

# Leptomeningeal Metastases (s. Leptomeningeal Carcinomatosis, Neoplastic Meningitis)

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LM - proliferation of neoplastic cells in subarachnoid space.

N.B. "meningitis" is misnomer - inflammatory response may not be present!

- may occur at any stage in neoplastic disease - either as presenting sign or as late complication (frequently associated with cancer relapse elsewhere in body; usually close correlation between LM and osseous metastases).
- 1-8% of patients with cancer develop LM (in 25% such patients systemic cancer is under control).

## ETIOLOGY

1. Any systemic malignancy (hematogenously):
  - 1) breast (10-41%) Most patients with LM have breast cancer!
  - 2) lungs (24-70%)
  - 3) GI tract (2-20%)
  - 4) melanoma (2-15%)
  - carcinomas of head / neck can spread to meninges along cranial-nerve paths.
2. Hematologic cancers → LYMPHOMATOUS MENINGITIS, LEUKEMIC MENINGITIS
3. Primary or metastatic CNS tumors (direct meningeal seeding via CSF) → LEPTOMENINGEAL GLIOMATOSIS. see p. Onc1 >>

## PATHOLOGY

- multifocal or diffuse infiltration of leptomeninges (in sheetlike fashion) along surface of brain / spinal cord ("sugar coating").
- tumor masses may extend into Virchow-Robin spaces.
- LM causes partial BBB disruption once tumor size has increased enough to stimulate growth of its own vasculature.
- LM may coexist with parenchymal CNS metastases.

## CLINICAL FEATURES

- subacute meningitis (but patient is afebrile with preserved consciousness):

Affected multiple CNS levels

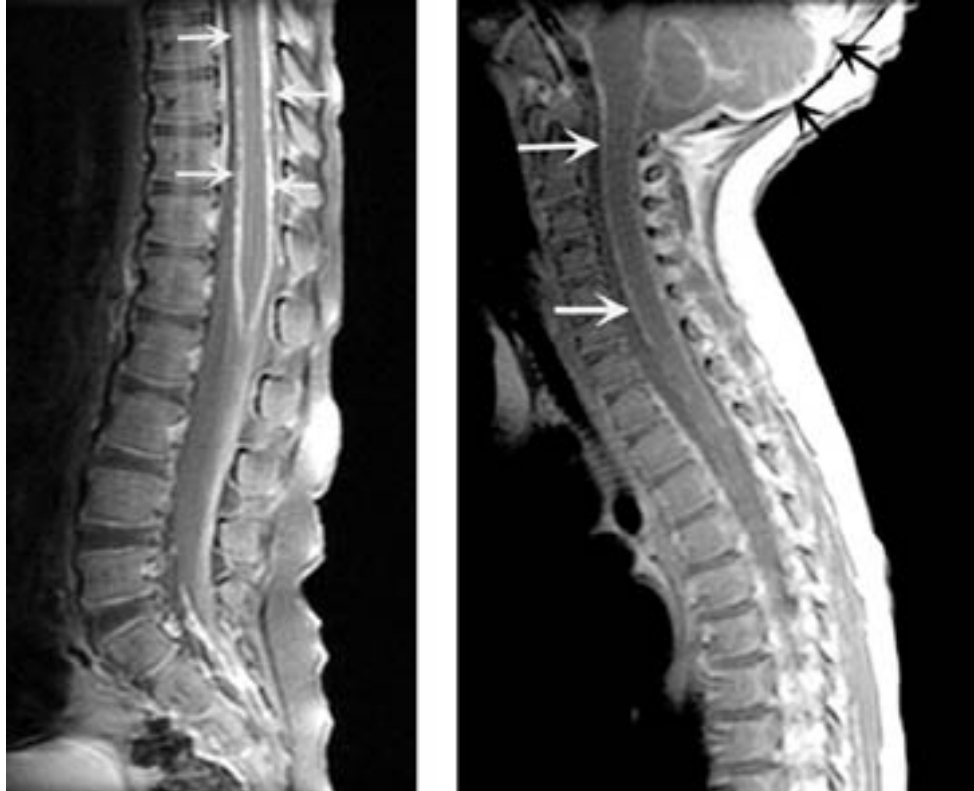
1. Meningeal symptoms.
2. CSF flow obstruction → ICP↑, hydrocephalus.
3. Local tumor infiltration → progressive multiple cranial nerve palsies (94%), radiculopathies, myelopathy, focal deficits (e.g. gait disturbance due to cerebellar or cauda equina involvement).
4. Alterations in nervous tissue metabolism\* → seizures, encephalopathy (headache, lethargy, behavior changes).
 

\*competition for glucose between malignant cells and neurons
5. Occlusion of blood vessels (as they cross subarachnoid) → infarcts.

## DIAGNOSIS

1. Gadolinium-enhanced MRI of area of maximal symptomatology: linear or finely nodular leptomeningeal enhancement extending into sulci and following convolutions of brain (usually follows positive CSF cytologic findings by 6 months), tumor masses in cisterns, sulci, or periependymal regions; nodularities or thickening of nerve roots (especially evident in cauda equina, even in absence of clinical symptoms).
  - 60% CT scans appear normal.

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):



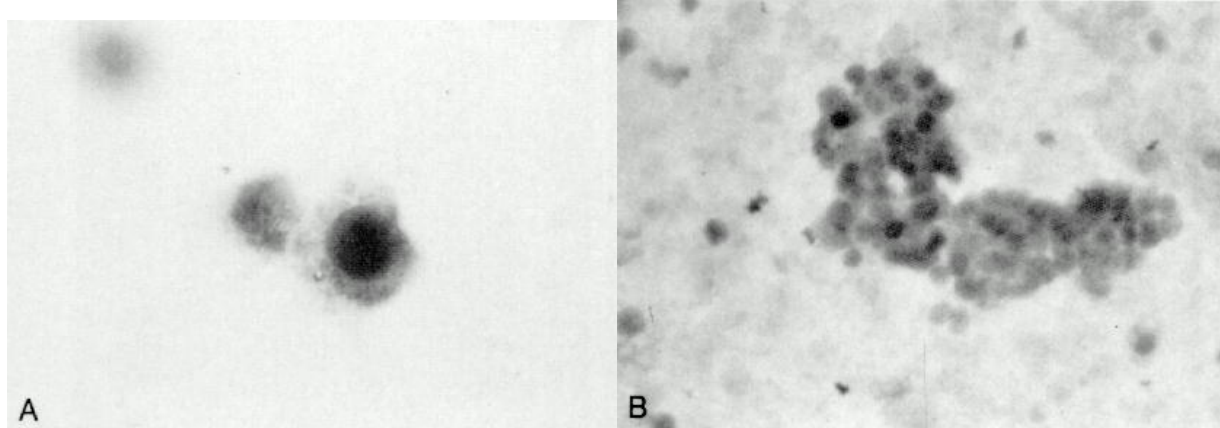
- **CARCINOMATOSIS OF DURA MATER** (common in carcinoma of breast) - focal curvilinear or diffuse contrast enhancement closely applied to inner table of skull, which does not follow convolutions of gyri.

2. **Periodic CSF examinations** (most useful test!!!): *Normal CSF profile does not exclude diagnosis!*
  - 1) **opening pressure** ↑ (50%)
  - 2) **protein** ↑ 50-200 (up to 1200) (80%)
  - 3) **glucose** ↓ normal ÷ ↓↓↓ (< 40 mg/dl in 37% cases) - due to abnormal glucose transport; tumor cells also use much glucose.
  - 4) **xanthochromia** from leptomeningeal bleeding (most likely in LM from melanoma)
  - 5) **lymphocytes** ↑ (65%)
  - 6) **positive cytologic findings** (**carcinoma cells in CSF**)
    - false-negative* - 50% on first LP, 15% after 3 high-volume LPs (5% after 6 LPs)
    - false-positive* - reactive lymphocytes (difficult to distinguish from malignant lymphomatous cells)
  - 7) **biochemical markers** (poor sensitivity and specificity; levels decline with successful therapy):
    - CEA – adenocarcinomas;
    - α-fetoprotein, β-hCG – testicular cancers;
    - 5-hydroxyindoleacetic acid (5-HIAA) – carcinoid tumors;
    - immunoglobulins – multiple myeloma;
    - LDH isoenzyme-5 – breast or lung tumors;
    - glial fibrillary acidic protein (GFAP) – gliomas.

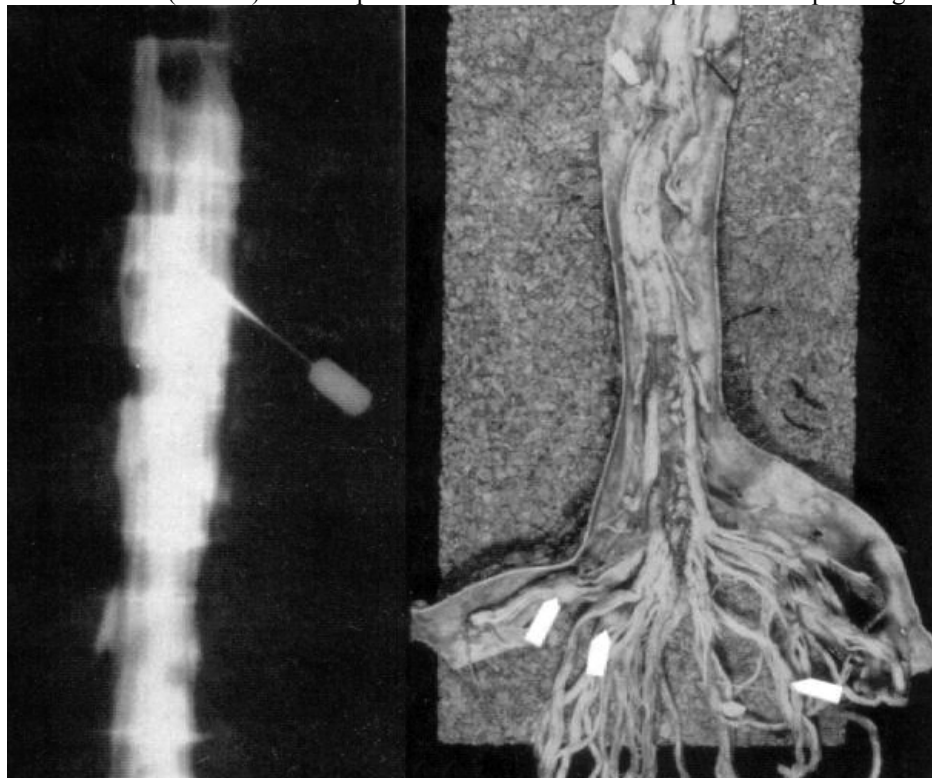
3. **Leptomeningeal biopsy** – only if no evidence of primary tumor and CSF is negative.

Malignant cells in CSF:

- A. Isolated large cells with increased nuclear-to-cytoplasm 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.
- *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
- if symptomatic increased ICP does not improve with steroids → place **ventriculoperitoneal shunt**.

## RADIOTHERAPY

- **focal external beam radiotherapy** to *symptomatic sites* and regions where imaging has demonstrated *bulk disease* (nodules > 5 mm).
- radiation treats areas such as *nerve-root sleeves*, *Virchow-Robin spaces*, and *interior of bulky lesions* that chemotherapy does not reach.
- dosages range from 20 Gy in 1 week to 30 Gy over 3-4 weeks.
  - lymphomatous and leukemic meningitis - 30 Gy over 10 doses*

### Intrathecal CHEMOTHERAPY

- chemotherapy treats *subclinical leptomeningeal deposits* and *tumor cells floating in CSF*, preventing further seeding.
- administered after radiotherapy.
- preferred route - 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.
- *CSF flow abnormalities* are common (70% patients have ventricular outlet obstructions, abnormal spinal canal flow, or impaired flow over cortical convexities - these can be reversed with radiotherapy) - *CSF-flow study* is recommended for all patients at initiation of intrathecal chemotherapy; if obstruction is noted → defer therapy (whole neuraxis radiotherapy is reasonable alternative).

#### Drugs:

**METHOTREXATE (MTX)** – first line!; because meningeal infiltration interferes with drug clearance, CSF concentrations can be unpredictable (maintain concentration near  $10^{-6}$  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)

N.B. combination of MTX and cranial irradiation may cause *necrotizing leukoencephalopathy*. see p. Rx11 >>

**CYTARABINE (CYTOSINE ARABINOSIDE, ARA-C)** – second-line agent; not effective for solid tumors but effective in *LEUKEMIC / LYMPHOMATOUS MENINGITIS*; available in liposome-encapsulated form (DepoCyt) - administered q2weeks (rather than 2-3 times week).

**THIOTEPA** – third-line agent; cleared from CSF within minutes with less neurologic toxicity than MTX.

### PROGNOSIS

- *without therapy*, most patients survive 4-6 weeks (death due to progressive neurologic dysfunction).
- *with therapy*, most patients die from systemic cancer complications rather than neurologic complications of LC.
- median survival:
  - 7 months for LM from **breast cancers**
  - 4 months for LM from **small-cell lung carcinomas**
  - 3.6 months for LM from **melanomas**.

Exception - *LEUKEMIC / LYMPHOMATOUS MENINGITIS* - can be eradicated completely from CNS!

BIBLIOGRAPHY for ch. “Neuro-Oncology” → follow this [LINK >>](#)