Inflammatory disease of the Meninges in Surgical Neuropathology

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Disclosures

• I have no relevant financial relationships to disclose
Learning Objectives

• Describe the basic structure of the meninges and the nomenclature of the pathological processes occurring in the meninges
• Identify common inflammatory conditions which can be encountered in surgical meningeal biopsies
• List criteria supportive and against the diagnosis of meningeal IgG4-related disease
Outline

• Focused discussion of meningeal pathological processes
  • From a Surgical Pathology point of view
  • “meningeal enhancement”
• Inflammatory Meningeal Diseases:
  • IgG4-related disease Infectious
  • Other inflammatory disorders (including sarcoid, granulomatosis with polyangiitis, rheumatoid arthritis)
  • Infectious diseases
Meningeal Disease

- Pachymeninges (“thick”) = dura mater
- Leptomeninges (“thin”) = arachnoid & pia mater
Dura

Outer

Inner

Arachnoid

Cap cells

Pia
# Meningeal Inflammatory/Infectious Diseases

<table>
<thead>
<tr>
<th>Agent</th>
<th>Site</th>
<th>Type</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>Epidural Space</td>
<td>Acute</td>
<td>Epidural Abscess</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Subdural Space</td>
<td>Subacute</td>
<td>Subdural Empyema</td>
</tr>
<tr>
<td>Parasitic (Protozoan)</td>
<td>Meninges</td>
<td>Chronic</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Fungal</td>
<td>• Pia &amp; Arachnoid</td>
<td></td>
<td>• Leptomeningitis</td>
</tr>
<tr>
<td></td>
<td>• Dura</td>
<td></td>
<td>• Pachymeningitis</td>
</tr>
</tbody>
</table>

## Type
- Acute
- Subacute
- Chronic

## Diagnosis
- Epidural Abscess
- Subdural Empyema
- Meningitis
- Leptomeningitis
- Pachymeningitis
“Hypertrophic meningitis” refers to the robust thickening of the meninges, diffuse or nodular.
Case Presentation

- 52-year-old man with a 24-mo history:
  - “C5 fracture” after a fall
  - Developed neck pain, which became severe & persistent (6 mo)
  - Developed tingling involving right and left hand - primarily 4th and 5th finger of each hand (3 mo)
  - Developed difficulty opening bottles with his hands (6 mo)
  - Developed leg weakness and gait deterioration (4 mo)
Before you receive the biopsy – Differential diagnosis

- Infection (bacterial, fungal, other)
- Sarcoid
- IgG4 related disease
- Rheumatoid arthritis
- Lymphoma/leukemia
- Drop or hematogenous metastasis
- Primary diffuse meningeal gliomatosis
- Primary diffuse meningeal melanocytic tumor
- Meningeal enhancement related to CSF hypotension
- Idiopathic pachymeningitis
IgG4 (>50/HPF)

IgG (IgG/IgG4 ratio at least 50%)
Diagnosis

Chronic lymphoplasmacytic inflammation with storiform fibrosis and increased IgG4, consistent with IgG4 related disease
Meningeal IgG4-Related Disease

• Most commonly involves pachymeninges
• Intracranial > spinal
• May involve meninges alone or together with:
  – Adjacent orbital, sinus and brain structures, including pituitary stalk/gland
  – Other organs throughout the body
• Elevated serum IgG4, highly sensitive, specificity around 60%
  – False negative frequent in cases without systemic involvement

Age Distribution by Decade

N=34, 21M - 13F

Semin Neurol 2014;34:395-404
Meningeal IgG4-RD Pathogenesis

• Fibrosis results from a non-specific fibroblast activation caused by aberrant immune response to a “still unknown antigen”

• Likely a complex immune response behind IgG4 production, IL-10 mediated, diverting a “classical T-helper type 2 (Th2) response” in favor of IgG4

• IgG4 excess concentration could be regarded as a counter-regulatory mechanism to dampen inflammation rather than the primary driver
Meningeal IgG4-Related Disease: Diagnostic Histologic Criteria

• Major histologic features associated with IgG4 related disease include:
  • Dense lymphoplasmacytic infiltrate
  • Fibrosis, arranged at least focally in a storiform pattern
  • Obliterative phlebitis
• Increased number of IgG4 + plasma cells (> 10 per HPF)
• Ratio of IgG4+/IgG+ plasma cells >40%
• Combination of at least 2 of the major histologic features with IHC cutoffs for plasma cells are diagnostic of IgG4-related disease

Mod Pathol. 2012 Sep;25(9):1181-92
IgG4-related autoimmune pancreatitis

Fibrosis arranged at least focally in a storiform pattern
Dense lymphoplasmacytic infiltrate
Obliterative phlebitis
# Variability of histopathology of IgG4-related disease

<table>
<thead>
<tr>
<th></th>
<th>Inflammation</th>
<th>Fibrosis</th>
<th>Phlebitis</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lacrimal gland</strong></td>
<td>No unique features</td>
<td>Typical storiform fibrosis is relatively uncommon. More often collagenous fibrosis</td>
<td>Sometimes lacks obliterative phlebitis</td>
<td></td>
</tr>
<tr>
<td><strong>Salivary gland</strong></td>
<td>Often associated with conspicuous lymphoid follicle formation</td>
<td>Storiform fibrosis is rare in parotid and minor salivary glands</td>
<td>Sometimes lacks obliterative phlebitis</td>
<td></td>
</tr>
<tr>
<td><strong>Lymph node</strong></td>
<td>No unique features</td>
<td>Fibrosis is only seen in inflammatory pseudotumor-like lesions</td>
<td>Most often lacks obliterative phlebitis</td>
<td>Five histological patterns*</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td>Small aggregates of neutrophils may be present in alveolar spaces or within the inflammatory infiltrates</td>
<td>Sometimes lacks storiform fibrosis, particularly in non-solid lesions (eg, interstitial pneumonia)</td>
<td>No unique features</td>
<td>Obliterative arteritis is often seen in pulmonary manifestations, particularly solid lesions</td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
<td>No unique features</td>
<td>No unique features</td>
<td>Obliterative phlebitis is less common particularly in needle biopsies</td>
<td></td>
</tr>
</tbody>
</table>

*(1) multicentric Castleman's disease-like, (2) follicular hyperplasia, (3) interfollicular expansion, (4) progressive transformation of germinal center, and (5) nodal inflammatory pseudotumor-like.*
Meningeal IgG4-RD: Major Histologic Criteria

- Dense lymphoplasmacytic infiltrate
- Storiform Fibrosis
- Obliterative Phlebitis
65-year-old woman with left ear and face pain

Differential diagnosis: idiopathic pachymeningitis, infectious and inflammatory granulomatous processes, granulomatosis with polyangiitis, and dural based tumors such as meningioma or less likely lymphoma and dural-based metastasis.
65-year-old woman with left ear and face pain

- Dense lymphoplasmacytic infiltrate
- Storiform Fibrosis at least focally
- IgG4/IgG >40% (normal ratio 4-5%)
- ± 40 + plasmacells
- ± 100 + plasmacells
# IgG4-related meningeal disease: clinico-pathological features and proposal for diagnostic criteria

<table>
<thead>
<tr>
<th>#</th>
<th>Lymphoplasmacytic infiltration</th>
<th>Fibrosis</th>
<th>Phebitis</th>
<th>IgG4+ cells/HPF</th>
<th>IgG4/IgG ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Severe; giant cells present</td>
<td>Minimal</td>
<td>Moderate</td>
<td>54.2</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
<td>46.6</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>Severe</td>
<td>Moderate</td>
<td>41.6</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>Moderate</td>
<td>Minimal</td>
<td>11.8</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>Severe; lymphoid follicles; giant cells present</td>
<td>Severe</td>
<td>Moderate</td>
<td>26.8</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>Moderate</td>
<td>None</td>
<td>None</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Minimal</td>
<td>Severe</td>
<td>None</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Minimal</td>
<td>Severe</td>
<td>None</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Moderate; lymphoid follicles</td>
<td>Moderate</td>
<td>None</td>
<td>2.2</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>Moderate</td>
<td>None</td>
<td>None</td>
<td>0.2</td>
<td>1</td>
</tr>
</tbody>
</table>
IgG4-related meningeal disease: 
clinico-pathological features and proposal for diagnostic criteria

Comparison of IgG4-related and non-IgG4-related cases

<table>
<thead>
<tr>
<th></th>
<th>IgG4-related (n = 5)</th>
<th>Non-IgG4-related (n = 5)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG *</td>
<td>97.3 (39.8–71.4)</td>
<td>17.6 (0–40.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>IgG4*</td>
<td>36.2 (11.8–54.2)</td>
<td>0.6 (0–2.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>IgG4/IgG ratio (%)</td>
<td>42 (24–60)</td>
<td>3 (0–8)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Positive plasma cells / HPF
Meningeal IgG4-Related Disease: Diagnostic Histologic Criteria

• The major histologic features associated with IgG4 related disease include:
  • Dense lymphoplasmacytic infiltrate
  • Fibrosis, arranged at least focally in a storiform pattern
  • Obliterative phlebitis

• Additional features include:
  • Phlebitis without obliteration of the lumen
  • Increased numbers of eosinophils

• Features **inconsistent** with IgG4 related disease include:
  • Epithelioid cell granulomas and prominent neutrophilic infiltrate
Two Features **Inconsistent** with IgG4 Related Disease
Epithelioid Cell granulomas and Prominent Neutrophilic Infiltrate

IgG4 (>30/HPF)
IgG (IgG/IgG4 ratio ± 30%)

Mod Pathol. 2012 Sep;25(9):1181-92
Sarcoidosis and The Nervous System

- Worldwide disease – regional ethnic predilection (african american in USA, white people in Europe/Sweden)
- Non necrotizing granulomatous inflammation
  - Well formed granulomas
  - Presence of giant cells
- Central Nervous System (Brain and Spinal cord)
  - Intraparenchymal lesions
  - Leptomeningeal involvement
  - Dura based mass mimicking meningioma
- Peripheral Nervous System
Leptomeningeal & Parenchymal Granulomatous Inflammation
Sarcoidosis mimicking Meningioma
Sarcoidosis mimicking Meningioma

Immediately Postoperatively

Following Steroid Therapy for approximately a year
Granulomatosis with Polyangiitis: Current Definition

• Form of systemic vasculitis
• Any organ may be involved
  – Upper respiratory tract, lung or kidney – involvement of all 3 sites uncommon
  – CNS involvement, especially in isolation, is rare
• Microscopically associated with necrotizing “granulomatous” lesions
• ANCA (usually cANCA) positive
  – Stimulus initiating the autoantibody (ANCA) formation is not yet known
  – ANCA activates neutrophils
  – Neutrophils release cytokines with damage of endothelial cells
  – Cellular interactions - inflammation
Granulomatosis with Polyangiitis: Classic “full blown” Lesions

- Geographic Necrosis
- Granulomatous Inflammation
- Small Vessel Vasculitis
- Inflammatory Background

- Surrounding areas of necrosis
- Neutrophils
Granulomatosis with Polyangiitis: Early Lesions

- Microscopic Collections of Neutrophils - Microabscess
- Neutrophilic Necrosis & Collagen Necrosis
66-year-old M - bilateral pachymeningeal thickening
Rheumatoid Arthritis

- Chronic inflammatory disorder with symmetric, peripheral erosive polyarthritis of unknown etiology
- Extra-articular manifestations: lungs, kidneys, heart, skin, eyes, muscle, peripheral and central nervous systems
- CNS & PNS involvement & manifestations in RA
  - Extradural pannus or vertebral body collapse with spinal cord compression (atlanto-axial subluxation)
  - Peripheral neuropathy
  - Meningitis

Neuropathology 2016; 36, 93–102
Rheumatoid Meningitis

• Rare, most commonly occurs in the setting of longstanding severe RA
  – In a review of 48 cases, 50% of patients had a history of RA for 10 or more years
  – Only in 5 patients, there was no prior RA history, but developed joint symptoms at the time or shortly after onset of meningitis

• Pachymeningitis and/or leptomeningitis
  – Meningeal inflammation (83%), rheumatoid nodules (56%), vasculitis (38%)

• Focal neurologic symptoms / cranial neuropathy most frequent
  – Also cognitive dysfunction, seizures, headaches

• In the past (before 1985) high mortality, often diagnosed at autopsy

Neuropathology 2016; 36, 93–102
69 F – known history of rheumatoid arthritis

MRI coarse confluent leptomeningeal enhancement

Rheumatoid nodule
Surrounding epithelioid histiocytes
Giant cells
Plasma cell predominance
78-year-old, Rheumatoid Arthritis (10 years)

Focal leptomeningeal enhancement
Extra-axial enhancing nodules
Rheumatoid Meningitis

Right frontal biopsy

- Leptomeninges
- Extensive Necrosis
- Chronic inflammation
- Cortex

Measurements:
- 10 mm
- 3 mm
Rheumatoid Meningitis

Necrosis
Rheumatoid Meningitis

- Necrosis
- Multinucleated Giant Cell
- Mostly Plasma Cells

Histological features of Rheumatoid Meningitis include necrosis, multinucleated giant cells, and a predominant infiltration of plasma cells.
Necrotizing granulomatous inflammation should prompt consideration of infection, until proven otherwise.
Mycobacterial Meningitis
Blastomycosis

48-year-old M
56-year-old with progressive decline & pachymeningitis

Only on deeper levels
56-year-old with progressive decline & pachymeningitis

Only on deeper levels

Necrosis

KP1

PAS

GMS
If no cause is found and no specific pathologic finding is present, then it is “idiopathic”
Idiopathic Hypertrophic Pachymeningitis
Idiopathic Hypertrophic Pachymeningitis
Inflammatory Pseudotumor

- 30-year-old man
- Decreased left visual acuity and ocular motion
- Left eye pain
- Left cavernous sinus lesion
Inflammatory Pseudotumor
Meningeal biopsy in intracranial hypotension: meningeal enhancement on MRI

Neurology 1995; 45:1801-7
Outline

• Focused discussion of meningeal pathological processes
  • From a Surgical Pathology point of view
  • “meningeal enhancement”

• Inflammatory Meningeal Diseases:
  • IgG4-related disease Infectious
  • Other inflammatory (sarcoid, granulomatosis with polyangiitis)
  • Infectious diseases
Q&A
References

1. Semin Neurol 2014; 34:395-404
2. Mod Pathol. 2012 Sep; 25(9):1181-92
3. Acta Neuropathol 2010; 120:765-76
4. Neuropathology 2016; 36, 93–102