Neoplastic Meningitis (s. Leptomeningeal Metastases, Leptomeningeal Carcinomatosis)

Etiology

Pathology

Clinical Features

Diagnosis

Etiology

Pathology

Clinical Features

Diagnosis

Gadolinium-enhanced MRI

1. Enhancing deposits (patchy finely nodular or linear):
   a) nerve roots – appear as thickening of nerve roots (especially evident in cauda equina, even in absence of clinical symptoms)
   b) leptomeningeal - extending into sulci, cisterns, perisigmoidal regions, and following convolutions of brain (usually follows positive CSF cytologic findings by 6 months)
2. Matting of nerve roots of cauda equina
3. Indefinite - communicating hydrocephalus, bilateral transsphenoidal edema, effacement of convexity sulci.

60% scans appear normal (high-resolution MRI is necessary in spine).

Dural carcinomatosis (common in carcinoma of breast) - focal curvilinear or diffuse contrast enhancement closely applied to inner table of skull, which does not follow convolutions of gyri.

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Clinical Features

- Leptomeningeal irritation:
  - Classic vignette: CN3 palsy + foot drop.

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- Multifocal neurological symptoms!

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- Multifocal neurological symptoms!
- differential of meningeal enhancement: infections, previous SAH, previous LP or intrathecal chemotherapy, prior neurosurgical procedures (e.g. placement of intraventricular CSF leak).

  N.B. in patient with high KPS score and active systemic cancer in whom neuroimaging strongly suggests NM, some physicians justify treatment even if CSF cytology is negative.

A. Patchy nerve root enhancement, mottling of nerve roots of cauda equina, and nodular deposits (arrows) in acute lymphocytic leukemia.

B. Linear, continuous enhancement of mega-structured subarachnoid cisterna magna (arrows) in metastatic melanoma.

Carcinomatous spinal meningitis (postcontrast MRI): diffuse pial enhancement along cord surface (arrows): Dural metastasis from breast carcinoma (postcontrast T1-MRI): heterogeneously enhancing mass with irregular surface that arises from dura over right cerebral convexity; it displaces underlying brain and causes considerable low signal edema within it; dural ‘tail’ extending away from tumor (arrowhead):

Marked enhancement of leptomeninges in cerebral sulci and superficial folia of superior cerebellum (arrows):

CSF

< 5% have completely normal CSF profiles

Definitive diagnosis - malignant cells in CSF; sensitivity depends:

1) lumbar or cisternal CSF (more reliable than intraventricular CSF)
2) second specimen increase sensitivity from 50-60% to 80%
3) CSF from location nearest to area of greatest involvement
4) CSF sample volume > 10.5 mL (however, most cytopathologists prefer serial samples obtained on different dates rather than single large-volume specimen)

Periodic CSF examinations - most useful test!!

Most sensitive indicator - elevated protein (> 45 mg/dL in 80-90% patients)

- normal CSF protein reading is relatively strong (but not absolute) evidence against diagnosis
- high elevations (500-1200 mg/dL) - either advanced NM or partial / complete blockage of CSF flow from cephalad locations.

CSF profile normal does not exclude diagnosis!
NEOPLASTIC MENINGITIS

Other:
- lumbar CSF pressure > 15 cmH2O (30-57% patients).
- glucose: normal or ↓ (< 40 mg/dl in 31-55% cases) - due to abnormal glucose transport; tumor cells also use much glucose.
- reactive lymphocytes (65%) → false-positive CSF (difficult to distinguish from malignant lymphomatous cells).
- xanthochromia from leptomeningeal bleeding (most likely in NM from melanoma).
- if gene rearrangements in particular malignancy are known → fluorescent in situ hybridization (FISH), flow cytometry, PCR.
- biochemical markers (poor sensitivity and specificity; levels decline with successful therapy):
  - carcinoembryonic antigen (CEA) – adenocarcinomas;
  - α-fetoprotein, β-hCG – testicular cancers;
  - 5-hydroxyindoleacetic acid (5-HIAA) – carcinoid tumors;
  - immunoglobulins – multiple myeloma;
  - LDH isoenzyme - breast or lung tumors;
  - glial fibrillary acidic protein (GFAP) – gliomas.

**CSF FLOW STUDIES**
- assessed by nuclear medicine (99mTc-labeled albumin).
- partial or total CSF flow blockage is identified in 30-70% patients - outcome is poorer.
- should be done before initiating treatment – to identify CSF flow blockage:
  - to prevent accumulation of high concentrations of administered drug in areas of CSF blockage;
  - to identify areas that would not receive adequate drug concentration beyond areas of blockage.
- CSF blocks can be opened with focal radiation therapy.

**MENINGEAL BIOPSY**
- indication - patient with high clinical suspicion of NM but repetitively negative CSF cytology.
- most patients are not appropriate candidates (poor performance status and comorbid conditions).
- sensitivity and specificity are low when there is no target on MRI.
- malignant cells in CSF:
  A. Isolated large cells with increased nuclear-to-cytoplasmic ratio and fine clumps of cytoplasmic pigment (malignant melanoma).
  B. Clump of cohesive cells of primitive neuroectodermal tumor and extensive meningeal seeding.

Myelogram and autopsy specimen from same patient - intradural filling defects in myelogram (A) that correspond to tumor nodules (arrows) on multiple nerve roots and thoracic spinal cord in pathologic specimen (B):

**TREATMENT**
- entire neuraxis must be treated, as tumor cells are disseminated widely by CSF flow.
- treatment increases patient's quality of life by extending time to neurological progression.
- fixed focal neurologic deficits (e.g. cranial-nerve palsies) do not improve, but encephalopathies can improve dramatically with treatment.
- Treat systemic cancer, as patient is likely to die from that.

**SURGERY**
1. Placement of intraventricular reservoirs (e.g., Ommaya) for CSF access.

N.B. clinical studies have not shown statistically significant improvement in overall survival when comparing intraventricular vs. intralumbar drug administration (exception - childhood ALL).
2. Ventriculoperitoneal shunting for hydrocephalus or if symptomatic increased ICP does not improve with steroids.
   - questionnable benefit in patients with end-stage disease.
   - potential dissemination of malignant cells to abdomen.
   - ineffective drug delivery to CSF (siphoning of administered drug from intraventricular reservoir. H: in-line on-off or programmable valves*).
   * temporary closure of shunt valves has not yet been shown in clinical studies to sustain therapeutic levels of drug in CSF or to improve survival.

3. Meningeal biopsy.

## RADIOThERAPY (CRANIOspinal Irradiation)

### Indications
1. focal RT to areas of bulky disease (nodules > 5 mm) - radiation treatment areas such as nerve-root sleeves, Virchow-Robin spaces, and interior of bulky lesions that chemotherapy does not reach
2. focal RT to symptomatic sites often provides palliative benefit
3. patients with medulloblastoma or plexus who are considered poor risks for surgery
4. salvage therapy in patients for whom initial therapy for leptomeningeal meningitis has failed.
5. dosages range from 20 Gy in 1 week to 30 Gy over 3-4 weeks.

- because CSI encompasses much of bone marrow, resulting hematologic toxicity may affect ability to provide substantial cytotoxic chemotherapy in future regimens.
- toxicity of intrathecal or high-dose systemic methotrexate is increased after whole-brain RT (H: administer MTX before RT)

## CHEMOTHERAPY

- for younger patients with high KPS scores and controlled systemic disease
- many patients are too ill for aggressive therapy: supportive or hospice care.
- penetration (CSF concentration/systemic blood concentration):
  - thiopeta (90%)
  - topotecan (30%-30%)
  - temozolomide (30%)
  - produced responses in NM accompanying malignant gliomas cytarabine (ara-C; 20-28%) MTX (3%)

## INTRACATH CHEMOTHERAPY
- chemotherapy treats subclinical leptomeningeal deposits and tumor cells floating in CSF.
- preventing further seeding.
- administered after radiotherapy.
- some studies show that IT treatment provides no differences in outcome.
- N.B. for most neoplasms, survival has not yet been shown to be superior to intrathecal treatment.

### Disadvantages and Limitations
1. more neurotoxicity (than systemic chemo)
2. inadequate penetration of CNS parenchymal surfaces → limited efficacy in gross lesions (> 5 mm diameter)
3. limited efficacy in blocked CSF pathways (CSF compartmentalization)
4. short half-life and cell cycle specificity (only 55% of CSF tumor cells cycle in 10-day span; half-life of most IT agents is only minutes - few hours)
5. some agents are not converted to active metabolites within CSF (e.g. triethylene phosphoramide (TEPA), active metabolite of thiopeta, is not measurable in CSF after IT administration).

### Preferred routes - implanted subcutaneous reservoir (e.g. Ommaya device) and ventricular catheter (rather than LP)
1. intraventricular injection is easy and ensures entry into CSF.
2. when injected into ventricle, drug follows normal CSF flow and thus reaches all parts of CSF space.
3. repetitive LPs are arduous and painful.
4. 10-15% of LPs do not deliver all of drug intended to reach subarachnoid space.

### Drugs:
- METHOTREXATE (MTX) – first line (FDA approved for lymphomatous and leukemic meningitis)
  - because meningeal infiltration interferes with drug clearance, CSF concentrations can be unpredictable (maintain concentration near 10³ M)
  - can cause acute arachnoiditis (self-limiting and resolves within 24-72 hrs); transverse myelitis is rare idiosyncratic reaction (begins 30 min ÷ 48 h after intrathecal treatment)
- TOPOTECAN (C; 20-28%)
- CYTOSINE ARABINOSIDE (ara-C; 20-28%)
- CYTARABINE (cytosine arabinoside; ara-C) – second line agent; not effective for solid tumors but effective (FDA approved) in leptomeningeal lymphomatous meningitis; available in liposome-encapsulated form (DepoCyt) – administered q2weeks (rather than 2-3 times / week).
- TEOPIRAMINE – third line agent; cleared from CSF within minutes with less neurologic toxicity than MTX.
- other drugs reported in IT use (not approved by FDA): mafosfamide, etoposide, rituximab, interferon alfa, topotecan.

Randomized Clinical Trials of Intrathecal Chemotherapy for Neoplastic Meningitis
Selected Phase I and II Studies of Treatment of Neoplastic Meningitis

PROGNOSIS
- average survival time – 3.5-6 months
  - without therapy → death due to progressive neurologic dysfunction in 4-6 weeks
  - with therapy, most patients die from systemic cancer complications rather than neurologic complications
- treatment to date has not had significant effect on survival.
- Exception – LEUKEMIC/LYMPHOMATOUS MENINGITIS (esp. ALL) can be eradicated completely from CNS!
- favorable prognostic factors:
  1) young age
  2) Karnofsky Performance Scale (KPS) score > 70
  3) long duration of symptoms
  4) controlled systemic disease
  5) lack of encephalopathy or cranial nerve deficits
  6) low CSF protein levels
  7) breast cancer (11-25% alive at 1 year, 6% - at 2 years).
  8) hematologic malignancies - curable
  9) lack of bulky leptomeningeal deposits
- median survival
  - 3 months for NM from breast cancers
  - 4 months for NM from small-cell lung carcinomas
  - 3.6 months for NM from melanomas.

BIBLIOGRAPHY for ch. “Neuro-Oncology” → follow this LINK >>

Viktor's Notes℠ for the Neurosurgery Resident
Please visit website at www.NeurosurgeryResident.net