Neurologic Complications of Cancer and Cancer Treatment

Michael J. Bradshaw, MD
Assistant Professor of Neurology
Chicago Medical School/Rosalind Franklin University of Medicine and Science, Billings Clinic

Disclosures
 No original thought
 Sense of humor also questionable
 Ravenclaw is (obviously) the best house
 Also most pompous
 Off-label treatment of paraneoplastic neurologic disorders is discussed

Overview
 Neurologic Complications of Cancer
   Metastatic
   Non-metastatic
     Paraneoplastic autoimmune encephalitis
   Neurologic Complications of Cancer Treatment
     Chemotherapy
       Radiation (sorry)
     Anti-tumor immunotherapy- autoimmune encephalitis

Introduction
 Neurologic complications affect ~15-30% of cancer patients
 Decrease quality of life and may shorten life
 Incidence is increasing
 Mechanisms
   Direct invasion of the nervous system
   Autoimmune reactions to cancer or cancer treatment
   Toxicity of treatment
 Manifestations range from CNS to muscle disease and everything in between

Most Common Solid Tumor Mets to CNS

<table>
<thead>
<tr>
<th>Type of Complication</th>
<th>Common Histologies</th>
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<tbody>
<tr>
<td>Brain parenchymal metastases</td>
<td>Melanoma, non-small cell lung cancer, small cell lung cancer, breast, renal</td>
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<tr>
<td>Epidural spinal cord compression</td>
<td>Lung (non-small cell lung cancer), breast, melanoma, Hodgkin disease, non-Hodgkin lymphoma, sarcoma, prostate</td>
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<tr>
<td>Leptomeningeal carcinomatosis</td>
<td>Breast, lung, melanoma, lymphoma, leukemia</td>
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Metastatic Disease
 Brain
 Cranial nerves/meninges
 Spinal cord
 Peripheral nerves
Clinical Manifestations

+ Focal neurologic dysfunction
+ Focal deficits
+ Mass effect/herniation syndromes
+ Seizures
+ Ischemic or hemorrhagic stroke
+ Headache (e.g. dural venous sinus thrombosis)

MRI

+ Most common pattern is multiple metastases about the gray-white junction (A)
+ Hemorrhagic metastases (B)
+ Pachymeningeal metastasis (C)
+ Leptomeningeal metastasis (D)

Treatment

+ Depends upon individual factors
+ Location of metastasis, tumor type, extent of disease, etc.
+ Surgical resection
+ Radiation (whole brain or stereotactic radiosurgery)
+ Chemotherapy
+ Immunotherapy
+ Prognosis heavily depends upon underlying tumor type/extent of metastatic disease

Case

+ 52 yoM with 6 weeks progressive vision loss
+ Right eye, then left eye
+ New non-positional headaches
+ Lhermitte’s phenomenon
+ Radiating sensation down the spine with neck movements

+ Left anosmia, right relative afferent pupillary defect, severe bilateral disc edema
+ Acuity: finger counting at 1 foot OD and 4 feet OS with large central scotoma. Mild nuchal irritability.
Case

- CSF: opening pressure 31, 28 WBC (79% lymphs), glucose 27 (low), protein 162 (high), cytology and flow cytometry negative
- CT C/A/P normal
- Infectious and autoimmune workup negative; transient improvement with IVMP, then progressed
- NSG/ENT → biopsy of olfactory groove mass

Teaching Point:
Leptomeningeal Carcinomatosis

- Most commonly breast (~43%), lung (~29%), gastrointestinal (~7%) and melanoma (~6%)
- Basal cisterns of the brain and caudaequina are most often affected
- MRI, CSF cytology or both
  - MRI demonstrates leptomeningeal thickening/contrast enhancement (nonspecific)
  - Cytology is relatively insensitive, search for systemic malignancy and/or biopsy may be necessary
- Median survival 2-3 months

Peripheral Neuropathy Evaluation in Cancer Patients

- Diabetes, thyroid? → A1c, TSH/T4, etc.
- Direct effect of cancer?
  - Metastasis/invasion → imaging
- Paraneoplastic?
  - Autoimmune → paraneoplastic labs (antibody panel)
  - Nutritional → B12, folate, B6, thiamine, copper, vitamin E
  - Other → SIEP/SPEP

Paraneoplastic Neuropathy

<table>
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<tr>
<th>Cancer</th>
<th>Neuropathy</th>
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<tbody>
<tr>
<td>Small cell lung cancer</td>
<td>Paraneoplastic anti-Hu antibody</td>
</tr>
<tr>
<td></td>
<td>Dorsal root ganglionopathy</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Axonal sensorimotor</td>
</tr>
<tr>
<td>Thymoma</td>
<td>Anti-CV2 antibody sensorimotor</td>
</tr>
<tr>
<td>Waldenström macroglobulinemia</td>
<td>Axonal sensorimotor</td>
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Peripheral Neuropathy Evaluation in Cancer Patients

- Diabetes, thyroid? \(\Rightarrow\) A1c, TSH/T4, etc.
- Direct effect of cancer?
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- Paraneoplastic?
  - Autoimmune \(\Rightarrow\) paraneoplastic labs (antibody panel)
  - Nutritional \(\Rightarrow\) B12, folate, B6, thiamine, copper, vitamin E
  - Other \(\Rightarrow\) SIEP/SPEP
- Chemotherapy
- Next slide

Chemotherapy

- Most common neurologic complication is peripheral neuropathy
- 30-70% of patients on chemotherapy
- Sensory predominant (dorsal root ganglia are outside BBB)
- Dose-dependent and can persist long after completing treatment (“coasting”)

Paraneoplastic Neurologic Disorders

- Autoimmune response to tumor antigens \(\Rightarrow\) neurologic dysfunction
- Can be predominantly T-cell (intracellular targets) or B-cell mediated (extracellular targets)

Paraneoplastic Neurologic Disorders

- All areas of nervous system can be affected
- Typically present with subacute, progressive neurologic dysfunction
- Diagnostic evaluation depends on the syndrome
- Many antibodies are associated with specific cancer risk
- Identifying and treating the underlying malignancy is CRITICAL
Autoimmune Neurologic Disorders: A Useful Paradigm

**Intracellular targets**
- Classic paraneoplastic disorders
- Older, less responsive to treatment
- Primarily T-cell mediated*
- Antibody is a marker of disease activity

**Extracellular targets**
- May or may not be paraneoplastic
- Younger, responsive to treatment
- Primarily B-cell/humoral mediated*
- Antibody is directly pathogenic

*Exceptions exist, e.g. GFAP

**Treatment Paradigm**

**Intracellular targets (classic paraneoplastic disorders)**
- Primarily T-cell mediated
- IVMP
- Cyclophosphamide or cytotoxic chemotherapy against primary tumor
- IVIg may play role

**Extracellular targets**
- Primarily B-cell/humoral mediated
- IVMP
- Plasma exchange
- IVIg
- Rituximab

**Case**
- 22 yoF with URI, headache → memory loss, hallucinations, confusion → seizures
- Catatonic (waxy flexibility, passively resists eyelid opening), generalized hyperreflexia with bilateral Babinski
- CBC, CMP UA normal
- Brain MRI normal
- LP: 106 wbc (87% lymphs), normal glucose, protein, infectious PCR panel negative

Presumptive diagnosis:
- NMDAR encephalitis
- Treated with plasma exchange, IV methylpred
- Ovarian teratoma identified and removed
- CSF NMDAR + (serum neg)
- Full recovery over several weeks → months

**NMDAR Encephalitis: Clinical**
- ~80% women, ~40% <18 years old
- Most common trigger: ovarian teratoma
- Also, HSV-1 encephalitis
- No trigger in ~55%
- NMDAR GluN1 IgG is pathogenic
- Clinical syndrome is well-described and relatively consistent
NMDAR Encephalitis: Prototypical Antibody-Mediated Autoimmune Encephalitis

- Clinical syndrome
  - EEG may demonstrate extreme delta brush

MRI may be normal (60%) or have nonspecific T2 hyperintensities
- Rarely (~3%) can overlap with demyelinating syndrome
- PET with increased frontotemporal-to-occipital gradient (not commonly obtained)

CSF can be normal or lymphocytic pleocytosis, elevated protein, oligoclonal bands/ elevated IgG index

Autoimmune encephalitis panel on CSF +/- serum
- Not useful acutely: takes too long to return
- CSF has higher sensitivity and specificity than serum

Antibody-Mediated Autoimmune Encephalitis Treatment

- IVMP 1g x 5-7d
- Plasma exchange x 5 sessions
- Tumor search and prompt removal
- IVIg
- Rituximab
- Cyclophosphamide

Case

- 38 yoF presents with several weeks of progressive ataxia
- Global ataxia including EOM, vocal ataxia, appendicular ataxia, axial ataxia with otherwise normal neurologic examination
- Initial CSF: normal
- Initial serum studies: normal

Empirically treated with IVMP, PLEX → IVIg
- Mammogram: breast cancer
- Serum: PCA1 IgG positive
- Breast cancer treated through oncology including cytotoxic chemotherapy
- Ataxia stabilized/persisted
**Paraneoplastic Cerebellar Degeneration**
- Metastasis (cerebellar), metabolic/nutritional deficits (thiamine, B12, folate, copper), autoimmune
- Primarily associated with SCLC, gynecologic/breast cancers, lymphoma
- Nearly all antibody syndromes are associated with PCD
  - Anti-Yo, Anti-Tr and anti-mGlur are predominantly associated with ataxia

**Ataxia in a Cancer Patient**
- Sensory ataxia (peripheral neuropathy/dorsal column) vs cerebellar?
  - Global cerebellar dysfunction in this patient
- Autoimmune:
  - Anti-Yo: breast, endometrium, fallopian tube, ovary
  - Anti-Tr: Hodgkin lymphoma
  - Anti-mGlur: Hodgkin lymphoma or no tumor
  - GAD-65
  - MS, NMO
  - AIDP
  - Post-viral
- Metabolic: B12, thiamine, copper, vit E, hypothyroidism, medications, etOH
- Infectious: CJD, HIV, celiac, viral (VZV)

**Final Case**
- 59 yoF with stage IV neuroendocrine carcinoma presents with several weeks of new tremors and “zombie like” behavior
- Unable to form new memories, disengaged from the world
- Primary tumor regressed with radiation, cisplatin, etoposide, but lung site progressed so was treated with new checkpoint inhibitor anti-tumor antibodies one month prior to presentation
- Brain MRI: T2 hyperintensity in the bilateral mesial temporal lobes and basal ganglia
- CSF: 25 WBC (lymphs), normal glucose, mildly elevated protein; negative infectious and autoimmune studies

**Case**
- Dx: checkpoint-inhibitor associated limbic encephalitis
- Treated with high dose IV methylprednisolone
- Tremor improved, cognition returned to near normal
- Tumor unfortunately progressed and she died of her cancer about a month later with in-home hospice

**Checkpoint Inhibitors**
- Inhibit inhibitors of T-cell cycle → hyperactivation of T cells → increased anti-tumor efficacy (etc.)
- Associated with immune-related adverse events, including neurologic (1-3%)
- Manifestations range from encephalitis to muscle disease
**Checkpoint Inhibitors**

- Also increase risk of traditional paraneoplastic disorders
- Treatment depends on underlying syndrome
- Does not seem to decrease anti-tumor efficacy
- Encephalitis tends to respond well to chemotherapy
  - May be a role for natalizumab for refractory cases
  - Prevents lymphocyte migration into the CNS
- May necessitate change in anti-tumor regimen

Questions