Intraoperative CNS Cytology by Pattern Recognition

Matthew A. Zarka, M.D.
Mayo Clinic Arizona
Scottsdale, Arizona

Presentation Bullet Points

• Definition of Practical Pattern Based Approach to Intraoperative CNS Cytology
• Method of CNS Squash Preparation
• Advantages and Limitations of Cytologic Smear Preparation
• The Importance of Clinical History
• Practical Architectural Pattern Approach to CNS Smear Cytology:
  – Basic Principles

A. Definition of Practical Pattern Based Approach to Intraoperative CNS Cytology

A consistent approach to rapid CNS smear diagnosis is to categorize lesions that exhibit a one or more cytologic architectural patterns first at low to intermediate magnification (40x, 100x, 200x), and then confirm ones impression of a lesion at high magnification (400x-600x). I term this the practical pattern recognition approach to cytologic smear diagnosis. These patterns do not necessarily rely on the presence of a specific cell type, for instance, astrocytes in a case of an astrocytoma. For example, a cytologic pattern may include a specific type of architectural structure that the tumor cells and associated stromal cells or blood vessels exhibit, such as a
papillary structure. Another pattern may encompass the interrelationship that clusters of neoplastic cells have with surrounding blood vessels, stromal tissue, extracellular matrix, or inflammatory cells. This approach first emphasizes grouping pathologic processes with an element or elements that they have in common with one another, and then subdividing these processes into their respective diagnostic categories based upon their unique cellular characteristics. This diagnostic approach is intuitive to many experienced cytopathologists, however, it is all too easy to rush to high power magnification when examining a case, carrying the risk of “missing the forest for the trees”.

B. Method of CNS Squash Preparation

Preparation of a squash preparation is simple. I prefer to prepare a smear slide by taking a small piece of tissue with a scalpel blade (less than 0.5 mm in diameter), placing the material on a slide, and subsequently smearing the specimen with another slide, holding the second slide at right angles to the first, and applying uniform pressure during smearing, similar to smearing a routine FNA specimen. If a stereotactic core biopsy is submitted, I will often remove a small piece of tissue from opposite ends of the core biopsy specimen and place both fragments of the same slide and subsequently and smear both pieces, in order to better evaluate the representative material that is present within that specific core specimen. The smear is immediately fixed in alcohol and stained with hematoxylin and eosin. Additional slides can be air dried and stained with a Wright stain. The most common artifacts include crush and air drying with loss of cytologic detail. It is important not to smear too large a specimen, which may yield a slide too thick for optimal cytologic detail. Recognition of the fine fibrillary processes that often are associated with glial tumors is dependent on a thin specimen.
C. Advantages and Limitations of Cytologic Smear Preparation

Cytologic Smears: Advantages

- Speed
- Ease of preparation
- Simplicity
- Cytologic preservation
- Small sample size

Cytologic Smears: Limitations

- Relies on tissue soft enough to smear
- Histologic architecture not apparent
- Relies on accurate localization by the surgeon

D. The Importance of Clinical History

When examining an intraoperative CNS case, it is essential to know the age of the patient and the location of the lesion in question before the specimen arrives in the frozen section suite. Other useful information includes the type and duration of clinical symptoms. For example, a history of seizures is more in keeping with a slower growing lesion such as a low grade astrocytoma, as compared to a rapid growing lesion such as a glioblastoma.
## Relative Frequency of Intracranial Tumors

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>&lt;3</th>
<th>3-15</th>
<th>15-65</th>
<th>&gt;65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulloblastoma</td>
<td>Pilocytic astrocytoma</td>
<td>Glioblastoma</td>
<td>Metastatic carcinoma</td>
<td></td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>Medulloblastoma</td>
<td>Anaplastic astrocytoma</td>
<td>Glioblastoma</td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Ependymoma</td>
<td>Astrocytoma</td>
<td>Anaplastic astrocytoma</td>
<td></td>
</tr>
<tr>
<td>Choroid plexus tumor</td>
<td>Astrocytoma</td>
<td>Meningioma</td>
<td>Meningioma</td>
<td></td>
</tr>
<tr>
<td>Teratoma</td>
<td>Choroid plexus tumors</td>
<td>Pituitary tumors</td>
<td>Acoustic schwannoma</td>
<td></td>
</tr>
</tbody>
</table>

## Distribution of Intracranial Lesions: Intraparenchymal

Intraparenchymal Supratentorial  
- Astrocytoma, anaplastic  
- astrocytoma, glioblastoma  
- oligodendroglioma  
- ependymoma

Intraparenchymal Infratentorial  
- cerebellar astrocytoma  
- medulloblastoma  
- ependymoma  
- hemangioblastoma
- metastatic neoplasms
- lymphoma
- inflammatory lesions
- vascular disorders

**Distribution of Intracranial Lesions: Extraparenchymal**

<table>
<thead>
<tr>
<th>Extraparenchymal Supratentorial</th>
<th>Extraparenchymal Infratentorial</th>
</tr>
</thead>
<tbody>
<tr>
<td>- meningioma</td>
<td>- schwannoma</td>
</tr>
<tr>
<td>- metastatic neoplasms</td>
<td>- meningioma</td>
</tr>
<tr>
<td>- epidermoid/dermoid cysts</td>
<td>- metastatic neoplasms</td>
</tr>
<tr>
<td></td>
<td>- glomus jugulare tumor</td>
</tr>
</tbody>
</table>

E. **Practical Architectural Pattern Approach to CNS Smear Cytology:**

- **Basic Principles**

When evaluating a lesion on a cytologic smear, pay particular attention to the following:

- Relationship of Neoplastic Cells to Blood Vessels
- Blood Vessel Type
- Type of Background (felt-like vs., fibrillary)

1. **Tumor distribution in relation to blood vessels**

- Gliomas: especially astrocytomas, usually demonstrate aggregation of tumor cells close to blood vessels; the concentration of tumor cells decreases the farther away the tumor cells are from a blood vessel: *Perivascular Gradient Pattern*
- Lymphoma: can infiltrate blood vessel walls but are often dispersed in a discohesive fashion away from blood vessels also: *Angiocentric and Diffuse Pattern*

- Metastatic carcinoma: clusters of malignant cells are distributed close to and away from blood vessels; variable with tumor type: *Randomized Clusters With and Without Vascular Affinity*

---

Perivascular Gradient Pattern

- Example: Anaplastic Astrocytoma

---

Angiocentric and Diffuse Pattern

- Example: Large Cell Lymphoma
Randomized Clusters With or Without Vascular Affinity

- Example: Metastatic Colonic Adenocarcinoma

2. Blood vessel type

- Thin walled blood vessels
  - Oligodendroglioma; Grade 2 and Grade 3 Astrocytomas
  - Metastatic Carcinoma
  - Lymphoma
  - Gliosis

- Vessels with endothelial cell proliferation
  - Glioblastoma
  - Metastatic Carcinoma
  - Lymphoma

Thin Walled Vessels
- Example: Ependymoma

- Example: Glioblastoma

---

3. The importance of presence or absence of fibrillary matrix.

- Normal brain matter is characterized by a felt like background.

- Astrocytomas: usually demonstrate the presence of fine, well defined glial processes in the background (fibrillary background)
  - Better seen without the microscope condenser
  - Oligodendrogliomas may have more of a pool table felt background
  - Gliosis may show a fibrillary background

- Metastatic carcinoma: fibrillary background generally absent; often a felt pattern
  - Watch for gliosis

- Lymphoma: fibrillary background generally absent; often a felt pattern
  - Watch for gliosis
Felt Pattern

- Example: Normal White Matter

Fibrillary Pattern

- Example: Astrocytoma

Summary: Pattern Based Approach to CNS Intraoperative Smear Preparations

I. Evaluate the Slide at Low-Intermediate Magnification (40-200x)

- What Is The Relationship of Neoplastic Cells to Blood Vessels?
- What Type of Blood Vessels Are There?
- What Type of Background: Fibrillary Versus Felt-Like?

II. Evaluate the Slide at High Magnification (400-600x)

- Look for cytologic features to confirm your low magnification impression
Intraoperative CNS Cytology by Pattern Recognition
Matthew A. Zarka M.D.
Mayo Clinic Arizona
Scottsdale, Arizona
Case 1

This is a 68 year old male with a history of a right nephrectomy for renal cell carcinoma 10 years ago, and seed implantation for prostate cancer 5 years ago. One month prior to admission, he began to have symptoms of confusion, slight unsteadiness with his posture, and headaches. CT scan shows a large peripheral enhancing mass in the right posterior temporal and parietal lobe, 5 cm in diameter, with adjacent vasogenic edema and mass effect.
## Relative frequency of intracranial tumors by age (yrs)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cancer Type</th>
<th>Age Group</th>
<th>Cancer Type</th>
<th>Age Group</th>
<th>Cancer Type</th>
<th>Age Group</th>
<th>Cancer Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3</td>
<td>Medulloblastoma</td>
<td>3-15</td>
<td>Pilocytic astrocytoma</td>
<td>15-65</td>
<td>Glioblastoma</td>
<td>&gt;65</td>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>3-15</td>
<td>Pilocytic astrocytoma</td>
<td></td>
<td>Medulloblastoma</td>
<td></td>
<td>Anaplastic astrocytoma</td>
<td></td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>15-65</td>
<td>Ependymoma</td>
<td></td>
<td>Ependymoma</td>
<td></td>
<td>Astrocytoma</td>
<td></td>
<td>Anaplastic astrocytoma</td>
</tr>
<tr>
<td></td>
<td>Choroid plexus tumor</td>
<td></td>
<td>Astrocytoma</td>
<td></td>
<td>Meningioma</td>
<td></td>
<td>Meningioma</td>
</tr>
<tr>
<td></td>
<td>Teratoma</td>
<td></td>
<td>Choroid plexus tumors</td>
<td></td>
<td>Pituitary tumors</td>
<td></td>
<td>Acoustic schwannoma</td>
</tr>
</tbody>
</table>
Distribution of intracranial lesions

- **Intraparenchymal - supratentorial**
  - Astrocytoma
  - Anaplastic astrocytoma
  - Glioblastoma
  - Oligodendroglioma
  - Ependymoma
  - Metastatic neoplasms
  - Lymphoma
  - Inflammatory lesions
  - Vascular disorders

- **Intraparenchymal - infratentorial**
  - Cerebellar astrocytoma
  - Medulloblastoma
  - Ependymoma
  - Hemangioblastoma
  - Metastatic neoplasms
  - Lymphoma
  - Inflammatory lesions
  - Vascular disorders
DDX: Small Blue Cell Tumor

- Glioblastoma/Anaplastic Astrocytoma: small cell variant
- Neuroblastoma
- Metastatic small cell carcinoma
- Pineoblastoma
- Pituitary adenoma
- Oligodendroglioma
- Lymphoma
- Central neurocytoma
Tumor distribution in relation to blood vessels

- **Gliomas**: especially astrocytomas, usually demonstrate aggregation of tumor cells close to blood vessels
- **Lymphoma**: can infiltrate blood vessel walls but are often dispersed away from blood vessels also
- **Metastatic carcinoma**: clusters of malignant cells are distributed close to and away from blood vessels; variable with tumor type
Anaplastic Astrocytoma

Large Cell Lymphoma

Metastatic Colonic Adenocarcinoma

Perivascular gradient

Angiocentric and Diffuse

Randomized Clusters +/- Vascular Affinity
Blood vessel type

• Thin walled blood vessels
  – Oligodendroglioma; Grade 2 and Grade 3 Astrocytomas
  – Metastatic Carcinoma
  – Lymphoma
  – Gliosis

• Vessels with endothelial cell proliferation
  – Glioblastoma
  – Metastatic Carcinoma
  – Lymphoma
Thin Walled Vessels

Ependymoma

Glioblastoma

Endothelial Cell Proliferation
CNS: The importance of presence or absence of fibrillary matrix

- Astrocytomas: usually demonstrate the presence of fine, well defined glial processes in the background
  - Better seen without the microscope condenser
  - Oligodendrogliomas may have more of a pool table felt background
  - Gliosis may show a fibrillary background
- Metastatic carcinoma: fibrillary background generally absent
  - Watch for gliosis
- Lymphoma: fibrillary background generally absent
  - Watch for gliosis
Normal White Matter

Astrocytoma

Felt Pattern

Fibrillary Pattern
Randomized Clusters with Vascular Affinity

Vessels With Endothelial Proliferation Felt Pattern

Metastatic Small Cell Carcinoma
Case 2

This is a 68 year old male with a history of mycosis fungoides who states over the last two and to three weeks he and his wife have noticed significant memory loss.

An MRI at time of admission demonstrates diffuse enhancement in the subependymal tissue of the body of lateral ventricles and in the splenium along the temporal horn. There is also a small amount of enhancement in the Virchow-Robin spaces of the left occipital and parietal lobes. The radiographic findings are consistent with CNS lymphoma.
Pattern Based Approach to Diagnosis

- Relationship of Neoplastic Cells to Blood Vessels
- Blood Vessel Type
- Type of Background
Glioblastoma, Small Cell Variant
Glioblastoma, Small Cell Variant
Summary: Pattern Based Approach To CNS Intraoperative Smear Preparations

- Evaluate The Slide At Low-Intermediate Power
  - What Is The Relationship of Neoplastic Cells to Blood Vessels?
  - What Type of Blood Vessels Are There?
  - What Type of Background: Fibrillar Versus Felt-Like?

Evaluate The Slide At High Power