Inflammatory and Infectious Diseases of the CNS

Christian Davidson, MD
Division of Neuropathology
Department of Pathology
University of Utah
Objectives

• Understand the history, imaging, and classic histopathology of demyelinating diseases
  • Multiple Sclerosis
  • Progressive Multifocal Leukoencephalopathy

• Understand the usual clinical history and basic histopathologic work-up of CNS infections:
  • Bacterial
  • Fungal
  • Parasitic CNS infections
Myelin Pathologies

Demyelinating
- Immune-mediated destruction of biochemically normal myelin
- Multiple sclerosis, PML, acute disseminated encephalomyelitis

Dysmyelinating (leukodystrophies)
- Inherited destruction of chemically (i.e. genetically) abnormal myelin
- May involve both central and peripheral myelin
- Metachromatic leukodystrophy, globoid cell leukodystrophy, adrenoleukodystrophy

Hypomyelinating
- Paucity of biochemically normal myelin deposition during development
- Alexander’s disease, vanishing white matter disease

Myelinolytic
- Intramyelinic edema of biochemically normal myelin
- Central pontine myelinolysis, vitamin B12 deficiency, toxins
Multiple Sclerosis

- Inflammatory, sporadic destruction of biochemically normal myelin by the immune system

- Clinical history:
  - Young women, often with vision problems
  - Neurologic symptoms related to the location of the lesion
  - Typically NOT diagnosed histologically
    - Two lesions separated in time and space (and typically, symptoms)
    - CSF Protein Electrophoresis shows oligoclonal bands

From “multiple-sclerosis-research.org”
MS- MRI (classic)
“Dawson’s Fingers”

From “mayoclinic.org/diseases-conditions/multiple-sclerosis/multimedia/multiple-sclerosis-mri-scan”
MS- MRI (mimicking tumor)

Multiple Sclerosis

- **Cellular components:**
- Reactive astrocytes
- Lymphocytes
  - Predominantly T-cells
  - Often perivascular
- Foamy macrophages
Reactive astrocytes

Smear: Abundant eosinophilic cytoplasm, numerous processes

Sentinels/squiddies, from ‘The Matrix’
Reactive astrocytes

Frozen: eosinophilic cytoplasm, evenly spread out
Astrocytes: Reactive vs neoplastic

Reactive

Grade III Astrocytoma
Astrocytes: Reactive vs neoplastic

Reactive astrocytes

Astrocytoma

GFAP Immunohistochemistry
Demyelination

Perivascular lymphocytes

Foamy macrophages
Demyelination Suspected on FS: What to report...

- “Inflammatory lesion present, macrophages and lymphocytes suggest demyelination; recommend flow cytometry AND broad microbial cultures”

- NOT....
  - “Demyelination, c/w multiple sclerosis”
  - “Favor MS”
Demyelination:
Work-up of permanent sections......
MS Plaques
B/L foci of MCP demyelination
Macrophages (highlighted by CD163 IHC)

T-cells (highlighted by CD3 IHC)
Loss of myelin (LFB)

Sparing of axons (Neurofilament IHC stain for axons)
Immunocompromised states

- HIV/AIDS
- Iatrogenic
  - Steroids
  - Antibodies (anti-TNF-\(\alpha\) or anti-\(\alpha_4\) integrin)
  - Transplant
  - Chemotherapy
- Marrow suppressive disease
  - Leukemia
  - MDS
  - Aplastic anemia
- Congenital
  - CVID
- Others

ALWAYS CULTURE!!!!
Progressive Multifocal Leukoencephalopathy (PML)

• First suggested to be an opportunistic infection by EP Richardson in 1961
• Caused by JC virus
• Polyomavirus (others are SV40 and BK)
  • dsDNA virus
  • Binds to sialic acid residues on the cell surface
• 75-80% of all adults infected (serology)
• Usually diagnosed clinically
• Symptoms:
  • mild change in mental status, progressing to encephalopathic symptoms
• Histo: foamy macrophages and bizarre oligodendroglial cells
PML: Imaging

• FLAIR shows
  • Sharp border beneath the subcortical U-fibers (arrow)
  • Hazy, ill-defined medial border (dashed arrow)

PML
Histology

Normal White Matter

PML
PML
Histology- mitoses
PML
Histology

Reactive astrocytes

Macrophages

GFAP

CD163
PML
Histology
# Bacterial/Fungal Infections

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Organisms</th>
<th>Clinical History</th>
<th>Work-up</th>
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</table>
| **Bacteria**      | **Meningitis** | **Neonates:** Group B Strep, E. coli, Streptococcus pneumoniae  
**Pediatric:** *Strep. pneumo, N meningitides, H. influenza*  
**Adult:** all the above + *Listeria monocytogenes* and Gram-negative bacilli  
**Immunocompromised:** *Strep. pneumo, Mycobacteria* | Fever, photophobia, stiff/painful neck | Gram, GMS, PAS-Fungus, AFB |
| **Abscess**       | **Staphylococcus aureus**  
**Streptococcus viridans**  
**Bacterioides** sp. | Neurologic symptoms dependent on location | Gram, GMS, PAS-Fungus, AFB |
| **Fungus**        | **Meningitis** | **Cryptococcus** (immunocompromised),  
*Coccidioides, Blastomyces* | Fever, photophobia, stiff/painful neck | Gram, GMS, PAS-Fungus, AFB |
| **Abscess**       | **Cryptococcus** (immunocompetent),  
*Aspergillus, Mucor* | Neurologic symptoms dependent on location | Gram, GMS, PAS-Fungus, AFB |
Mycobacterium tuberculosis

- Microscopy shows **giant-cell granulomatous inflammation with caseating necrosis**

- Other findings:
  - Inflammation can lead to fibrinoid necrosis in veins and arteries
  - Endarteritis obliterans

- Fungi That Can Be Associated with Necrotizing Granulomas
  - Cryptococcus
  - Blastomyces
  - Coccidioides
  - Aspergillus
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<td>Toxoplasmosis</td>
<td><em>Toxoplasma gondii</em></td>
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Toxoplasmosis

Abundant necrosis

Bradyzoite

Tachyzoites

Toxo IHC
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Cysticercosis

Scolex with hooks and suckers (arrow)

Outer surface = wavy eosinophilic lamina
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Amoebiasis

Perivascular *Acanthamoeba*

*Acanthamoeba* cysts

*Balamuthia mandrillaris*

*Naegleria fowleri*

- Amoeba can mimic macrophages.
- Note the small nucleus with large **karyosome**.
- *Balamuthia* karyosomes are less prominent.

From ResearchGate

From med-chem.com
Leukocyte-rich lesions
‘Day-of-frozen-section’ special requests

• Lymphocytic Infiltrate?
  • Flow cytometry

• All inflammatory lesions
  • Broad microbial cultures (aerobe, anaerobe, fungal, AFB)
Thank you!

Please contact me at
christian.davidson@path.utah.edu
with any questions.