melanoma
• Mesenchymal lesions- spindle cell lesions
• Small cell carcinoma
• Lymphoma

Monaco SE et al, Cytojournal 2010
• Reserve cell hyperplasia
• Benign lymphoid cells
• Small cell carcinoma
• Non-small cell carcinoma
  – With neuroendocrine features/LCNEC
  – Basaloid carcinoma
• Lymphoma
• Small round blue cell tumors

Crapanzano JP & Saqi A, Diagn Cytopathol 2010
Monaco SE et al, Cytojournal 2010
## Pitfalls of NE Tumors & Mimics

<table>
<thead>
<tr>
<th></th>
<th>Lymphocytes/ Lymphoma</th>
<th>Carcinoid</th>
<th>SCLC</th>
<th>LCNEC</th>
<th>Basaloid carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell arrangement</td>
<td>Discohesive, Pseudo- epithelioid clusters in some</td>
<td>Discohesive and Loosely cohesive; rosettes; associated with blood vessels</td>
<td>Cohesive and discohesive</td>
<td>Cohesive</td>
<td>Cohesive ± nuclear palisading at the edge of groups</td>
</tr>
<tr>
<td>Nuclei</td>
<td>Small, round, coarse chromatin</td>
<td>Small, round, monomorphism, stippled chromatin; no molding</td>
<td>Small, molding, pleomorphism, stippled chromatin</td>
<td>Larger; occasional molding</td>
<td>Coarse chromatin, oval/ spindle cell nuclei</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>May be prominent in immature cells/ lymphoma</td>
<td>Inconspicuous</td>
<td>Inconspicuous, occasional nucleoli in “intermediate” type</td>
<td>Prominent</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Scant/Absent, Basophilic</td>
<td>More abundant, granular; “plasmacytoid”</td>
<td>Scant/Absent</td>
<td>More abundant, granular</td>
<td>More abundant, Dense</td>
</tr>
<tr>
<td>Background</td>
<td>Lymphoglandular bodies</td>
<td>Branching capillaries; Occasionally necrotic (atypical carcinoma)</td>
<td>Apoptotic and Necrotic</td>
<td>Apoptotic and Necrotic</td>
<td>Sometimes necrotic</td>
</tr>
</tbody>
</table>

Monaco SE et al, Cytojournal 2010
*EBUS & Background Material*

- **Tigroid-like Background**
  - Seminoma
  - Glycogenated tumors

- **Mucinous Background**
  - NonDx vs. Dx
  - Don’t overcall Mucinous Ca

- **Necrotic Background**
  - Benign vs. Tumor

- **Lymphoid Background**
  - Adequacy
  - Crushed lymphocytes
  - Lymphoma
  - SCLC/SRBCT

Beware of Mismatch Bkgd vs Cells
# Pitfalls of Background Material

## Table 2: Differential diagnosis based on background material

<table>
<thead>
<tr>
<th>Necrotic background</th>
<th>Mucinous background</th>
<th>Tigmoid background</th>
<th>Lymphoid background</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotizing granulomas</td>
<td>Nondiagnostic with mucin contamination</td>
<td>Germ cell tumor/Seminoma</td>
<td>Adequate, Negative for malignant cells with lymph node sampling</td>
</tr>
<tr>
<td>High grade tumor with necrosis</td>
<td>Negative for malignant cells with mucin contamination (lymphocytes present)</td>
<td>Glycogenated neoplasm (Squamous cell carcinoma, Ewing's Sarcoma, clear cell tumors, others)</td>
<td>Lymphoma</td>
</tr>
<tr>
<td></td>
<td>Mucinous adenocarcinoma</td>
<td></td>
<td>Mimics seen with small round blue cell tumors (example: necrotic/apoptotic background of small cell carcinoma)</td>
</tr>
<tr>
<td>Mucinous Cystic Neoplasms[33]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant neoplasm with mucin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>contamination</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• **Benign lymphoid cells**
  – Background: LGBs
  – Dyscohesive

• **Lymphoma**
  – Background: LGBs
  – Dyscohesive

• **Small cell carcinoma**
  – Background: apoptotic debris
  – Some cohesion, molding
Spindle cell lesions in the mediastinum

• **Difficult**
  – Better to be called *Spindle cell lesion or tumor*

• **DDx/Pitfalls of Spindle cell Lesions:**
  – Thymomas- spindle cell type
  – Neurogenic tumors
  – Metastasis: spindle cell melanoma, sarcomatoid carcinoma
  – Soft tissue neoplasms: schwannoma; inflammatory pseudotumor, etc
  – Benign Mimics: granuloma, fibrosis/scar
Pitfalls of Lymph Node FNA

• Subtyping Lymphomas can be difficult
• Heterogeneous Aspirates are not always benign
  – Mixed cell populations can occur in NHL, Hodgkin’s lymphoma, and cases with partial LN involvement
  – Low grade lymphomas (marginal zone lymphomas, follicular lymphomas) can mimic reactive lymphoid hyperplasia
• Small cell carcinoma & Neuroendocrine Carcinomas
• Myeloid (granulocytic) sarcoma/Chloroma
• Dyscohesive Non-lymphoid Large cell Malignancies
• Mimics of lymphoglandular bodies
  – Platelets, necrotic debris

Kishimoto et al, *Diag Cytopath* 2005
• Cases with extensive necrosis
  – Benign LN conditions with necrosis:
    inflammation/lymphadenitis, vasculitis, trauma/prior FNAB, autoimmune conditions (SLE), other
  – Malignant LN conditions with necrosis:
    metastatic carcinoma (colon, small cell, etc), NHL (Burkitt, DLBCL), HL
• **Usual:**
  - Reactive (Inflammatory/Infectious) Lesions:
    Abscess/fat necrosis/infection (fungal, other)
  - Tumor Necrosis:
    Primary vs Metastatic carcinoma, lymphoma, other tumors

• **Unusual:**
  - Ischemic necrosis/infarction:
    Infarcted Papillary lesions, Pulmonary infarct, Post-FNA, others
• Plasma cell neoplasms
  – Can mimic non-lymphoid conditions: melanoma, mesothelial cells, mesothelioma, carcinoma with plasmacytic differentiation
  – Usually CD45 and CD20 negative
  – IHC pattern: -CD20, -CD19, -CD45/LCA, +CD79a, +CD138, +CD56, +kappa/lambda

Lymphoid cells are usually vimentin positive, so in the absence of doing a panel of lymphoid markers, one may misdiagnose lymphoid lesions (particularly plasma cell neoplasms because LCA- & CD20-) as sarcomas.
Pitfalls/Diff Dx:
- Subtyping Lymphoma
- Reactive lymphoid hyperplasia
- Small cell carcinoma & Neuroendocrine Carcinomas
- Myeloid (granulocytic) sarcoma

Small Cells

Chronic lymphocytic leukemia (CLL/SLL)
Mantle cell lymphoma (MCL)
Follicular lymphoma (FL)
Marginal zone lymphoma (MZL)
Lymphoplasmacytic lymphoma (LPL)

Medium Cells

Lymphoblastic Lymphoma
Burkitt Lymphoma

Large Cells

Pitfalls/Diff Dx:
- Hodgkin Lymphoma
- Non-lymphoid large cell malignancies

Diffuse Large B cell Lymphoma (DLBCL)
Other Large cell lymphomas
Difficulties in FNAB Diagnosis of Lymphoma

- Lack of architecture
- Heterogeneous lymphomas
- Dyscohesive neoplasms in the differential
- Need for enough material for ancillary studies
  - Difficult cases with fibrosis, necrosis or extensive cellular damage
Difficulties in FNAB Diagnosis of Hodgkin Lymphoma

- **Heterogeneous Background**
  - Mimic of Reactive Lymphoid Hyperplasia

- **Scant cellularity**
  - Particularly in cases of nodular sclerosing HL
  - May benefit from concurrent core biopsy

- **Need for enough material for ancillary studies**
  - To exclude other Large cell lymphomas (ALCL, TCRBCL)
  - To exclude other possibilities, such as viral infection (EBV or HSV)

Das DK et al, *Diagn Cytopathol* 2009
Large Cell Malignancies

- Lymphoma
  - NHL
  - HL
- Plasma cell neoplasms
- Poorly-differentiated carcinoma
- Sarcoma
- Seminoma
- Melanoma
Granulation tissue can mimic spindle cell neoplasms

Adipocytic Tumors
- Largest group of mesenchymal tumors
- Mature adipocytes from lipoma vs soft tissue around lesion
  - The diagnosis of “Lipoma” requires clinical +/- radiologic correlation
  - Pseudolipoblasts can be seen in other conditions

Metastatic melanoma and metastatic carcinomas with sarcomatoid features

Large Cell Lymphomas
- Remember that vimentin positivity is very non-specific
  - Lymphomas are vimentin+, and in the context of an incomplete immunohistochemical profile may lead you falsely interpret a lesion as mesenchymal

Singh et al, Adv Anat Path, 2004
Pitfalls of Thyroid FNA

- Hyperplastic Nodules
- Parathyroid Sampling mimics FL/FN
- Suboptimal/Less than optimal cases
  - Inadequate sampling is a major cause of FNs
- Cystic lesions with no follicular cells
- Always look for any cytologic atypia or malignant features
  - Papillary Thyroid Carcinoma
  - Metastatic neoplasms
Pitfalls Of Serous Effusion

- Reactive mesothelial cells
- Histiocytic Hyperplasia
- Atypical mesothelial proliferation
- Mesothelioma:
  - Well-differentiated, uncommon variants
  - Mesothelioma vs. reactive mesothelial cells
  - Mesothelioma vs. adenocarcinoma
- Mucinous tumors vs. mucinous carcinomas
- Serous tumors vs. serous carcinoma
Lymphocyte-rich effusions
• Hematopoietic malignancies
• Epithelial malignancies: small cell ca, small round blue cell tumors
• Metastatic ductal carcinoma (elderly patients)
• Ductal carcinoma with a prominent plasmacytoid appearance
• Small-cell carcinoma of the lung
• Non-Hodgkin lymphoma
• Neuroendocrine carcinoma
• Lobular and ductal carcinoma of the breast
• Gastric adenocarcinoma
• Ewing's sarcoma/SRBCT
Pitfalls Of Effusion with Large Cell Pattern

- Adenocarcinoma (breast, lung, ...).
- Poorly differentiated adenocarcinoma
- Malignant melanoma
- Hepatocellular carcinoma
- Malignant mesothelioma
- Squamous cell carcinoma of the lung
- Renal cell carcinoma
- Malignant melanoma
- Adrenal cortical carcinoma
- Reactive mesothelial cells
- Rheumatic effusion
Pitfalls Of Effusion with Acinar /Clustering Cell Patterns

ACINAR

- Colonic adenocarcinoma
- Cholangiocarcinoma
- Ovarian epithelial neoplasms
- Lung adenocarcinoma
- Pseudomyxoma peritonei
- Mesothelial hyperplasia
- Endometriosis
- Endosalpingiosis

Clustering

- Adenocarcinoma
- Squamous cell carcinoma
- Small cell carcinoma
- Neuroendocrine carcinoma
- Mesothelioma
- Mesothelial hyperplasia
- Pelvic effusion clustering
- Endometriosis
- Endosalpingiosis
• Cells with Degenerative mesothelial vacuoles vs. mucin containing vacuoles
• Most common: degenerative changes in mesothelial cells and non-mucinous malignancies.
• Non-mucinous tumors: serous carcinoma, mesothelioma, squamous cell carcinoma, lymphoma
• Other/Mimics: LE cells in lupus effusions
Sources of Errors & Atypia in Urine Cytology

1. Viral Infection: HPV; Polyoma; Herpes
2. Neobladder & Degenerative Changes
4. Reactive & Reparative Changes, and Necrosis
5. Chemotherapy/Radiotherapy/BCG Tx
6. Contamination: endometrial cells; Seminal Vesicle Cells
7. Cystitis Glandularis
8. Pitfalls of Necrosis
Pitfalls Of CSF

• Normal Specimen
  • Acellular or paucicellular with a few lymphocytes and monocytes.
  • Any other marked cellularity suggests malignancy.
• The danger of false positive diagnoses of malignancy is very great.
Pitfalls Of CSF

• Normal specimen
  – Acellular or paucicellular with a few lymphocytes and monocytes.

• Any other marked cellularity suggests malignancy.

• The danger of false positive diagnoses of malignancy is very great.
Pitfalls Of CSF

• Sources of contamination.
  • Staining options must be considered: DQ & Pap stains.
  • Background renders "foreign" cells: ? malignancy:
  • Ependymal and choroid plexus cells,
  • Peripheral blood components,
  • Fragments of CNS tissue & bone marrow (megakaryocytes)
  • Chondrocytes, skin, muscle, or adipose tissue.
  • Fluids from fracture: bacteria, fungi (*Candida*), or ciliated reparatory cells
  • Ventricular or reservoir samples often contain brain tissue.
  • Talc particles and corpora amalacea may be mistaken for fungi.
  • Primitive (blast-like) cells can be seen in CSF of neonates (hemorrhage or hydrocephalus.
  • Mollaret meningitis (recurrent aseptic meningitis)
Secondary CNS malignancy will have a previous history of cancer or a synchronous manifestation of their neoplasm in some other site.

Occult carcinomas with leptomeningeal manifestations usually originate in the lung or the stomach.

Breast carcinoma commonly involves the CSF, but is clinically apparent prior to meningeal spread in most instances.

Hematopoietic malignancies uncommonly present as occult malignancy.

CSF lymphocytosis may show striking reactive patterns and it may cause false positive diagnoses of lymphoma. Repeat lumbar punctures may not improve the situation, as the procedure itself can give rise to reactive lymphocytes that may resemble leukemic blasts or the cells of malignant lymphoma.
The 1985 Rome Conference on Poor-Prognosis ALL defined extramedullary disease in the CNS at diagnosis as more than 5 leukocytes per micro liter and "morphologically unequivocal blasts from a cytocentrifuged sample." This problem is periodically revisited as our ability to detect very low levels of involvement based on immunostains for cell surface markers and TdT improves. While the significance of some developments is not yet clear, a few patients with low cell counts and rare blasts will experience CNS relapse.
• Special training and experience are required
• Many breast masses are more deeply situated than the fingertips would suggest.
• Masses that are small, mobile, or cystic are common (technical difficulties).
• The yield of FNA declines for lesions <1cm or >4 cm.
• The overall yield of FNA increases with even a fourth or fifth puncture.
Pitfalls Of Breast FNAs

- Cellular alterations due to inflammation or degeneration (mimicker of ca)
- Cellular changes of fibroadenoma, or gynecomastia.
- Male breast ca vs. gynecomastia.
- Papillary lesions vs. mimickers (fibroadenoma, met papillary ca.)
- Proliferative lesions of ductal epithelium;
- Masses with growth of spindle cells
- Problems related to uncommon carcinomas and their mimics.
- Myxoid changes: fibroadenoma vs. mucinous carcinoma.
- Lactational change and false positive.
- Granular cell tumors can mimic carcinoma clinically & radiographically.
- Apocrine carcinoma (contrasted with benign apocrine cells)
- Tubular carcinoma (contrasted with tubular adenoma)
- Metaplastic carcinoma with squamous differentiation vs. metastatic ca.
Uncommon examples of ductal ca with acute inflammation
Lymphocytic infiltration with ductal ca of the usual types
Lymphocytic infiltration with medullary carcinoma
Lymphocytic infiltration when the masses represent LN met.
Lymphocytic infiltrate vs. lymphoma.
FAT necrosis.
Necrosis and regenerative atypia in infarction in fibroadenomas
Necrosis and regenerative atypia in infarction in a papillary lesion
Squamous or apocrine metaplasia in fibroadenomas
Proliferative ductal epithelium with a cribriform architecture
Proliferative ductal epithelium with a micropapillary architecture
Proliferative ductal epithelium with collagenous spherulosis
Necrosis of comedo DCIS,
Pitfalls In Liver FNA

3 main areas:

• Not recognizing lesions with normal liver components
• Misinterpretation of well differentiated hepatocellular carcinoma
• Failure to differentiate poorly differentiated hepatocellular carcinoma from metastatic tumors
REFERENCES

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