Grand Rounds

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Case Presentation

49M presents with four month history of weakness, inability to close eyelids, and irritation to both eyes

Pertinent Hx: 40 lbs of weight loss, bilateral facial numbness, generalized weakness, occasional diplopia

(-): Fever, chills, SOB, GI/GU issues, relation to time of day.

Case Presentation

dVasc: 20/40 OU

EOMS: -1/-2 abduction deficit OS, otherwise full

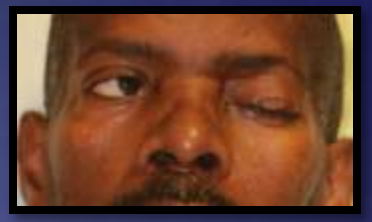
Cranial Nerves:

- Diminished sensation in V1-3 bilaterally
- Bilateral facial n. palsy

Motor and sensory examination wnl

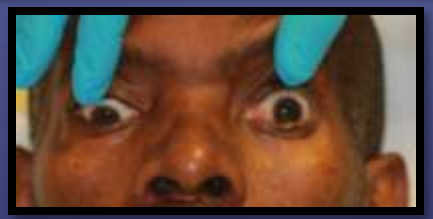
SLE and fundus exam normal



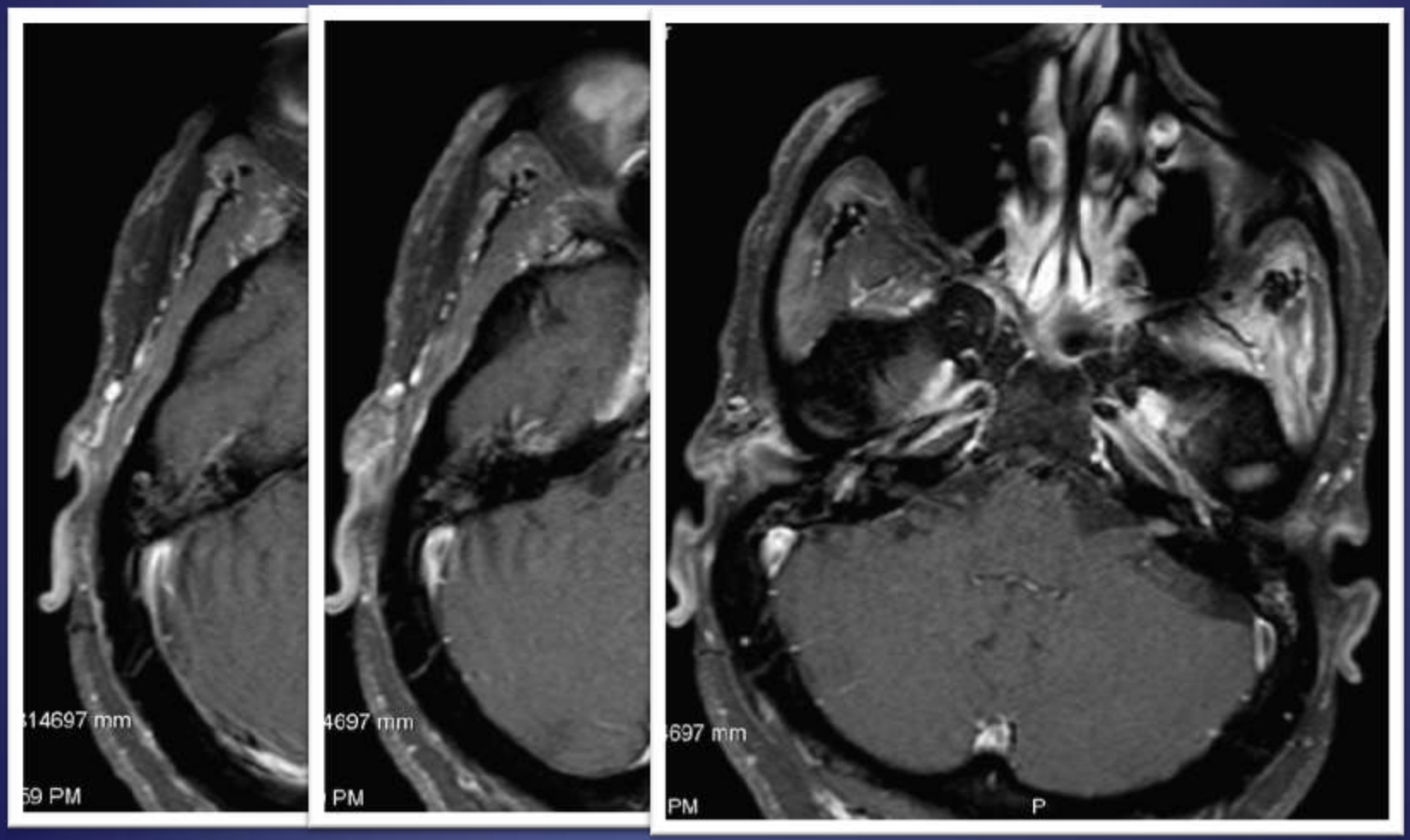








NEXT STEP?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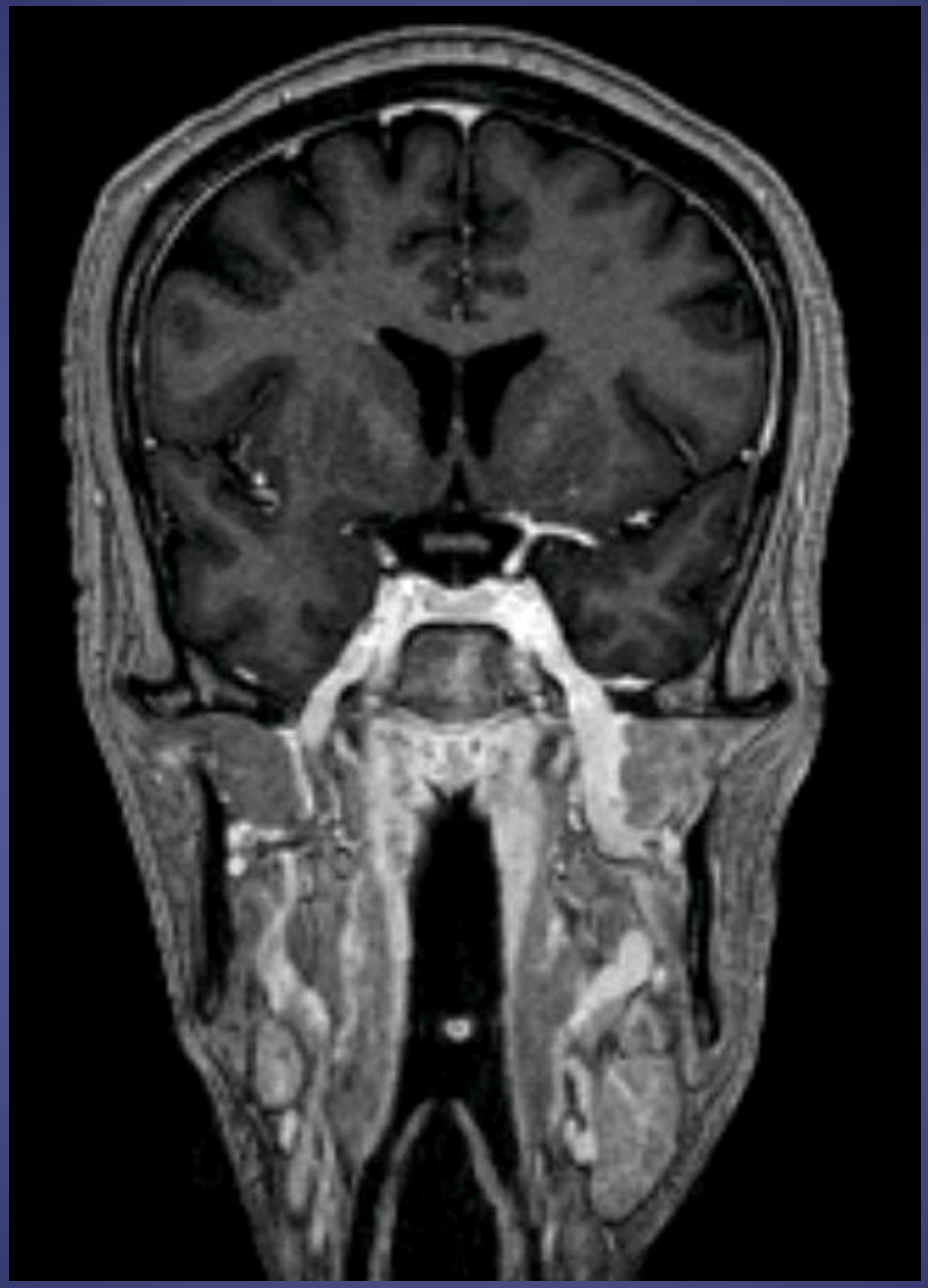

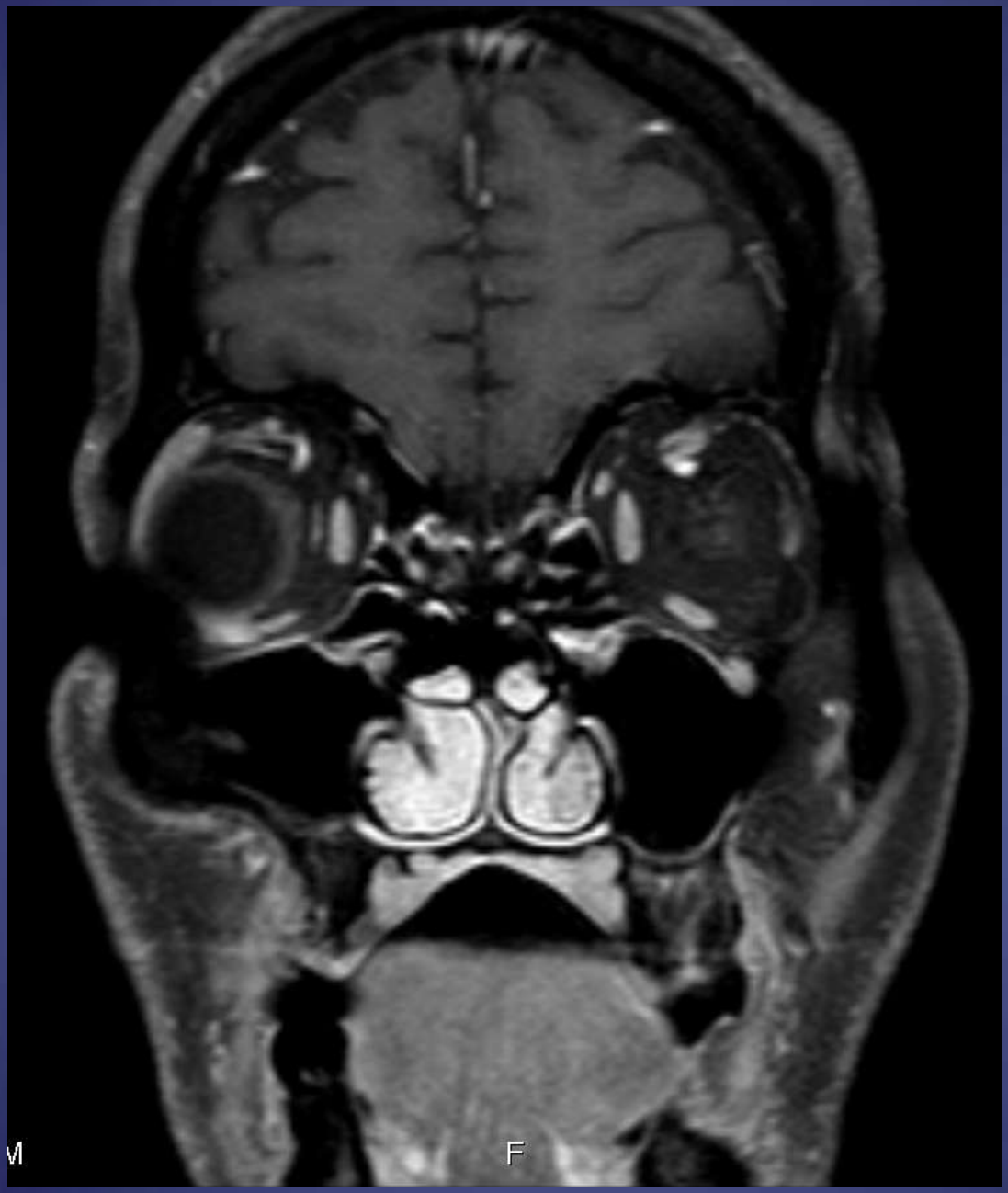
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NEXT STEP?

CSF Diagnostic Testing

Protein total: 355 (elevated)

Glucose 29 (decreased)

WBC 135 (0-5; highly elevated, Lymph 61%, Mono 35%)

RBC 90 (<5; elevated)

(-):

ACE, immunofixation, West Nile, Bact/Viral/Fungal/AFB cultures, agglutination, VDRL, Myelin basic protein, electrophoresis

CSF Antibody Testing

Antibodies: IgG: not sufficient quantity, IgA 15.1, IgM 1.6 (elevated)

Cytology: increased lymphocytes and monocytes, CD3 (+), (-) CD20, (-) CD117

Flow Cytometry: CSF with **T/LGL lymphocytosis**, 99% T-Cells CD3+/CD56+/CD57+

Impression: T-Cell Lymphocytosis, "typically reactive"

*FLOW CYTOMETRY:

Limited morphologic examination of the cytospin smears prepared from flow cytometry specimen shows small round mature lymphocytes. Immunophenotyping of the received CSF specimen by flow cytometry shows a T-cell population (99% of the gated lymphocytes) with no aberrant loss or aberrant expression of T-cell markers. No B-cell population or NK cell population is detected by Flow analysis. CD3+/CD56+ T/LGL lymphocytes represent 99% of the gated lymphocytes. They also express CD57 and are negative for CD16 and negative for CD8. Impression: Presence of a population of T/LGL in the CSF.
Refer to leukemia/lymphoma evaluation for complete immunophenotypic profile.

COMMENTS:

A) Large granular T-cell lymphocytosis can be seen in elderly patients and as a reactive process secondary to viral infections, neoplasms, autoimmune disorders (i.e. rheumatoid disorders, collagen vascular disease), and therapy (i.e. chemotherapy, bone marrow transplantation). Persistent, progressive expansion of large granular T-lymphocytes in the absence of a secondary etiology with symptomatic cytopenias is suggestive of a clonal expansion (i.e. large granular lymphocytic leukemia). If clinically indicated, molecular analysis of the T-cell receptor gamma gene (15930X) and cytogenetic karyotyping (14600X) may be helpful. Clinical correlation and follow up is suggested.
Please see peripheral blood flow cytometry report; CH616204

DIAGNOSIS/INTERPRETATION:

A) Peripheral Blood (Flow Cytometry)
Peripheral blood with no morphologic or immunophenotypic evidence of a lymphoproliferative disorder or presence of blasts.

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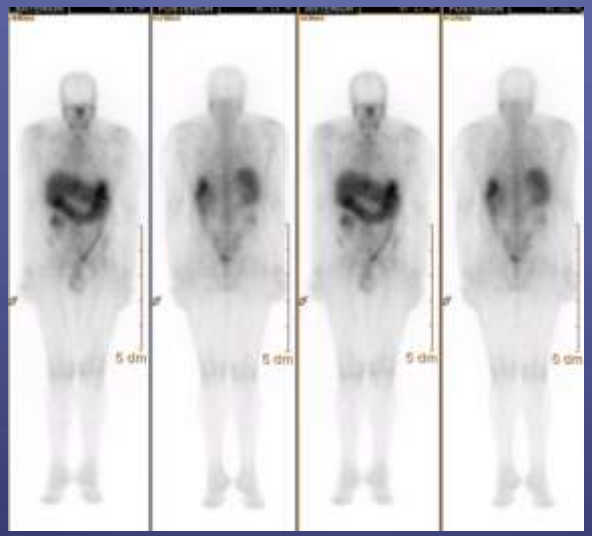
*FLOW CYTOMETRY:
Limited morphologic examination of the smears prepared from flow cytometry specimen shows mature WBCs. The lymphocyte count, morphology and immunophenotype are within normal limits. CD4:CD8 ratio is slightly elevated (5.9). NK cells (13% of gated lymphocytes), T/LGL (2% of gated lymphocytes), blast gated cells, granulocyte gated cells and monocyte gated cells are within normal limits. Please see CSF flow cytometry report; CH616022

Other Imaging

CT Chest/Abd/Pelvis: WNL, no LAD, only multiple hypoattenuating lesions <1cm in the liver.

Whole-body Gallium Scan: WNL



Hospital Course

Week 1-2: Progressive bilateral complete facial palsy with exposure keratopathy. Undergoes tests as noted.

Week 3: No improvement, with progressive weight loss and no improvement in facial palsy.

Begun on 1 mg/kg PO steroids.

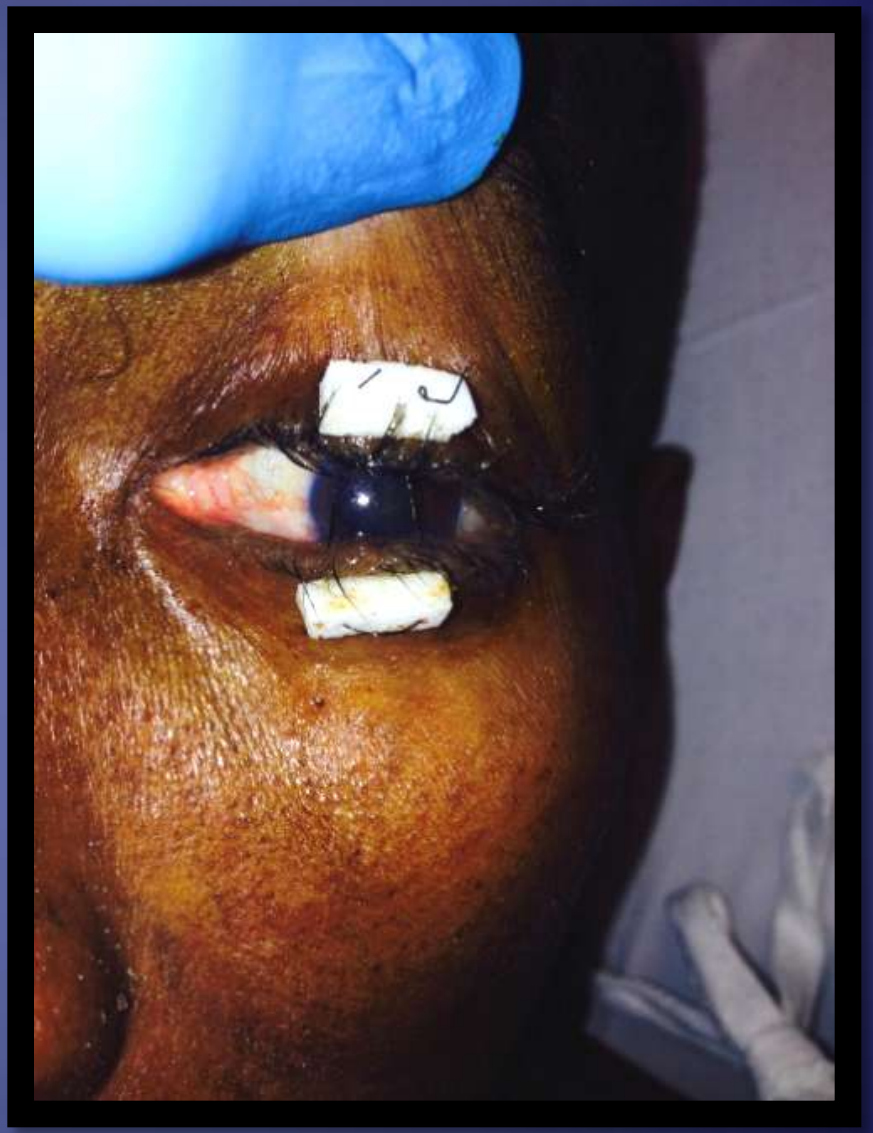
Week 6: Still no improvement, now with hyponatremia.

Presumed secondary to siADH

Admitted, placed on IV dexamethasone.

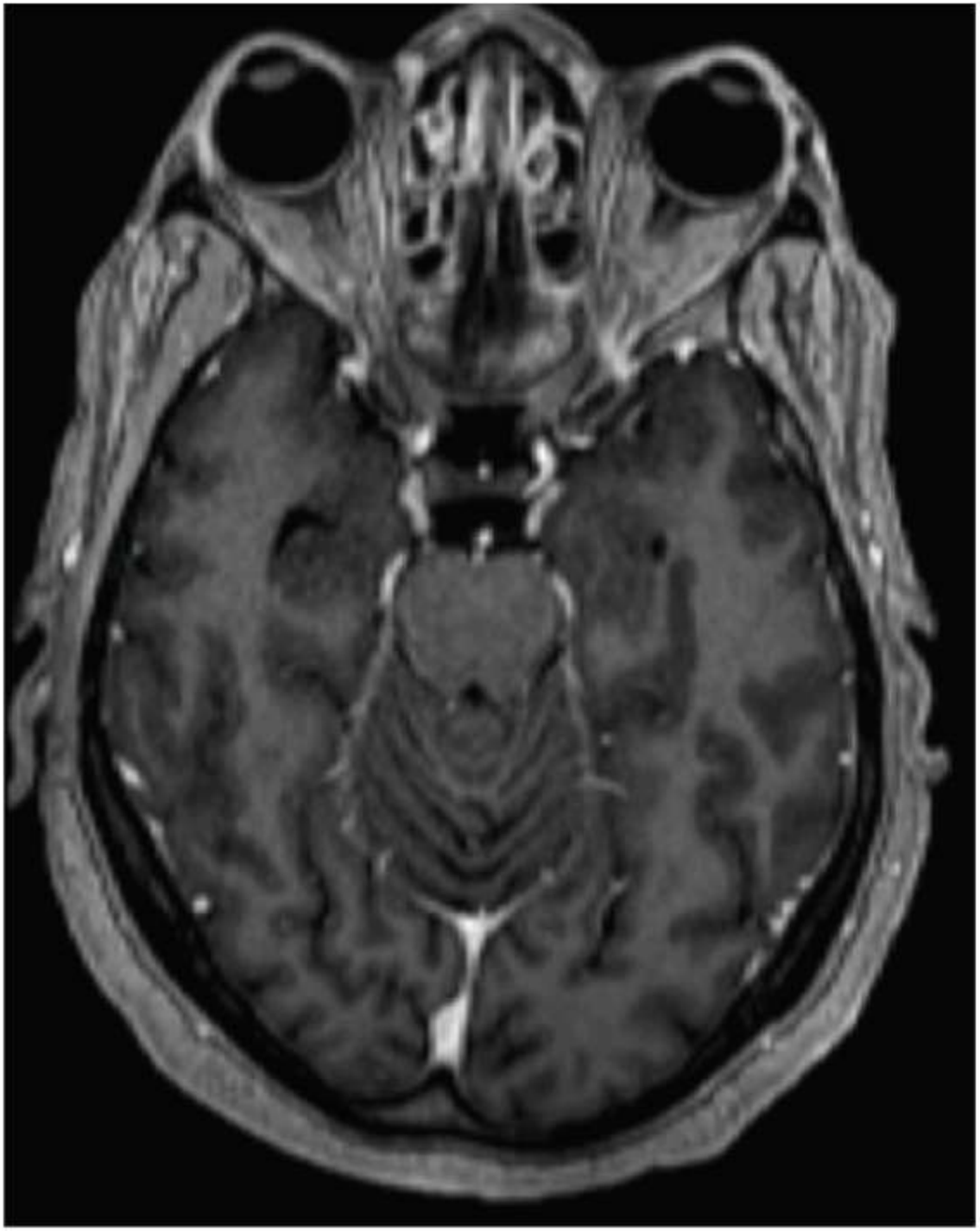
Repeat MRI with new extension of enhancing lesions into the internal acoustic canal, through Meckel's Cave, and through the foramen rotundum. Subjective improvement of facial numbness. Liver biopsy not possible.

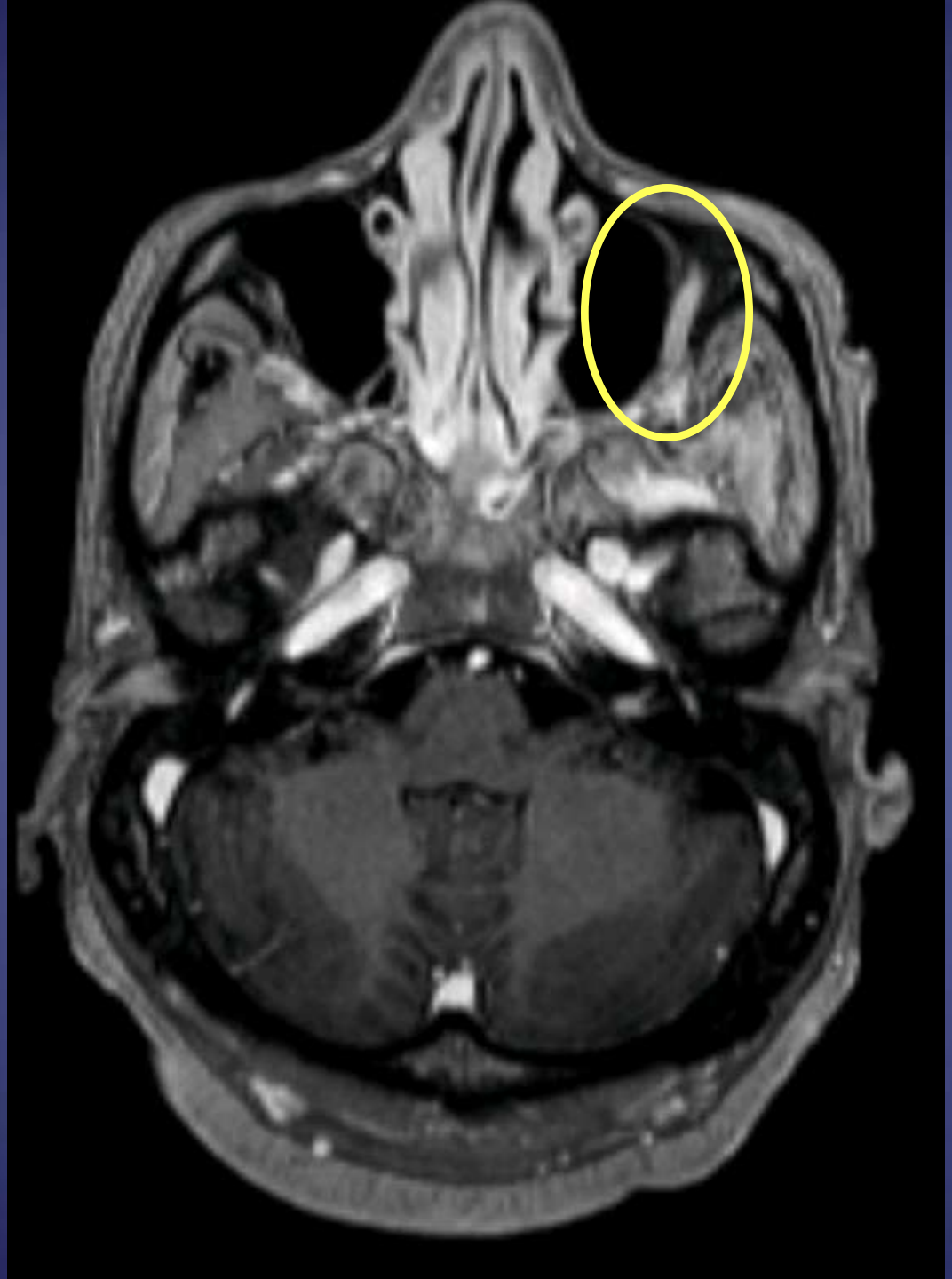
Week 8:

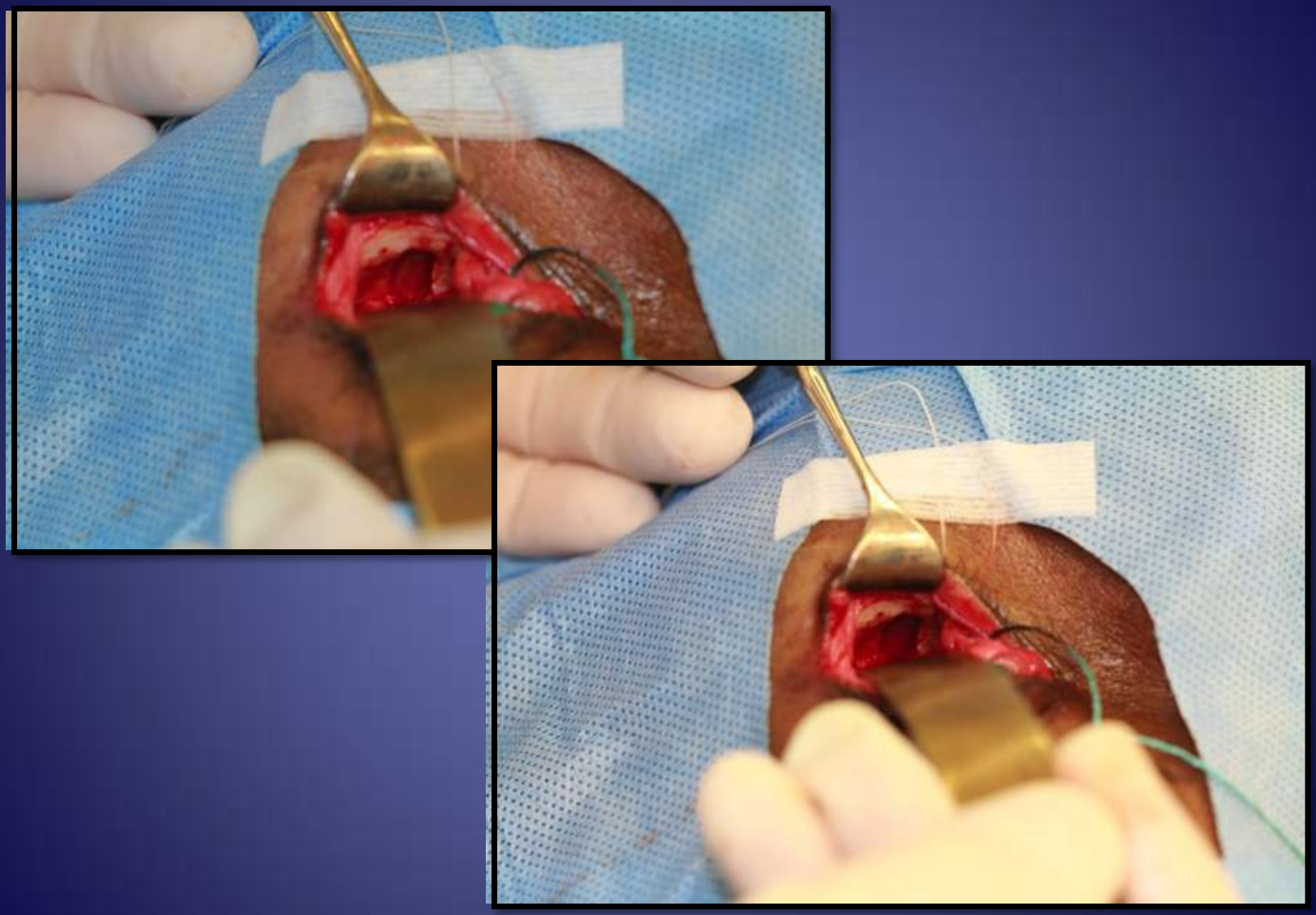


What to do next?

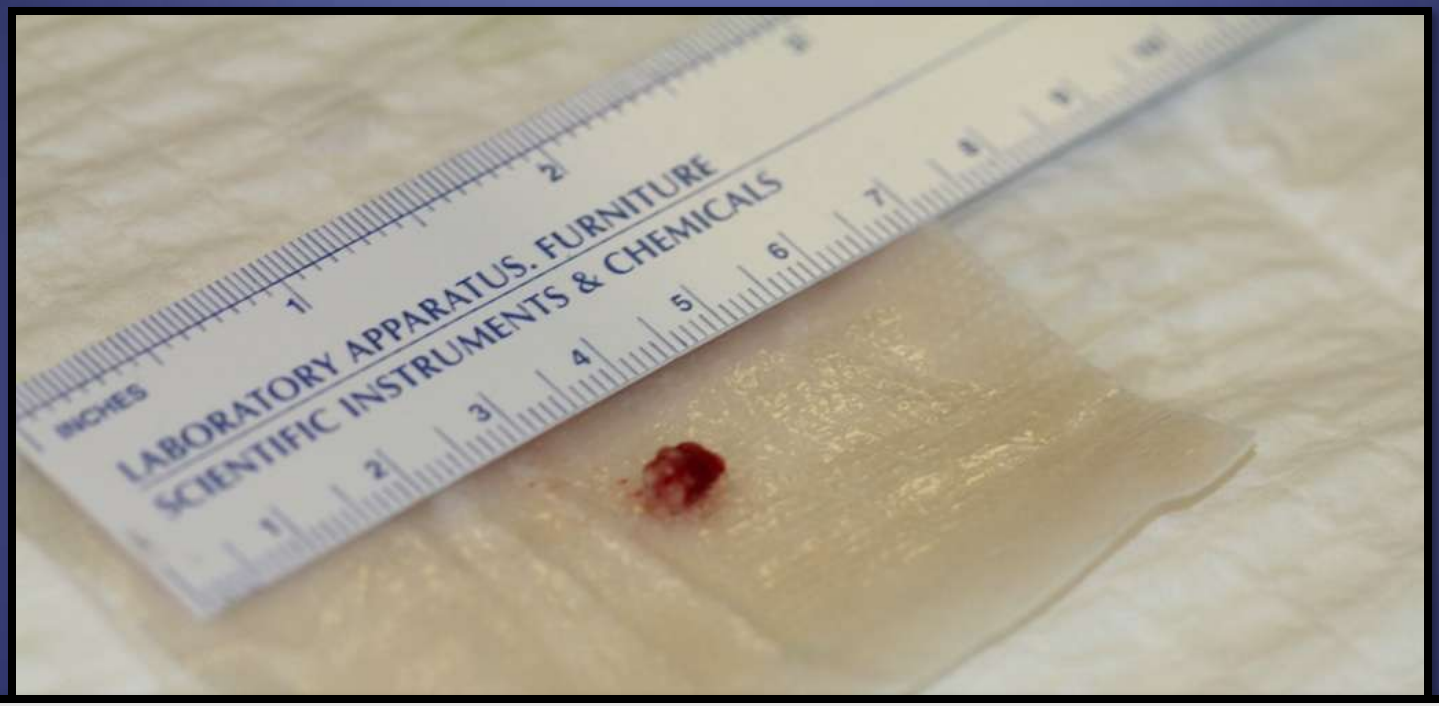
- Diagnostic dilemma:
  - What can be the cause for an enhancing bilateral lesion affecting multiple cranial nerves?
    - Inflammatory? (Sarcoid?) Serum/CSF (-) ACE/Lysozyme, Chest CT (-), Gallium (-)
    - Infectious? Never any systemic signs, all testing (-), better on steroids
    - Paraneoplastic Syndrome? SiADH (+), Gallium (-),
    - Leptomeningeal Carcinomatosis? CSF studies all (-), Gallium (-)







Pathology Review

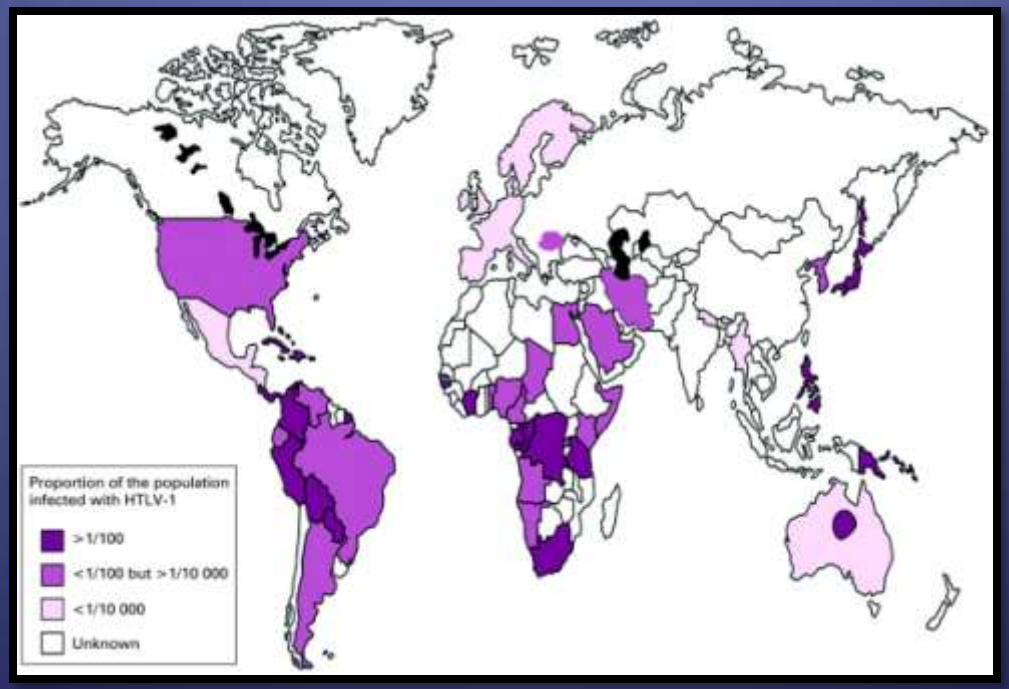


In summary, patient is a 49 yo, M, presented as multiple cranial nerve palsy, positive serum test for HTLV-1 antibody. Recent CSF flow cytometry study reported CSF with involvement by mature T-cell neoplasm, favor adult T-cell leukemia/lymphoma (See Quest Diagnostic report CH623049). The morphologic and immunophenotype features combined with clinical information are consistent with involvement by adult T cell leukemia/ lymphoma.

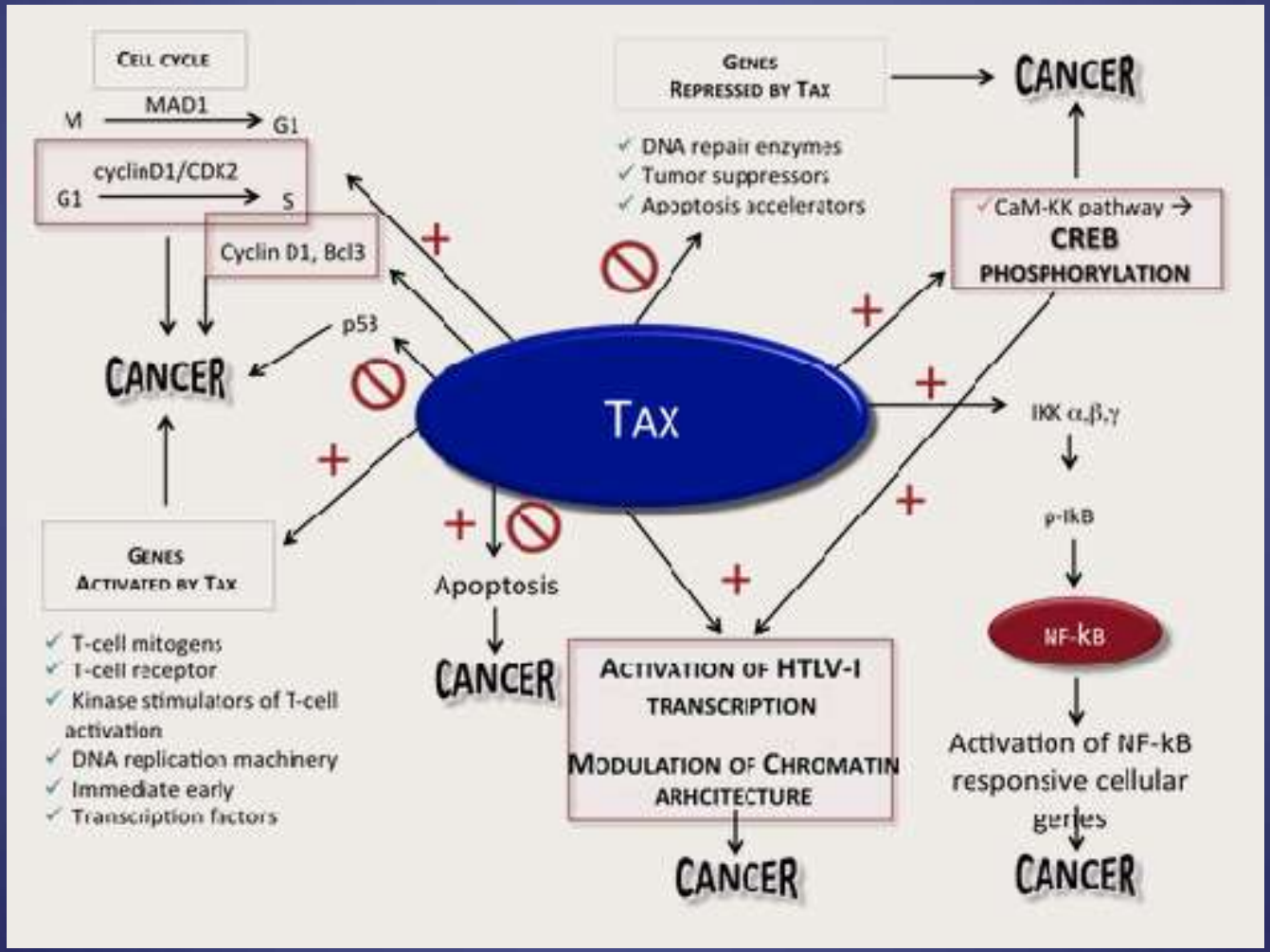
HTLV-1

Human T-cell Leukemia Virus

- Discovered in 1980, first pathogenic retrovirus found
- Routes: Breast milk, sexual intercourse, blood transfusions (IV)
- 5%: Aggressive T-cell leukemia
- 15-20 million infected



Pathogenesis

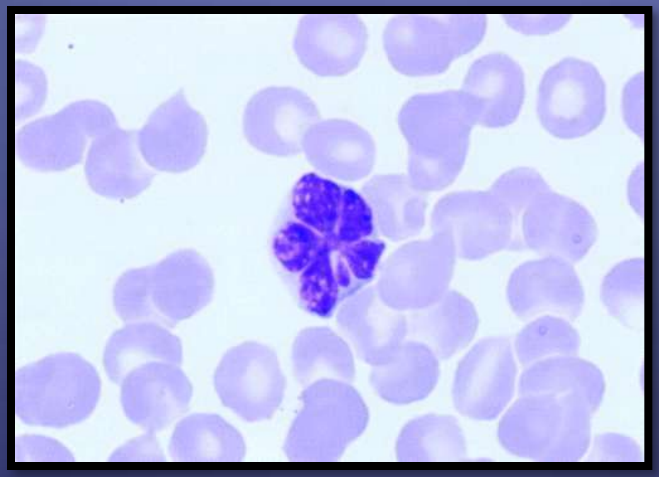


HTLV-1 Associations

- Adult T-lymphocytic Leukemia/Lymphoma
- HTLV-1-associated myelopathy / tropical spastic paraparesis (HAM/TSP)
- Uveitis
- Sicca syndrome
- Polymyositis
- Arthropathy
- Neurological (spastic bladder, ED, weakness, hyperreflexia, peripheral neuropathy)

Adult T-cell Leukemia/Lymphoma

- 1977: Uchiyama and Takatsuki – "flower cells," separate clusters in Japan
- 1980: Gallo- association with HTLV-1
- 1990s: clusters found in the Caribbean, tropical Africa, South America, Middle East.



Clinical Features

- Various! Depends on organ involved.
- Vast majority: Lymph nodes +/- Peripheral blood
- ATLL cells, opportunistic infections, hypercalcemia are main causes of high morbidity and mortality
- Lymph nodes, liver, spleen lesions
  - Less common – GI, bone, CNS
- Hypercalcemia – 31%
  - 50% of acute-type ATLL

Diagnostic Criteria

Table 1
Diagnostic criteria for clinical subtypes of adult T-Cell leukemia-lymphoma.

	Smoldering	Chronic	Lymphoma	Acute
Anti-HTLV-I antibody	+	+	+	+
Lymphocyte ($\times 10^3/\mu$UL)	<4	≥4	<4	[a]
Abnormal T lymphocytes	≥5%[d]	+[c]	≤1%	+[c]
Flower cells with T-cell marker	[b]	[b]	No	+
LDH	≤1.5 N	≤2 N	[a]	[a]
Corrected Ca^{2+} (mEq/L)	<5.5	<5.5	[a]	[a]
Histology-proven lymphadenopathy	No	[a]	+	[a]
Tumor lesion				
Skin and/or lung	[a]	[a]	[a]	[a]
Lymph node	No	[a]	Yes	[a]
Liver	No	[a]	[a]	[a]
Spleen	No	[a]	[a]	[a]
Central nervous system	No	[a]	[a]	[a]
Bone	No	No	[a]	[a]
Ascites	No	No	[a]	[a]
Pleural effusion	No	No	[a]	[a]
Gastrointestinal tract	No	No	[a]	[a]

HTLV-1, human T-lymphotropic virus type I; LDH, lactate dehydrogenase; N normal upper limit.
With permission from Shimoyama M, Members of the Lymphoma Study Group (1984–1987): Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma. Br J Haematol 1991; 79:428.

[a] No essential qualification except terms required for other subtype(s).

[b] Typical "flower cells" may be seen occasionally.

[c] If the proportion of abnormal T lymphocytes is less than 5% in peripheral blood, a histologically proven tumor lesion is required.

[d] Histologically proven skin and/or pulmonary lesion(s) is required if there are fewer than 5% abnormal T lymphocytes in peripheral blood.

Prognostic Indicators

- Performance status (Karnofsky)
- Age >40
- ⬇Albumin
- Hypercalcemia

ECOG	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on selfcare. Totally confined to bed or chair

- Less so: cytopenias, marrow involvement, high IL-5,

Treatment

Table 2
Strategy for the treatment of adult T-Cell leukemia-lymphoma.

Smoldering-or favorable chronic-type ATL

- Consider inclusion in prospective clinical trials
- Symptomatic patients (skin lesions, opportunistic infections, etc): consider AZT/IFN or watch and wait
- Asymptomatic patients: consider watch and wait

Unfavorable chronic- or acute-type ATL

- If outside clinical trials, check prognostic factors (including clinical and molecular factors if possible):
  - Good prognostic factors: consider chemotherapy (VCAP-AMP-VECP evaluated by a phase III trial against biweekly-CHOP) or AZT/IFN (evaluated by a meta-analysis on retrospective studies)
  - Poor prognostic factors: consider chemotherapy followed by conventional or reduced intensify allo-HSCT (evaluated by retrospective and prospective Japanese analyses, respectively).
  - Poor response to initial therapy: consider conventional or reduced intensity allo-HSCT

Lymphoma-type ATL

- If outside clinical trials, consider chemotherapy (VCAP-AMP-VECP)
- Check prognostic factors (including clinical and molecular factors if possible) and response to chemotherapy:
  - Good prognostic factors and good response to initial therapy: consider chemotherapy followed by observation
  - Poor prognostic factors or poor response to initial therapy: consider chemotherapy followed by conventional or reduced intensity allo-HSCT.

So how rare is primary CNS lymphoma secondary to ATLL?

Why was this so hard to diagnose?

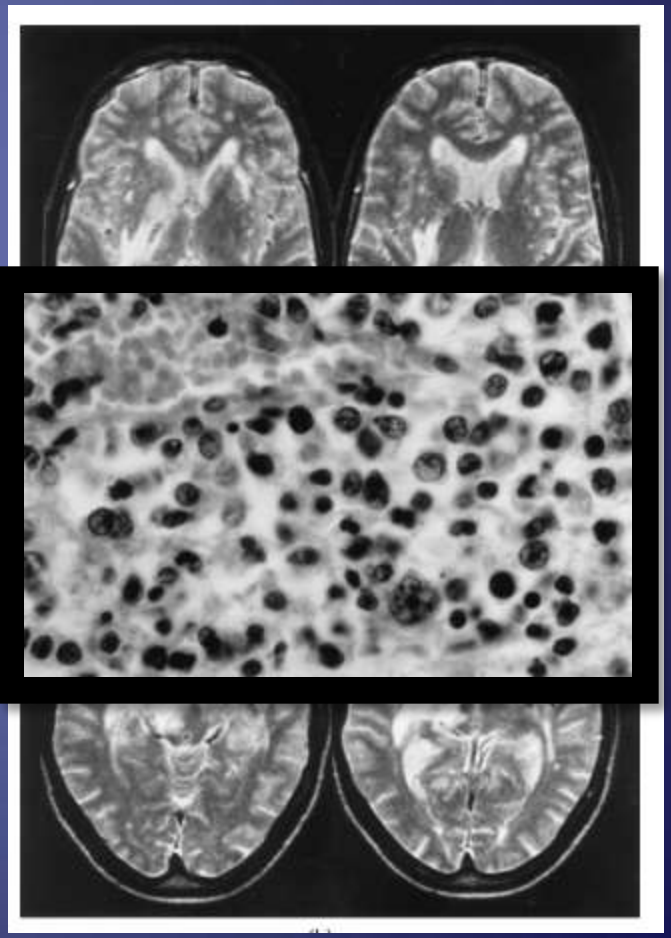
JOURNAL OF THE NEUROLOGICAL SCIENCES

HTLV-I associated primary CNS T-cell lymphoma

drew G. Marshall[a], Rachel Pawson[b], Maria Thom[a], Thomas F. Schutz[c], Francesco Scaravilli[a], Peter Rudge[a,*]

[*]The National Hospital for Neurology and Neurosurgery, and Institute of Neurology, Queen Square, London, UK

- First case reported of ATLL-associated primary CNS lymphoma (1997)
- 42 year-old African-Caribbean male, one month hx of lethargy, anorexia, unsteadiness
- ATLL by stereotactic bx
- Expired secondary to respiratory and cardiac arrest



Haematologia, Vol. 31, No. 4, pp. 365–367 (2002)

Primary lymphoma of the central nervous system and HTLV-I infection

ENRIQUE J. CALDERÓN[1,*,†], MIGUEL A. JAPÓN[2], ISIDORO CHINCHÓN[2], VICENTE SORIANO[3,†] and FRANCISCO J. CAPOTE[4,†]

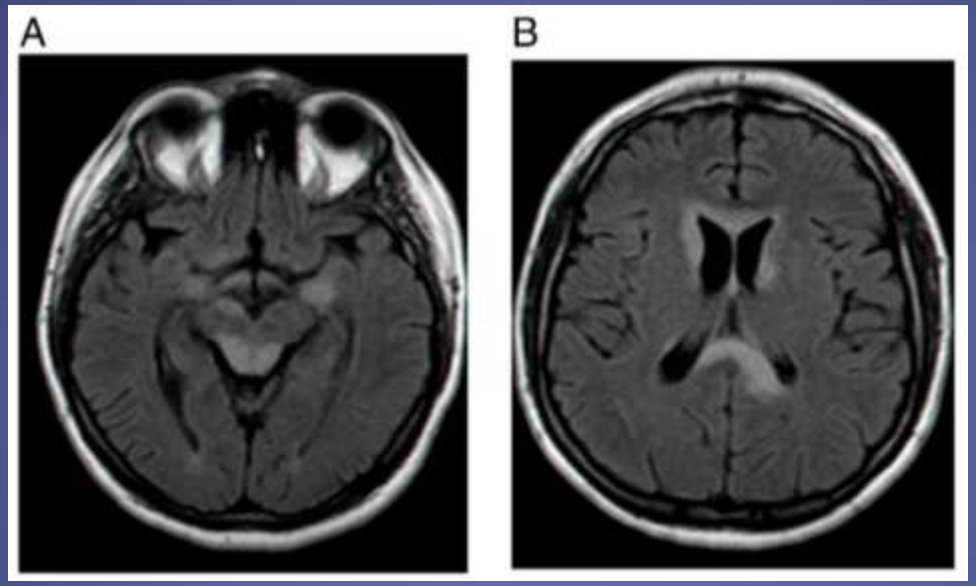
[1] *Department of Internal Medicine, Virgen del Rocío University Hospital, Seville, Spain*

- Case report of two Spanish men with primary CNS T-cell lymphoma
- Both IV drug abusers who were HIV (+)
- One HTLV-1 (+)
- Not proven to be ATLL by biopsy
- Both expired soon after presentation

Journal of the Neurological Sciences

Primary brain T-cell lymphoma in an HTLV-1 serologically positive male

Itay Lotan [a], Alexander Khlebtovsky [a], Edna Inbar [b], Julia Strenov [c], Ruth Djaldetti [a], Israel Steiner [a,*]



29 year old male from Uzbekistan, with recurrent episodes of confusion, drowsiness, lack of time perception, and visual hallucinations of 4 months' duration.

HTLV (+) – only discovered when attempted blood donation 12 years prior.

Only diagnosed ATLL on temporal lobe biopsy.

Expired 14 months after diagnosis.

Journal of the Neurological Sciences

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Table 1
Previously reported patients with HTLV-1-associated brain T-cell lymphoma.

Mode of diagnosis	Imaging findings	Clinical findings on examination	Clinical presentation	Patient's age and sex
Two consecutive stereotactic brain biopsies	Mild swelling of the Rt pons and midbrain. High signal from the internal capsule to the centrum semiovale	Drowsiness, hemiparesis, broad-based gait	Progressive lethargy, anorexia, unsteadiness	42, male [4]
Open brain biopsy	NA	NA	NA	29, male [5]
Autopsy	NA	NA	NA	34, male [5]
Open brain biopsy	Cerebellar mass lesion with perifocal edema	Spastic paraparesis, no cerebellar signs	10 years history of progressive paraparesis followed by 3 months of headache	63, female [6]

NA — not available.

Back to our patient!

- The patient was finally diagnosed via infraorbital nerve biopsy.
- Received one dose of methotrexate intrathecal
- Was scheduled for Ommaya reservoir by neurosurgery for further intrathecal chemotherapy
- Left hospital against medical advice to seek second opinion
- Showed up one Friday at 4PM to resume treatment “feeling worse”...

Reflective Practice

This was an excellent case that required me to delve into the literature for further workup of a diagnostic dilemma. It required me to take ownership of my patient and make certain that he received the proper attention and care he deserved for a difficult case to diagnose. It also required the ophthalmology team to think outside the box for a biopsy. Furthermore, the team worked together with neurology, hematology/oncology, pathology, and neurosurgery in order to properly manage this patient.

Patient Care, Practice-Based Learning and Improvement

Core Competencies

Patient Care- Took care to provide patient care that was compassionate and appropriate, and effective

Medical Knowledge- Recognized the signs and symptoms of intracranial lymphoma, evaluated for associated medical issues and symptomology, and attempted to treat patient using standardized and a well-thought out plan of care.

Practice-based Learning and Improvement- demonstrate the ability to investigate and evaluate the care of our patients, including improving our methods of management of intracranial lymphoma with regard to scant literature.

Interpersonal and Communication Skills- demonstrate interpersonal and communication skills with a difficult and problematic patient that will result in the effective exchange of information

Professionalism- demonstrate a commitment to carry out professional responsibilities and an adherence to ethical principles despite many obstacles

Systems-based Practice- demonstrate the ability to call effectively on other resources, such as primary care and ancillary staff in the system to provide optimal health care.

References

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Thank You

- Dr Temnogorod
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