

TUMOR BOARD: CONSULTATIONS IN CANCER NEUROLOGY I

Jaishri Blakeley, MD

Johns Hopkins School of Medicine

David Schiff, MD

University of Virginia

Amy Pruitt, MD

University of Pennsylvania

This course is a case-based simulation of the types of cancer-related consultations frequently fielded by neurologists. The first hour includes detailed discussions of cases representing 1) medical management problems arising during the course of cancer treatment; 2) cutaneous manifestations of neuro-oncologic problems and new treatment strategies for these; 3) diagnostic problems in which the diagnosis of cancer such as CNS lymphoma is not yet certain; 4) how to proceed when the nature of a recurrent MRI abnormality requires clarification with advanced imaging or other modality.

The second hour will use cases to demonstrate examples of infectious complications of tumor therapy, hematopoietic cell transplant-associated problems, complications of new immune checkpoint inhibitors, and emerging strategies for common systemic cancers.

The mock tumor board format uses the Audience Response System. The three faculty will offer opinions and solicit audience input. This syllabus provides participants with clinical questions and background references to participate in the consultations. (To retain an element of realistic diagnostic challenge, problems are not arranged in chronologic order.) This material complements case-based discussions in the second part of this course.

Learning Objectives: Participants should understand the evidence base for treatment of common cancer-related problems such as stroke and seizure and consider the rapidly evolving spectrum of immune therapy-related complications. They will also recognize less common radiographic and dermatologic clues to efficiently diagnose neurological problems that impact survival and quality of life.

This is a rapidly changing field as indicated by the next slide!

Oncology Drugs Approved since you graduated from medical school

2016	2015	2015	2015
Calcezinib (RCC after anti-angiogenic therapy)	Pembrolizumab (initial treatment melanoma)	Cobimetinib (Melanoma BRAF V600 E, _)	Gefitinib (NSCLC EGFR mutated)
Venetoclax (CLL with 17p deletion and one prior rx)	Alectinib (ALK+ metastatic NSCLC)	Ipilimumab (melanoma with + nodes)	Ramucicamab (combined with FOLFIRI colorectal)
Defibrotide (VOD following HSCT)	Uridine triacetate (emergency rx of 5-FU or capecitabine overdose)	Talinogene laherparepvec Oncolytic viral therapy for melanoma	Ibrutinib (Waldenstrom's, mantle cell lymphoma (2013) CLL (2014))
Crizotinib (NSCLC ROS1-positive)	Elotuzumab (multiple myeloma after 3 rx's)	Tralectedin (liposarcoma)	Lenvatinib (thyroid cancer)
Everolimus (neuroendocrine tumors of GI or lung origin)	Necitumumab (with gemcitabine /cisplatin for squamous NSCLC)	Irinotecan liposome injection, pancreas progressing on gemcitabine	Panobinostat (Myeloma)
Obinutuzumab (follicular lymphoma refractory to rituximab)	Nivolumab (RCC after prior anti-angiogenic therapy)	Nivolumab NSCLC after platinum Melanoma V600 wild type	ETC.
Palbociclib (in combination with fulvestrant) HR+Her2 - breast cancer	Trametinib (BRAF V600E or K melanoma)	Pembrolizumab NSCLC with PD-1 ligand	
Eribulin (Liposarcoma after anthracycline)	Ixazomib multiple myeloma (1 st oral proteasome inhibitor)	Brentuximab (auto-HSCT) Hodgkin lymphoma	
Ofatumumab (CLL)	DAAatumumab Melanoma	Carfilzomib myeloma	
	Osimeetinib (EGFR T790M positive NSCLC)	Sonidegib (Basal cell)	

I. Medical Management of Patients with Brain Tumors

Common problems arising during active tumor treatment are related to vasogenic edema, seizures, and coagulopathy. Steroid complications are summarized here:

Complications of Corticosteroids

Common

- Myopathy
- Weight gain/edema
- Behavioral changes
- Insomnia
- Diabetes
- Tremor
- Visual blurring
- Reduced taste and olfaction
- Cerebral atrophy
- Osteoporosis-kyphoplasty/vertebroplasty

Uncommon

- Psychosis/hallucinations
- Hiccups
- Dementia
- Seizures
- Epidural lipomatosis
- Avascular necrosis hips
- Allergy suppression
- RPLS/PRES??
- **GASTRIC irritation**
- **INFECTIONS (pjp)**
- **DEPENDENCE**

A complicated differential diagnosis arises when a cancer patient has a sudden new focal deficit as the differential diagnosis of **stroke in a cancer patient** is different from that of noncancer patients and must include tumor and infection-related issues. The table below indicates a broad differential of this problem.

► **Ischemic Stroke**

Coagulopathy

- Nonbacterial thrombotic endocarditis
- Disseminated intravascular coagulation^a
- Hyperviscosity

Paradoxical embolus (lung tumors, venous thromboembolism^a)

Venous sinus thrombosis (dehydration, tumor invasion)

Infection

- Varicella-zoster virus vasculopathy
- Bacterial or fungal endocarditis
- Fungal vascular invasion (eg, *Mucor*, *Aspergillus*)

Neoplasms

- Intravascular lymphoma
- Vascular compression or invasion (dural, leptomeningeal, parasellar)
- Tumor emboli (myxoma, lung tumors)

Radiation-induced vasculopathy

- Carotid stenosis after neck radiation
- Small vessel (lacunar) disease^a
- Moyamoya disease
- Angiitis

Chemotherapy and targeted molecular agents

- L-Asparaginase
- Bevacizumab and other VEGF or VEGF receptor inhibitors^a
- Thalidomide
- Estrogens
- Tamoxifen

► **Hemorrhagic Stroke**

Coagulopathy

Thrombocytopenia

Disseminated intravascular coagulation^a

Abnormal platelets

VEGF and VEGF receptor inhibitors^a

Hemorrhage into tumor (melanoma, germ cell, thyroid, renal)^a

Infectious aneurysm

Therapeutic anticoagulation^a

Head trauma (subdural, subarachnoid)

VEGF = vascular endothelial growth factor.

^a Particularly relevant to patients with primary or secondary brain tumors.

From Pruitt AA. Continuum 2015;21:314-31.

III Tumor or Not? Diverse manifestations of lymphoma

(Another) Great Imitator **CNS Lymphomas**

“Typical” PCNSL steroid responsive (sometimes) mass(es)
 Variants: dural, leptomeningeal, spinal cord- LETM*,
 intravascular*, ocular, neurolymphomatosis,
 CLIPPERS—expanding spectrum
 antecedent demyelinating or inflammatory lesion

CNS involvement in systemic lymphoma

Direct

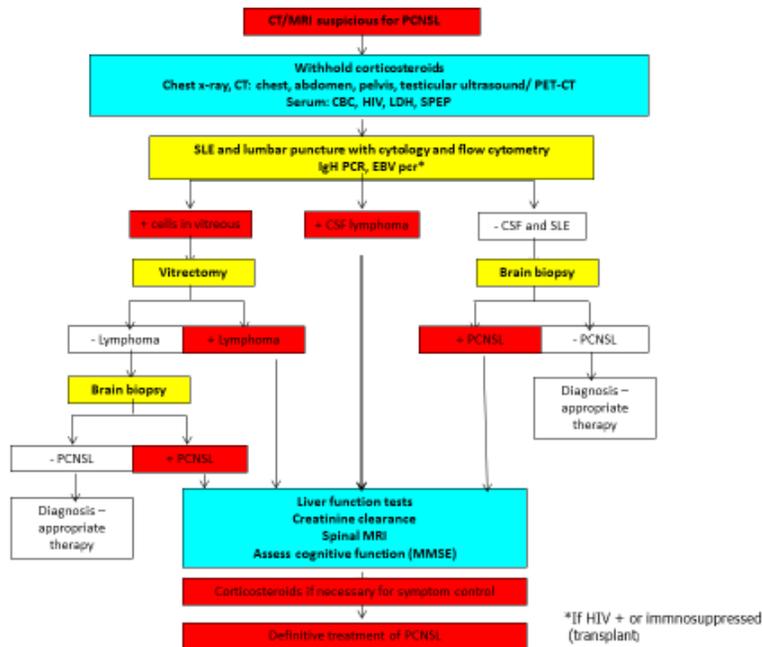
Paraneoplastic

PCNSL in immunocompromised:

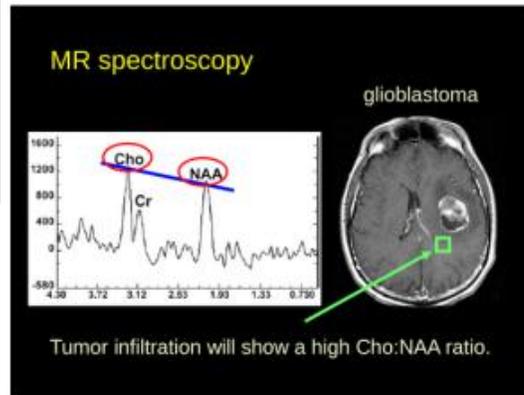
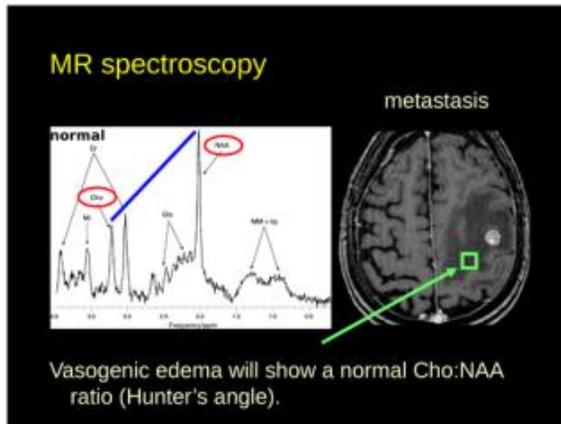
AIDS

Transplant recipients

* May have systemic symptoms (fever, sweats, weight loss)
 There are few randomized controlled clinical trials on this subject.
 10 years of international consortium
 AAN strength of evidence guidelines will be respected.



IV Tumor or Not? Neurologic consultants are often the “gatekeepers”, trying to arrive at a diagnosis before calling a neurosurgeon for a biopsy. They can use advanced imaging techniques but also new biomarkers in CSF to arrive at sometimes elusive diagnoses such as CNS lymphoma or to distinguish tumor recurrence from treatment-related pseudoprogression or pseudo-regression.



Slide courtesy of Dr. Joshua Klein

Tumor Board

A frequent neurologic consultation involves advice about choice of anti-epileptic drugs (AEDs). The following table emphasizes the large number of cytotoxic and targeted therapies that are negatively impacted by enzyme-inducing AEDs.

Chemotherapy agents negatively affected by concomitant use of EIAEDs

- **Corticosteroids**---bidirectional
- **Alkylating Agents**: carmustine, lomustine, nimustine, fotemustine, thiotepa, cyclophosphamide, ifosfamide
NOTE: NOT temozolomide
- **Mitotic Inhibitors**: vincristine, vinorelbine, paclitaxel, docetaxel
- **Topoisomerase Inhibitors**: irinotecan, topotecan, etoposide, doxorubicin
- **Antimetabolites**: methotrexate, pemetrexed
- **Signal Transduction Inhibitors**: imatinib, gefitinib, lapatinib, erlotinib, sorafenib, sunitinib, tipifarnib, everolimus, vemurafenib, temsirolimus, enzastaurin
- **Proteasome Inhibitors**: bortezomib

Drugs with increased toxicity on Valproate: nitrosureas, cisplatin, etoposide, irinotecan, vorinostat

Late recurrence of paroxysmal seizure-like episodes may not always represent seizures. We will discuss other paroxysmal events including SMART/ALERT syndromes.

Complications of new therapies:

The rapid development of effective therapies for many previously poorly treatable systemic neoplasms includes an array of new syndromes as complications of these promising modalities. Patients with cerebral metastases from non-small cell lung cancer, melanoma and non-Hodgkin lymphoma are now achieving durable remissions with PD1 and PDL1 inhibitors and trials of immune checkpoint inhibitors are underway for primary brain tumors as well as for progressive multifocal leukoencephalopathy. Among the recognized complications of these agents are:

PD1 and PDL1 inhibitors: pembrolizumab and nivolumab

- Anti-PD1 antibodies approved for melanoma, renal cell carcinoma, Hodgkin's lymphoma, NSCLC; clinical trials in other advanced solid tumors (GBM), atypical meningiomas, PML
- Adverse effects:
 - PRES
 - Demyelinating lesions – are they contraindicated in MS patients?
 - AIDP/CIDP, acute axonal neuropathy: our 2 patients, one GBS, one painful axonal neuropathy: IVIG
 - Hypophysitis
 - Myasthenia gravis
 - Enteric neuropathy
 - Transverse myelitis
 - Pseudoprogression of both primary and metastatic brain tumors
 - Autoimmune encephalitis*

Hottinger AF. Current Opinion Neurol 2016;29 epub
*Llams T. JAMA Neurol 2016;73:928

The Posterior Fossa: Urgent Syndromes to Recognize

When an oncology patient presents with posterior fossa signs and symptoms, not only is the situation often urgent but it also may be specifically circumscribed in its diagnostic possibilities. Thus recognition of the often treatable syndromes that are tropic to this region is essential. Posterior fossa signs may be the presenting sign of bacterial infection (*Listeria rhombencephalitis*, invasive fungal infections), can one of the more unusual localizations of posterior reversible encephalopathy syndrome (PRES) due to many agents (bevacizumab, sunitinib, and many others), unusual osmotic demyelination syndromes, CLIPPERS, Erdheim-Chester, akinetic mutism postoperatively or due to treatment complications (tacrolimus), and progressive multifocal leukoencephalopathy (PML). We will pay special attention to the multiple situations in which PML needs to be considered, including late survivors of hematopoietic cell transplantation and recipients of alkylating therapy, and we will address new approaches to treatment.

Reference List

- Armstrong AE, Gillan E, DiMario FJ. SMART syndrome in adult and pediatric patients. *J Child Neurol* 2013.
- Blakeley JO, Plotkin SR. Therapeutic advances for the tumors associated with neurofibromatosis type 1, neurofibromatosis type 2, and schwannomatosis. *Neuro Oncol* 2016;18:264-36
- Bowers DC, Nathan PC, Constine L, et al. Subsequent neoplasms of the CNS among survivors of childhood cancer: a systematic review. *Lancet Oncol*. 2013 Jul;14(8):e321-8.
- Braganza MZ, Kitahara CM, Berrington de González A, et al. Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. *Neuro Oncol*. 2012 Nov;14(11):1316-24.
- Chao ST, Ahluwalia MS, Barnett GH, et al. Challenges with the diagnosis and treatment of cerebral radiation necrosis. *Int J Radiat Oncol Biol Phys*. 2013 Nov 1;87(3):449-57.

- Cutsworth-Gregory JK, Lanzino G, Link MJ, et al. Characterization of radiation-induced cavernous malformations and comparison with a nonradiation cavernous malformation cohort. *Journal of Neurosurgery*. May 2015 /Vol. 122/No. 5/Pages 1214-1222.
- DeGraaff HJ, Wattjes MP, Rozemuller-Kwakkel AJ, et al. Fatal B-cell lymphoma following CLIPPERS. *JAMA Neurol* 2013;70:9115-918.
- DiGiacomo AM, Margolin K, Immune checkpoint blockade in patients with melanoma metastatic to the brain. *Semin Oncol* 2015;42:459-465.
- DiGiannatale A, Morana G, Rossi A, et al. Natural history of cavernous malformations in children with brain tumors treated with radiotherapy and chemotherapy. *J Neurooncol* (2014) 117:311–320.
- DiStefano AL, Berzero G, Vitai P, et al. Acute late-onset encephalopathy after radiotherapy: an unusual life-threatening complication. *Neurology* 2013;1:1014-1017.
- Dudesek A, Rimmele F, Tesar S, et al. CLIPPERS: review of an increasingly recognized entity within the spectrum of inflammatory CNS disorders. *Clin Exp Immunol* 2014;175:385-396.
- Franz DN, Agricola K, Mays M et al Everolimus for subependymal giant cell astrocytoma: 5- year final analysis. *Ann Neurol* 2015;8:929-38.
- Fullerton HJ, Stratton K, Mueller S, et al. Recurrent stroke in childhood cancer survivors. *Neurology* 2015;85:1056-64.
- Goldberg SB, Gettinger, SN, Mahajan A, et al. Pembrolizumab for patients with melanoma or non small-cell lung cancer and untreated brain metastases: early analysis of a nonradomised, open-label phase 2 trial. *Lancet Oncol* 2016;17:976-983.
- Golombievski EE, McCoyd MA, Lee JM Schneck MJ. Biopsy proven tumefactive MS with concomitant glioma: case report and review of the literature. *Front Neurol* 2015;6 article 150
- Joubert B, Desestret V, Rheims S. Brain pseudo-tumor inflammatory lesion associated with chronic myelomonocytic leukemia. *J Neurooncol* 2013; 113:149-150.
- Kaley TJ, Wen P, Schiff D, et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *Neuro-Oncology* 2015;17:116-121.
- Kalus S, DiMuzio B, Gaillar F. Demyelination preceding a diagnosis of CNS lymphoma. *J Clin Neurosci* 2016;24:146-148.
- Kiess AP, Wolchok JD Barker Ca et al. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: Safety profile and efficacy of combined treatment. *Int J Radiat Ocol Biol Phys* 2015;92:368-375.
- Kirkpatrick JP, Laack NN, Soltys SG, Brain metastases from melanoma: therapy at the crossroads. *Int J Rad Oncol Biol Phys* 2016;96:713-716.
- Lee EQ. Nervous system metastases from systemic cancer. *Continuum* 2015;21(2): 415-428
- Lin X, DeAngelis LM. Treatment of brain metastases. *J Clin Oncol* 2015;33:3475-3484.
- Longbrake EE, Cross AH. Effect of multiple sclerosis disease-modifying therapies on B cells and humoral immunity . *JAMA Neurol* 2016;73:219-225.
- Lubelski D, Abdullah KG, Weil RJ, Marko NF. Bevacizumab for radiation necrosis following treatment of high grade glioma: a systematic review of the literature. *J Neurooncol*. 2013 Dec;115(3):317-22.
- Nayak L, Pentsova E, Batchelor TT. Primary CNS lymphoma and neurologic complications of hematologic malignancies. *Continuum* 2015;21:355-72.
- Nolan CP, DeAngelis LM. Complications of chemotherapy and radiation therapy . *Continuum* 2015;21:429-451.
- Ortega MR, Usmani N, Patta-Herran C, et al. CLIPPERS complicating multiple sclerosis causing concerns o CNS lymphoma . *Neurology* 2012;79:615-716.
- Perry JR. Thromboembolic disease in patients with high-grade glioma. *Neuro-Oncol* 2012;14:73-80.
- Pruitt AA. Medical management of patients with brain tumors. *Continuum* 2015;21(2): 314 -31.
- Sechi GP, Serra A. Wernicke's encephalopathy : new clinical settings and recent advances in diagnosis and management. *Lancet Neurol* 2007;6:442-55.
- Short NJ, Connors JM. New oral anticoagulants and the cancer patient. *The Oncologist* 2014;19:82-93.
- Strowd PE, Strowd LC, Blakeley JO. Cutaneous manifestations in neuro-oncology :clinically relevant tumor and treatment associated dermatologic findings. *Sem Oncol* 2016;43:401-407.
- Taieb G, Duflos C, Renard D, et al. Long-term outcomes of CLIPPERS in a consecutive series of 12 patients. *Arch Neurol* 2012;69:847-755.