Neuropathology After Dark

Intraoperative Diagnosis

Gregory N. Fuller, MD, PhD
Professor and Chief Neuropathologist

M D Anderson Cancer Center
Houston, Texas
gfuller@mdanderson.org
Step 1 – Before you even think about setting foot in Frozen Section...
The 10 Most Common Pitfalls in Surgical Neuropathology
10 Principal Categories of Diagnostic Error

1. Mistaking normal structures for pathological processes
Marinesco Bodies

“paranucleolar bodies”
10 Principal Categories of Diagnostic Error

1. Mistaking normal structures for pathological processes
2. Mistaking non-neoplastic diseases for tumor
Demyelinating Pseudotumor

Irma E. Erana-Rojas, MD, Alvaro Barboza-Quintana, MD, Alberto G. Ayala, MD, and Gregory N. Fuller, MD, PhD

Demyelinating disease presenting as a solitary contrast-enhancing mass poses a diagnostic challenge for both radiologists and surgical pathologists. We report the cases of two female patients, aged 23 and 37 years, who exhibited the clinical and radiologic features of a space-occupying mass strongly suggestive of neoplasia. In both patients, magnetic resonance imaging showed a ring-enhancing parietal lesion. Intraoperative frozen sections in both patients displayed histologic features strongly suggestive of a glial neoplasm, including marked hypercellularity, a prominent astrocytic component, and easily identifiable mitotic figures. However, permanent sections showed additional and helpful histologic findings that included Creutzfeldt astrocytes and granular mitoses. Subsequent immunostaining showed that the hypercellularity was principally caused by macrophage infiltration (HAM-56 and CD68) and an associated reactive astrocytosis (glial fibrillary acidic protein). Additional confirmatory tests included special stains for myelin (Luxol-fast blue), which demonstrated focal, sharply margined loss of myelin, and for axons (silver stain for axons and neurofilament protein immunohistochemistry), which showed relative preservation of axons in areas of myelin loss. Together, the special stains confirmed the demyelinating nature of the lesions. The keys to avoiding misdiagnosing a demyelinating pseudotumor as a diffuse glioma include a general awareness of this potential pitfall, including the radiologic appearance of demyelinating pseudotumors as contrast-enhancing solitary masses that mimic tumor; knowledge of the characteristic histologic features, including Creutzfeldt astrocytes and granular mitoses; and a high index of suspicion for macrophage infiltration combined with a willingness to use appropriate confirmatory immunohistochemical studies in suspicious or uncertain cases. This approach will minimize the chance of misdiagnosis and subsequent use of inappropriate and deleterious therapies.

10 Principal Categories of Diagnostic Error

1. Mistaking normal structures for pathological processes
2. Mistaking non-neoplastic diseases for tumor
3. Mistaking one disease type for another
Looks like Giant Cell Glioblastoma...
Pleomorphic Xanthoastrocytoma (PXA)
10 Principal Categories of Diagnostic Error

1. Mistaking normal structures for pathological processes
2. Mistaking non-neoplastic diseases for tumor
3. Mistaking one disease type for another
4. Unfamiliarity with rare tumor types
10 Principal Categories of Diagnostic Error

1. Mistaking normal structures for pathological processes
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4. Unfamiliarity with rare tumor types
5. Failure to recognize common tumors in uncommon sites
Spinal Cord
Subependymoma
10 Principal Categories of Diagnostic Error

1. Mistaking normal structures for pathological processes
2. Mistaking non-neoplastic diseases for tumor
3. Mistaking one disease type for another
4. Unfamiliarity with rare tumor types
5. Failure to recognize common tumors in uncommon sites
6. Unfamiliarity with recently described tumors
10 Principal Categories of Diagnostic Error

1. Mistaking normal structures for pathological processes
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5. Failure to recognize common tumors in uncommon sites
6. Unfamiliarity with recently described tumors (WHO 2016!)
10 Principal Categories of Diagnostic Error

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4. Unfamiliarity with rare tumor types
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6. Unfamiliarity with recently described tumors
7. Failure to recognize misleading artifacts
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7. Failure to recognize misleading artifacts
8. Failure to recognize an inadequate or non-representative biopsy
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7. Failure to recognize misleading artifacts
8. Failure to recognize an inadequate or non-representative biopsy
9. Failure to perform an appropriate diagnostic procedure/molecular test
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6. Unfamiliarity with recently described tumors
7. Failure to recognize misleading artifacts
8. Failure to recognize an inadequate or non-representative biopsy
9. Failure to perform an appropriate diagnostic procedure/molecular test
10. Failure to formulate an appropriate differential diagnosis secondary to inadequate knowledge of pathology or patient
Disease Morphology

• Must know all of the *entities*

• Must know the *spectrum of morphology* for each entity!
WHO 2016

Over 120 Different Types of Brain Tumor
Disease Morphology

• Must know all of the entities

• Must know the *spectrum of morphology* for each entity!
### Glioblastoma: 18 Phenotypic Patterns

<table>
<thead>
<tr>
<th>Phenotypic Patterns</th>
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</thead>
<tbody>
<tr>
<td>Giant cell</td>
</tr>
<tr>
<td>Small cell</td>
</tr>
<tr>
<td>Spindle cell</td>
</tr>
<tr>
<td>Bland cell</td>
</tr>
<tr>
<td>Granular cell</td>
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<tr>
<td>Signet-Ring cell</td>
</tr>
<tr>
<td>Rhabdoid</td>
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<tr>
<td>Adenoid</td>
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<tr>
<td>Epithelioid</td>
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<tr>
<td>Myxoid</td>
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<tr>
<td>Inflammatory</td>
</tr>
<tr>
<td>Lipid-Rich</td>
</tr>
<tr>
<td>Macrophage-Rich</td>
</tr>
<tr>
<td>GBM w/ Sarcoma-like Foci</td>
</tr>
<tr>
<td>GBM w/ Ependymoma-like Foci</td>
</tr>
<tr>
<td>GBM w/ Oligo-like Foci</td>
</tr>
<tr>
<td>GBM w/ Advanced neuronal</td>
</tr>
<tr>
<td>differentiation</td>
</tr>
<tr>
<td>GBM w/ Neuronal phenotype</td>
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</tbody>
</table>

GN Fuller, Houston Neuropathology Review, 2018
Foundation

Normal Morphology

Disease Morphology

Clinical Information

Molecular Signature
Clinical Information is Critical!

Age
Location
Imaging Features
Relevant Clinical History
Current Clinical Presentation
Clinical Information is Critical!

Age
Location
Imaging Features
Relevant Clinical History
Current Clinical Presentation
Clinical Information is Critical!

Contrast-Enhancing Mass

Age

7yo

65yo
Clinical Information is Critical!

Contrast-Enhancing Mass

Age

7yo   Pilocytic, Medullobl
65yo  Met, GBM, PCNSL
Clinical Information is Critical!

- Age
- Location
- Imaging Features
- Relevant Clinical History
- Current Clinical Presentation
Clinical Information is Critical!

Location

- Intraventricular
- Lumbar cistern
- Cerebello-pontine angle
- Dura-based
Clinical Information is Critical!

- Age
- Location
- Imaging Features
- Relevant Clinical History
- Current Clinical Presentation
Clinical Information is Critical!

Age
Location
Imaging Features
Relevant Clinical History
Current Clinical Presentation
Relevant Clinical History

- Previous surgery and/or XRT?
- Known systemic malignancy or other systemic disease?
- Brain tumor predisposition syndrome?
10 Brain Tumor Predisposition Syndromes

- NF Type 1 (NF1)
- NF Type 2 (NF2)
- Schwannomatosis ("NF3")
- Von Hippel-Lindau
- Tuberous sclerosis
- Li-Fraumeni
- Cowden
- Turcot
- Naevoid basal cell carcinoma syndrome
- Rhabdoid tumor predisposition syndrome
Foundation
Normal Morphology
Disease Morphology
Clinical Information
Molecular Signature
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Molecular Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse Glioma</td>
<td>IDH Mutation</td>
</tr>
<tr>
<td>Oligodendrogli.</td>
<td>1p/19q Codeletion</td>
</tr>
<tr>
<td>Pilocytic Astr</td>
<td>KIAA 1549-BRAF</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>WNT/SHH/Non-A/B</td>
</tr>
<tr>
<td>AT/RT</td>
<td>INI-1/ BRG1 Mut/Del</td>
</tr>
<tr>
<td>RFGNT</td>
<td>PIK3CA Mutation</td>
</tr>
<tr>
<td>SFT / HPC</td>
<td>NAB2-STAT6 Fusion</td>
</tr>
</tbody>
</table>
BRAF V600E MUTATION

Papillary Craniopharyngioma 100%
Pleomorphic xanthoastrocytoma 66%
Ganglioglioma 40-60%
Epithelioid glioblastoma 50%
Extra-Cerebellar Pilocytic Astrocytoma 33%
Dysembryoplastic neuroepithelial tumor 30%
Cerebellar Pilocytic Astrocytoma 2%
Diffuse Gliomas 2%

(KIAA1549:BRAF FUSION in Pilocytic astrocytoma: 70%)
IOC for CNS Biopsies

Step 2

In the heat of battle – survival tools
“Intraoperative Consultation (IOC) for a brain biopsy is among the most stressful situations that a surgical pathologist will encounter.”
IOC

Principles
PRE-IOC Preparation
PRE-IOC Preparation

- **AGE** of the patient
PRE-IOC Preparation

- **AGE** of the patient
- **ANATOMIC LOCATION** of the lesion
PRE-IOC Preparation

• **AGE** of the patient

• **ANATOMIC LOCATION** of the lesion

• **IMAGING** characteristics of the lesion
PRE-IOC Preparation

• AGE of the patient
• ANATOMIC LOCATION of the lesion
• IMAGING characteristics of the lesion
• PAST MEDICAL HISTORY of the patient
PRE-IOC Preparation

• AGE of the patient

• ANATOMIC LOCATION of the lesion

• IMAGING characteristics of the lesion

• PAST MEDICAL HISTORY of the patient

• TYPE and DURATION of presenting signs & symptoms
PRE-IOC Preparation

• **AGE** of the patient

• **ANATOMIC LOCATION** of the lesion

• **IMAGING** characteristics of the lesion

• **PAST MEDICAL HISTORY** of the patient

• **TYPE** and **DURATION** of presenting signs & symptoms

• **WHAT TYPE of SURGICAL PROCEDURE?**
PRE-IOC Preparation

- **AGE** of the patient
- **ANATOMIC LOCATION** of the lesion
- **IMAGING** characteristics of the lesion
- **PAST MEDICAL HISTORY** of the patient
- **TYPE** and **DURATION** of presenting signs & symptoms
- **WHAT TYPE** of **SURGICAL PROCEDURE**?
- **WHAT WILL THE SURGEON NEED TO KNOW?**
PRE-IOC PRINCIPLES

• Know what the surgeon needs to know about the lesion intraoperatively!
PRE-IOC PRINCIPLES

• Well, what, *exactly*, does the surgeon need to know intraoperatively?
PRE-IOC PRINCIPLES

• The surgeon needs to know the critical pieces of information required to successfully complete the operation.
PRE-IOC PRINCIPLES

• The surgeon needs to know the critical pieces of information required to successfully complete the operation. The information supplied by the surgical pathologist will determine the subsequent course of the operation.
PRE-IOC PRINCIPLES

A few valid indications for IOC
PRE-IOC PRINCIPLES

A few valid indications for IOC

• Is adequate, representative tissue present?
A few valid indications for IOC

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• Is the disease an infectious process?
PRE-IOC PRINCIPLES

A few valid indications for IOC

• Is adequate, representative tissue present?
• Is the disease an infectious process?
• If tumor, is it of a type amenable to gross total surgical resection
PRE-IOC PRINCIPLES

A few valid indications for IOC

• Is adequate, representative tissue present?
• Is the disease an infectious process?
• If tumor, is it of a type amenable to gross total surgical resection
• Is viable GBM present? (if so, Gliadel wafer, Gliacyte balloon, laser thermal ablation, adenoviral therapy, or other intraoperative treatment can proceed)
PRE-IOC PRINCIPLES

- Know what the surgeon **DOES NOT** need to know about the lesion intraoperatively!
PRE-IOC PRINCIPLES

• Know what the surgeon **DOES NOT** need to know about the lesion intraoperatively!

  Important example: the *specific type* of diffuse glioma (astro vs oligo)
What is your frozen section diagnosis?
Astrocytoma
Oligodendroglioma
Mixed Oligoastrocytoma
FREEZING DISTORTS OLIGO NUCLEI AND MAKES THEM APPEAR MORE PLEOMORPHIC AND THUS ASTROCYTOMA-LIKE

THE CHARACTERISTIC CYTOPLASMIC CLEARING (PERINUCLEAR “HALOS”, “FRIED EGG”) IS ONLY SEEN IN FFPE TISSUE, NOT IN FROZEN SECTIONS
What is the most appropriate frozen section diagnosis?
“Diffuse glioma”
PRE-IOC PRINCIPLES

• Cytology and Architecture are Complementary – Use Both!
• Don’t freeze all of the tissue if possible
• Know what the surgeon needs to know about the lesion intraoperatively!
• Plan for tomorrow!
PRE-IOC PRINCIPLES

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PRE-IOC PRINCIPLES

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For very small biopsies (e.g., stereotactic bx), ensure adequate specimen for IHC:
PRE-IOC PRINCIPLES

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For very small biopsies (e.g., stereotactic bx), ensure adequate specimen for IHC:

  unstained touch preps
PRE-IOC PRINCIPLES

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For very small biopsies (e.g., stereotactic bx), ensure adequate specimen for IHC:

  unstained touch preps

  unstained sections cut from FS block
PRE-IOC PRINCIPLES

• Plan for tomorrow!

For very small biopsies (e.g., stereotactic bx), ensure adequate specimen for IHC:

- unstained touch preps
- unstained sections cut from FS block
- order unstained from paraffin block ("biopsy processing")
• Pre-IOC

• Intra-IOC
RULE #1

Perform a cytologic prep as a complement to the frozen tissue section!
Cytologic Prep Techniques

- Touch (Imprint)
- Smear (Squash, Crush)
- Scrape
- Drag
<table>
<thead>
<tr>
<th>Technique</th>
<th>Tissue Consistency</th>
<th>Representative Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Touch</td>
<td>Soft and discohesive</td>
<td>Pituitary adenoma</td>
</tr>
<tr>
<td>Smear</td>
<td>Soft</td>
<td>Gliomas, Most Brain Tumors</td>
</tr>
<tr>
<td>Scrape</td>
<td>Dense fibrous tissue</td>
<td>Dural and Paraspinal Metastases</td>
</tr>
<tr>
<td>Drag</td>
<td>Necrotic</td>
<td>Necrotic metastasis, Stereotactic radiosurgery site resection</td>
</tr>
</tbody>
</table>
INTRA-IOC

Specific Problems

Matte
INTRA-IOC ISSUES

• Specimen is non-representative
INTRA-IOC ISSUES

• Specimen is non-representative

How do you know?
INTRA-IOC ISSUES

Pre-Operative Imaging Studies!
(Critical)
INTRA-IOC ISSUES

• Specimen is very small
  (endoscopic bx or fragmented stereotactic bx)
INTRA-IOC ISSUES

• Specimen is very small
  (endoscopic bx or fragmented stereotactic bx)

Perform a cytologic preparation
(imprint or drag prep) before freezing the tissue fragment
Stereotactic Biopsy Grossing
Stereotactic Biopsy Grossing
INTRA-IOC ISSUES

• Specimen is *seriously* small!
INTRA-IOC ISSUES

• Specimen is *seriously* small!

So tiny, or of a consistency (e.g., gelatinous, myxoid) such that there is concern that it will not survive processing, or that the histotech will not be able to find the specimen in the tissue paper, potentially resulting in a final Dx of “Tissue Lost in Processing”!
INTRA-IOC ISSUES

• Specimen is *seriously* small!

*Options:*
INTRA-IOC ISSUES

• Specimen is seriously small!

Options:

• Make it someone else’s problem…
Options:
• *Make it someone else’s problem*…

A. Kevin Raymond, MD
INTRA-IOC ISSUES

• Specimen is *seriously* small!

*Options:*

• *Submit to Cytology Lab for cytospin*
INTRA-IOC ISSUES

• Specimen is *seriously* small!

**Options:**

• Submit to Cytology Lab for cytospin
• Smear entire specimen
INTRA-IOC ISSUES

• Specimen is severely cauterized
INTRA-IOC ISSUES

• Specimen is severely cauterized

_Bisect specimen and perform cytologic drag prep using freshly cut surface before freezing_
INTRA-IOC ISSUES

• Specimen is extensively necrotic
INTRA-IOC ISSUES

• Specimen is extensively necrotic

Perform cytologic drag preps on multiple tissue fragments on the same slide to maximize sampling and detection of any viable cells
INTRA-IOC ISSUES

• Specimen is extensively bony
INTRA-IOC ISSUES

• Specimen is extensively bony

Perform a cytologic drag prep
INTRA-IOC ISSUES

• Specimen is extensively bony

Perform a cytologic drag prep

Immerse in saline, shake vigorously, cytospin
**INTRA-IOC ISSUES**

- Specimen is densely fibrous
INTRA-IOC ISSUES

• Specimen is densely fibrous

*Perform a cytologic scrape prep before freezing*
Summary

What are the things that will help you the most at frozen section for a brain tumor?
Summary

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1. Know the patient’s history
Summary

What are the things that will help you the most at frozen section for a brain tumor?

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2. Look at the preop imaging studies and read the reports
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3. Know the procedure type & why it is being performed
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1. Know the patient’s history
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4. Know what the surgeon will need to know intraoperatively
Summary

What are the things that will help you the most at frozen section for a brain tumor?

1. Know the patient’s history

2. Look at the preop imaging studies and read the reports

3. Know the procedure type & why it is being performed

4. Know what the surgeon will need to know intraoperatively

5. Make a cytologic touch/smear/drag/scrape preparation(s)
End of Intraop Consultation!

Questions?