Is there a role for non-glucocorticoid immunomodulation in CNS-TB?

A case-based discussion

California Tuberculosis Controllers Association Spring Meeting

March 15, 2024

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END TB

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Disclosures

- I have no financial relationships to disclose.
- I have no conflicts of interest to disclose.

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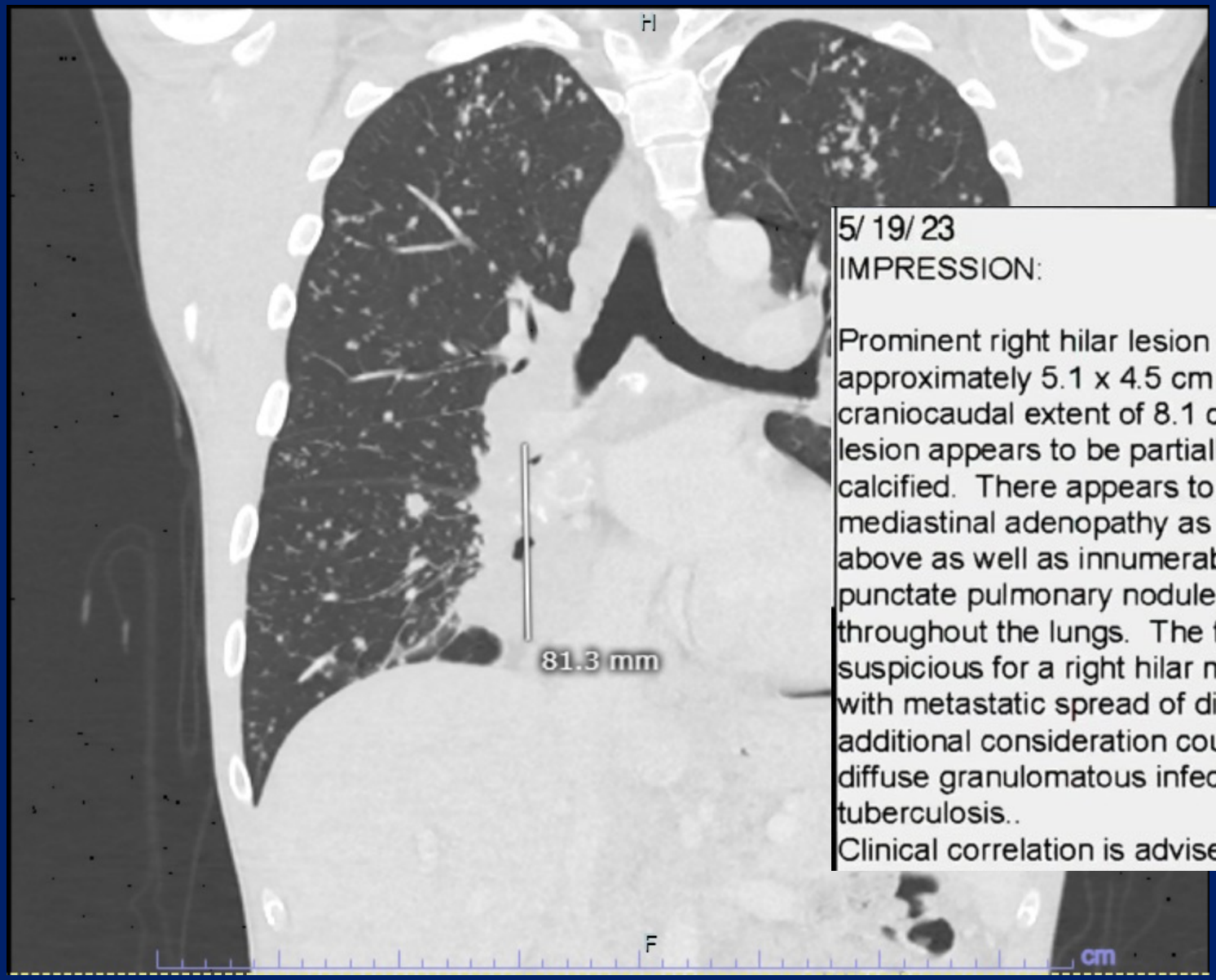
Learning Objective

- Understand how immunomodulating therapy may be utilized to improve CNS-TB treatment outcomes in patients with paradoxical reaction.

Case: initial presentation

- 33-year-old man
  - HIV-negative, US-born; non-Hispanic white
    - Recreational cannabis; occasional alcohol
    - Pharmacy clerk
    - Lived in southeast Asia for 5 years as an English teacher
  - Presented with generalized weakness and fatigue in May 2023
  - Subjective diplopia on lateral gaze, intermittent headaches, as well, despite unremarkable exam
  - Found to have hyponatremia, hilar lymphadenopathy



5/ 19/ 23
IMPRESSION:

Prominent right hilar lesion measuring approximately 5.1 x 4.5 cm with a craniocaudal extent of 8.1 cm. This lesion appears to be partially calcified. There appears to be associated mediastinal adenopathy as detailed above as well as innumerable punctate pulmonary nodules distributed throughout the lungs. The findings are suspicious for a right hilar malignancy with metastatic spread of disease. An additional consideration could include diffuse granulomatous infection such as tuberculosis..
Clinical correlation is advised.

Case: **sarcoidosis,** or what?

Date: 5/3/23 **IGRA** Type: QFT ☐ Positive ☐ Indeterminate ☒ Negative

TB 1 Antigen	IU/mL	0.48
TB 2 Antigen	IU/mL	0.44
NIL	IU/mL	0.36
Mitogen	IU/mL	>10.00

5/4/2023 cervical lymph node biopsy:

FINAL DIAGNOSIS

A. **Right cervical lymph node core biopsy:**
   - **Granulomatous lymphadenitis.**
   - **Negative special stains for acid-fast bacilli and fungus.**

5/8/23: AFB smear(-), culture(-) from BAL x 1

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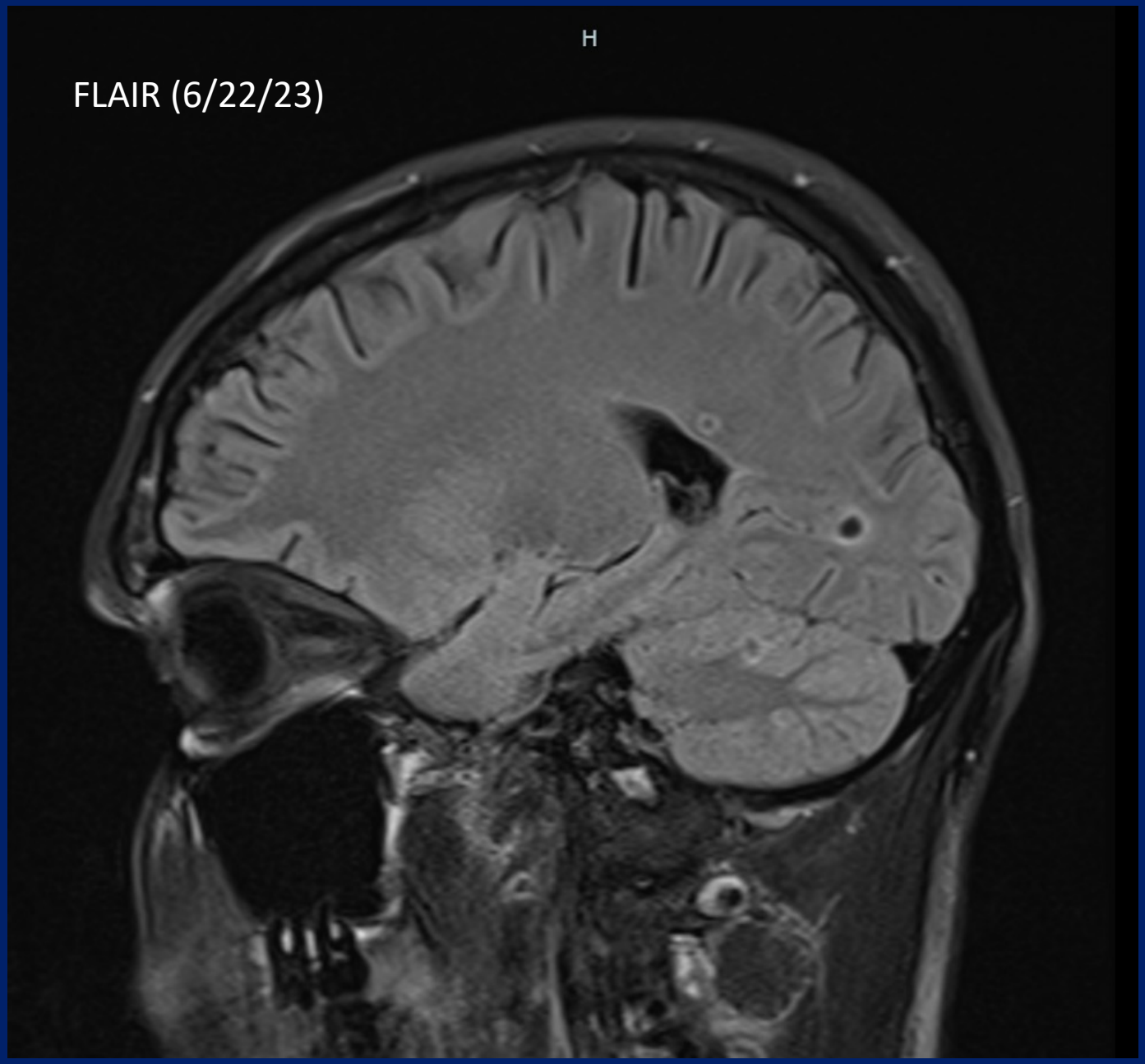
Case: **neurosarcoidosis,** or what?

CSF (5/24/23): glucose 22, protein 237; 1 nucleated cell

MRI brain with contrast 5/24/2023 demonstrated 2 enhancing lesions with adjacent edema in the left cerebellum and left lateral ventricle approximately 5 mm; mild leptomeningeal enhancement at the skull base; small acute infarct right basal ganglia ~6 mm.

- **5/25/23: started on prednisone 45mg BID (~1.5mg/kg):**
  - **gradual improvement in strength;**
  - **transferred to County's acute rehab facility;**
  - **discharged after ~1 month**



FLAIR (6/22/23)

Case: prednisonopenia, or what?

- **7/8/23: presents to ER with lethargy/confusion, low-grade fever (Tm 100.6F), recurrent hyponatremia**
  - **Per outpatient pharmacy records, unclear if prednisone (and TMP-SMX prophylaxis) prescriptions were filled upon discharge ~2 weeks prior**

Date/Time	Specimen	Smear	PCR	Culture
7/10/23 1330	CSF	1+	Detected Rif resist-NOT detected	MTBc
7/12/23 0000	Tracheal asp	4+		MTBc

Centers for Disease Control and Prevention

National Center for Emerging and Zoonotic Infectious Diseases (NCEZID)

Division of High-Consequence Pathogens & Pathology (DHCPP)

Infectious Diseases Pathology Branch (IDPB)

Molecular Testing Report

Results:

Specimen	Test	Result
PCR		
Rt cervical lymph node core biopsy (5/4/23)	Mycobacterium genus 16S rRNA	Negative
Rt cervical lymph node core biopsy (5/4/23)	Mycobacterium tuberculosis complex (IS6110)	Positive for Mycobacterium tuberculosis complex species

2 x 2: Two facilities x two months

- At just the acute rehab facility, ~100 exposed individuals were identified.
  - Over 50% were patients.

https://dhs.lacounty.gov/rancho/patient-programs-and-services/don-knabe-wellness-center/

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Case: empiric TBM treatment…?

- **Anti-TB treatment initiated promptly (7/11/23):**
  - **rifampin 600mg (PO) +**
  - **isoniazid 300mg/B6 +**
  - **ethambutol 1200mg +**
  - **pyrazinamide 1500mg**
- **Anything else…?**
  - **Recommended IV dexamethasone 0.1mg/kg/dose Q6 hours (7/14/23)**
    - **Dexamethasone not started until 8/4/23**
  - **IV RIF + LVX + LZD also recommended (7/14/23)**

ORIGINAL ARTICLE

N Engl J Med 2004;351:1741-51.

Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

Guy E. Thwaites, M.R.C.P., Nguyen Duc Bang, M.D., Nguyen Huy Dung, M.D., Hoang Thi Quy, M.D., Do Thi Tuong Oanh, M.D., Nguyen Thi Cam Thoa, M.D., Nguyen Quang Hien, M.D., Nguyen Tri Thuc, M.D., Nguyen Ngoc Hai, M.D., Nguyen Thi Ngoc Lan, Ph.D., Nguyen Ngoc Lan, M.D., Nguyen Hong Duc, M.D., Vu Ngoc Tuan, M.D., Cao Huu Hiep, M.D., Tran Thi Hong Chau, M.D., Pham Phuong Mai, M.D., Nguyen Thi Dung, M.D., Kasia Stepniewska, Ph.D., Nicholas J. White, F.R.C.P., Tran Tinh Hien, M.D., and Jeremy J. Farrar, F.R.C.P.

Thwaites et al: Dexamethasone in TBM

N Engl J Med 2004;351:1741-51

Table 2. Outcome Nine Months after Randomization, According to Disease-Severity Grade and HIV Status.*

Outcome and Group	Dexamethasone	Placebo	Relative Risk (95% CI)	P Value
	no./total no. (%)			
Death				
All patients	87/274 (31.8)	112/271 (41.3)	0.69 (0.52–0.92)	0.01
Grade				
I	15/90 (16.7)	26/86 (30.2)	0.47 (0.25–0.90)	0.02
II	38/122 (31.1)	50/125 (40.0)	0.71 (0.46–1.1)	0.11
III	34/62 (54.8)	36/60 (60.0)	0.81 (0.51–1.29)	0.38
Relative risk of death stratified according to grade†			0.68 (0.52–0.91)	0.007
HIV status				
Negative	57/227 (25.1)	67/209 (32.1)	0.72 (0.51–1.02)	0.07
Positive	27/44 (61.4)	37/54 (68.5)	0.86 (0.52–1.41)	0.55
Undetermined	3/3 (100)	8/8 (100)	1.16 (0.71–1.91)	0.71
Relative risk of death stratified according to HIV status‡			0.78 (0.59–1.04)	0.08

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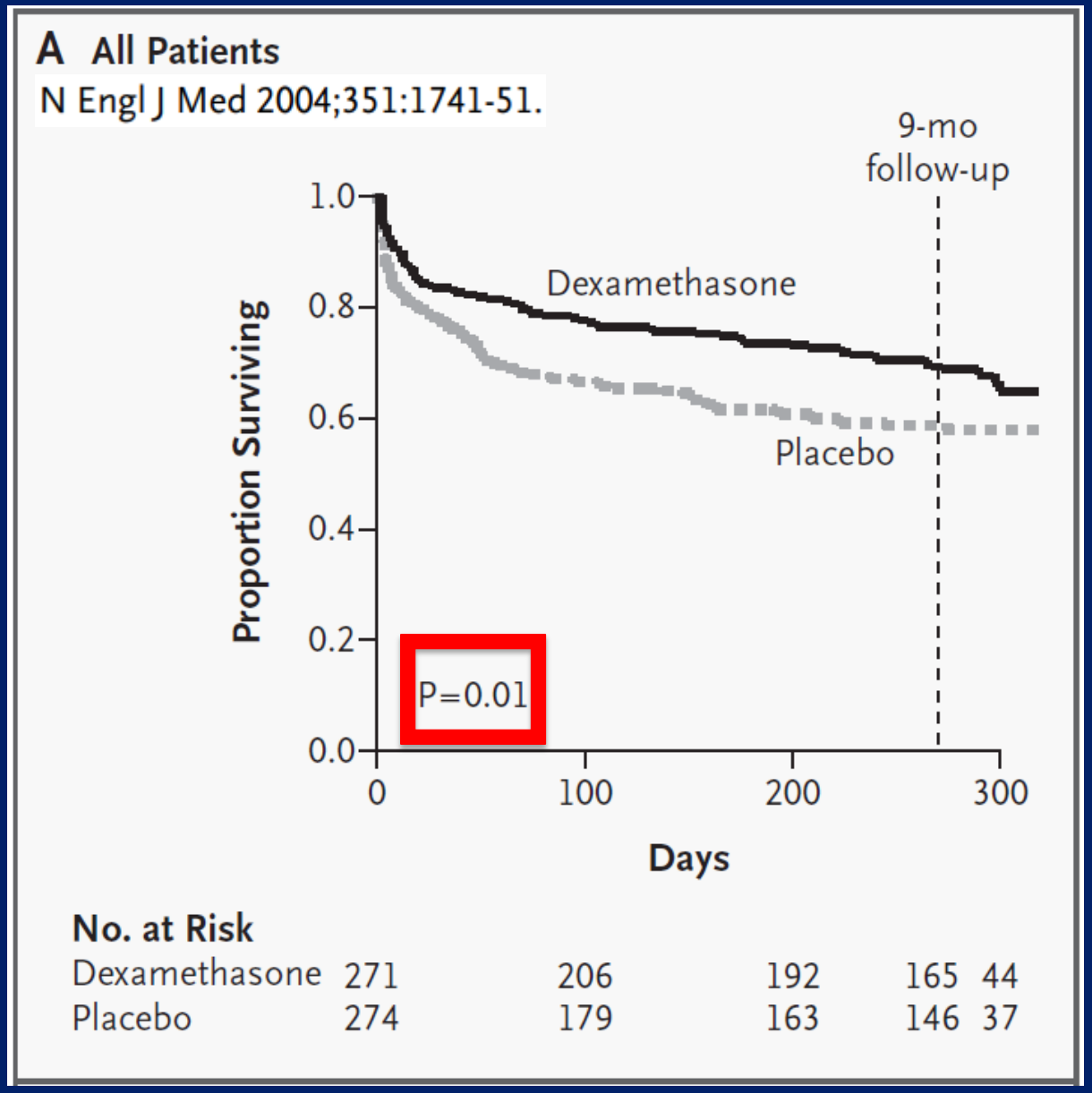
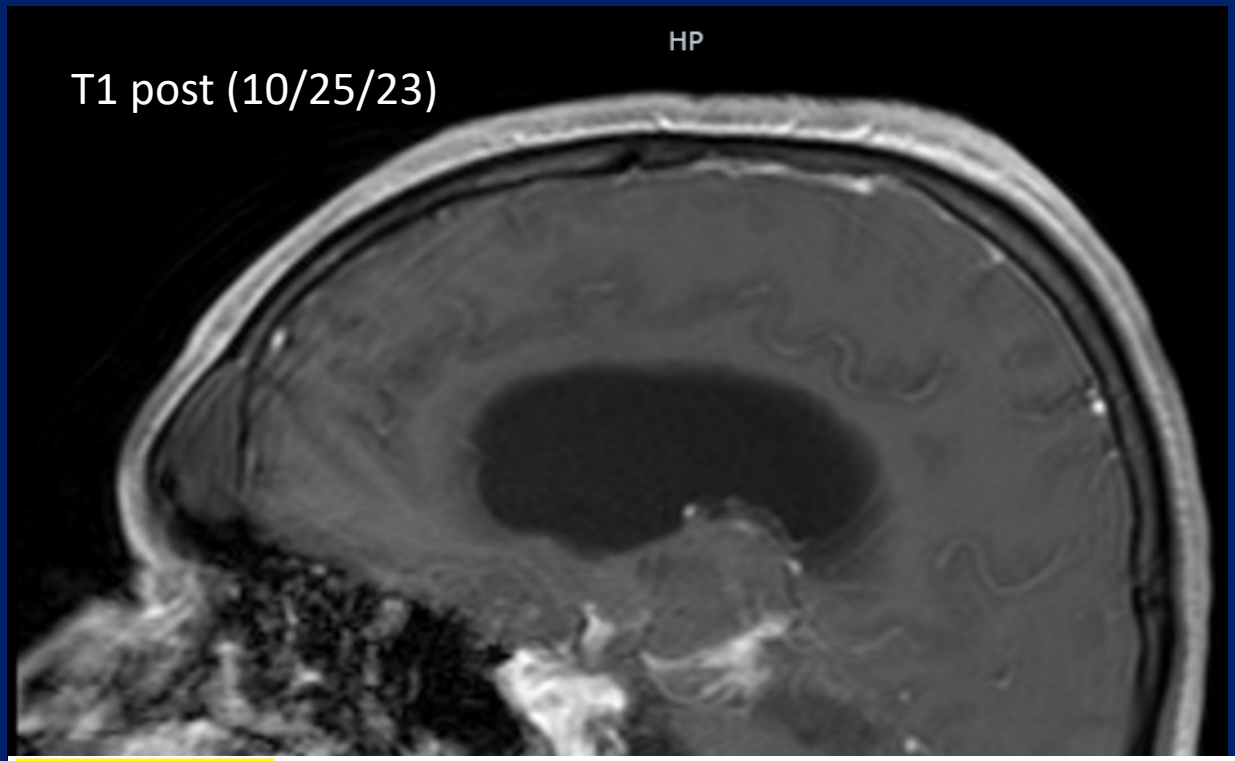

A All Patients
N Engl J Med 2004;351:1741-51.
9-mo follow-up
1.0
0.8
0.6
0.4
0.2
0.0
Proportion Surviving
Dexamethasone
Placebo
P=0.01
0
100
200
300
Days
No. at Risk
Dexamethasone 271 206 192 165 44
Placebo 274 179 163 146 37

Treatment response and course: 7-10/2023

- 8/4-8/24/23: dexamethasone tapered quickly with recurrence of fevers, but with relative radiographic stability (7/16 vs. 8/23/23)
- 8/25/23: dexamethasone dose increased to 0.1mg/kg/dose Q6 hours, but with quick tapering every ~5 days, despite recurrence of high-grade fevers and worsening encephalopathy



10/25/23 Repeat MRI brain

Impression:

Interval development of essentially circumferential enhancement around the upper brainstem/cerebral peduncles, possible infectious.

There remains a focus of enhancement in the left frontotemporal lobe and left cerebellum as was present previously.

There remains ventriculomegaly and probable transependymal edema, grossly similar to previous.

Old right basal ganglia infarct.

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The Center creates, enhances, and disseminates state-of-the-art resources and models of excellence and performs research to control and eliminate tuberculosis in the United States and internationally.

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Option 2: Email: Currytbcenter@ucsf.edu

Option 3: *New!* Visit: CITC.idcrowd.org, register as a member, and complete the information requested

In the voicemail message or email, please provide the following:

1. *Full name (please clearly spell out your name)*
2. *Your organization, city, and state*
3. *Your email address*
4. *Telephone number and the best times to reach you within the next 48 hours*
5. *A brief summary of your question; please do not include the patient's name or any other unique identifiers*

Your request will be forwarded to a consultant that is on duty.

Clinical Infectious Diseases

MAJOR ARTICLE

Effectiveness of Adjunctive High-Dose Infliximab Therapy to Improve Disability-Free Survival Among Patients With Severe Central Nervous System Tuberculosis: A Matched Retrospective Cohort Study

Abi Manesh,[1] Priyanka Gautam,[1] Selwyn Selva Kumar D,[1] Pavithra Mannam,[2] Anitha Jasper,[2] Karthik Gunasekaran,[3] Naveen Cherian Thomas,[4] Rohit Ninan Benjamin,[5] Leeberk Raja Inbaraj,[6] Emily Devasagayam,[1] Mithun Mohan George,[1] Rajiv Karthik,[1] Ooriapadickal Cherian Abraham,[3] Harshad A. Vanjare,[2] Ajith Sivadasan,[5] Prabhakar Thirumal Appaswamy,[5] Edmond Jonathan,[7] Joy S. Michael,[8] Prasanna Samuel,[9] and George M. Varghese[1]

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Clin Infect Dis 2023 Nov 17;77(10):1460-1467. doi: 10.1093/cid/ciad401.

Infliximab for CNS-TB in south India (2019-2022)

Clin Infect Dis 2023 Nov 17;77(10):1460-1467. doi: 10.1093/cid/ciad401.

- **Retrospective cohort study** (N = 90, 2:1 matching)
  - **Single center** (~200 CNS-TB patients/year)
  - **CNS-TB** = TB meningitis (TBM), tuberculomas, tuberculous vasculitis, spinal involvement, optochiasmatic TB
- **Intervention:** IV infliximab 10mg/kg once per month, up to 3 doses
  - Infliximab doses were stopped early if there was a complete response or futility of response
  - Consensus between at least 2 ID physicians required for intervention

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Infliximab for CNS-TB in south India (2019-2022)

Clin Infect Dis 2023 Nov 17;77(10):1460-1467. doi: 10.1093/cid/ciad401.

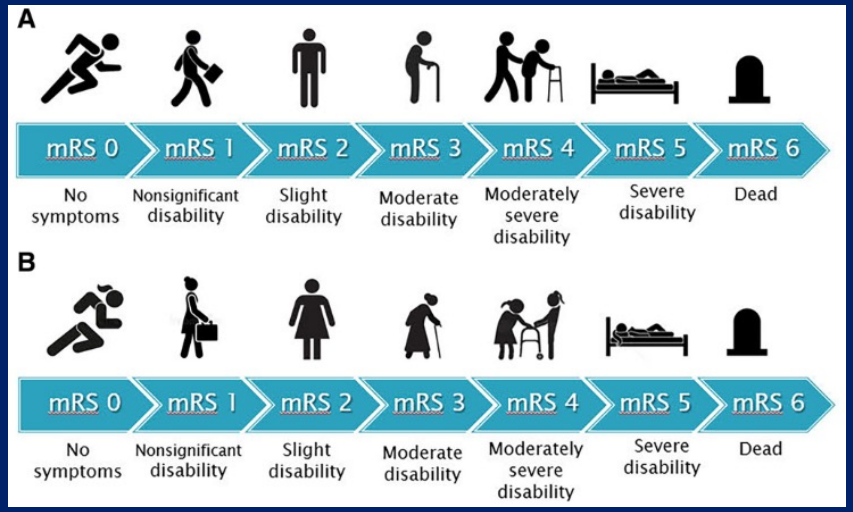
- **Cohort A (infliximab):** new-onset or persistent unimproved deficits despite weight-optimized ATT and steroids with:
  - Refractory symptomatic tuberculomas;
  - Recurrent clinical worsening on steroid tapering;
  - Optochiasmatic TB with visual deficits;
  - Recent-onset arachnoiditis with paraparesis
- **Cohort B (standard of care = ATT + steroids):**
  - 10-year historical cohort selected at same institution
  - Matched for Medical Research Council (MRC) grades and modified Rankin scale (mRS) scores

MRC & mRS

- Medical Research Council grade:
  - **Grade I:** Glasgow coma scale (GCS) 15; no focal neurological signs
  - **Grade II:** GCS 11-14; or GCS 15 with focal neurological signs
  - **Grade III:** GCS ≤ 10

Clin Infect Dis 2017 Feb 15;64(4):501-509.

- Modified Rankin Scale score:



Stroke 2021;52(9):3054-3062.

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- **Primary outcome:** disability-free survival (mRS ≤ 2) at 6 months
  - Secondary outcomes:
    - Severe disability at 6 months: mRS 4-5
    - All-cause mortality
- Bivariate analyses, followed by multivariate analyses for factors reaching statistical significance ($p<0.05$)
  - Sensitivity analysis and evaluation of collinearity

Table 1. Baseline Characteristics of Patients With Tuberculous Meningitis in Cohort A and Cohort B

doi: 10.1093/cid/ciad401

Variable	Total (N = 90)	Cohort A (n = 30)	Cohort B (n = 60)	*P*
Age (mean ± SD), y	34.48 ± 11.8	31.10 ± 8.7	36.17 ± 12.8	.056
Sex, male, n (%)	54 (60)	15 (50)	39 (65)	.171
HIV-positive status, n (%)	7 (7.8)	1 (3.3)	6 (10)	.417
Microbiologically confirmed TB,[a] n (%)	53 (58.9)	22 (73.3)	31 (51.7)	.049
Lancet criteria (n = 84),[b] n (%)				
Definite	20 (22.2)	10 (33.3)	10 (16.6)	.209
Probable	55 (61.1)	14 (46.7)	41 (68.3)	
Possible	9 (10)	4 (13.3)	5 (8.3)	
Resistance,[c] n (%)	10 (11.1)	4 (13.3)	6 (10)	.726
Disseminated TB, n (%)	75 (83.3)	27 (90)	48 (80)	.369
TBM brain alone	66 (73.3)	19 (63.3)	47 (78.3)	.129
TBM brain + spinal cord	22 (24.4)	11 (36.7)	11 (18.3)	.056
Focal neurological deficits, n (%)	76 (84.4)	26 (86.7)	50 (83.3)	.767
Hemiparesis	32 (35.6)	8 (26.7)	24 (40)	.213
Paraparesis	21 (23.3)	9 (30)	12 (20)	.290
Visual impairment	19 (21.1)	8 (26.7)	11 (18.3)	.361
Arachnoiditis	21 (23.3)	7 (23.3)	14 (23.3)	1.000
Brain meningitis on imaging, n (%)	70 (77.8)	21 (70)	49 (81.7)	.209
Brain tuberculoma on imaging, n (%)	52 (57.8)	25 (83.3)	27 (45)	.001
Abnormal chest X-ray, n (%)	55 (61.1)	19 (63.1)	36 (60)	.760
Suboptimal dosing of ATT, n (%)	32 (35.6)	11 (36.7)	21 (35)	.876
Cumulative steroid dose (dexamethasone equivalents), median (IQR) (n = 86), mg	721.5 (387.7–1237.5)	717 (407.5–1344.1)	771.7 (383.5–1170)	.964
Paradoxical worsening,[d] n (%)	40 (44.4)	19 (63.3)	21 (35)	.011
MRC grades, n (%)				
Grade 1	10 (11.1)	3 (10)	7 (11.7)	.958
Grade 2	66 (73.3)	22 (73.3)	44 (73.3)	
Grade 3	14 (15.6)	5 (16.7)	9 (15)	
mRS scores at presentation, n (%)				
mRS grade 1–2	10 (11.1)	1 (3.3)	9 (15)	.155
mRS grade 3 to 5	80 (88.9)	29 (96.7)	51 (85)	

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Infliximab for CNS-TB in south India (2019-2022)

- Cohort A (n = 30)
  - Indications for infliximab:
    - 20 (67%) symptomatic multiple or large tuberculomas;
    - 8 (27%) spinal cord involvement with paraparesis;
    - 3 (10%) vision-threatening optochiasmatic arachnoiditis
  - # of doses of infliximab:
    - 19 (63%) patients received three (3) doses of infliximab;
    - 7 (23%) received two (2) doses;
    - 4 (13%) received one (1) dose

doi: 10.1093/cid/ciad401

Infliximab for CNS-TB in south India (2019-2022)

Table 2. Treatment Outcomes for Cohort A and Cohort B at 6 Months

doi: 10.1093/cid/ciad401

Variable	Total (N = 90)	Cohort A (n = 30)	Cohort B (n = 60)	RR (95% CI)	*P*
Successful outcome, post-therapy, mRS ≤2	38 (42.2)	19 (63.3)	19 (31.7)	2.3 (1.28–4.36)	.004
Unsuccessful outcome, post-therapy mRS 3–6	52 (57.8)	11 (36.7)	41 (68.3)		
Severe disability, post-therapy mRS scores 4 and 5	26 (28.9)	5 (16.7)	21 (35)	.4 (.21–1.14)	0.070
Mortality[a]	15 (16.7)	2 (6.7)	13 (21.7)	.3 (.09–1.34)	.081

Data are presented as n (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; RR, Relative risk; TBM, tuberculosis meningitis.

[a]In cohort A, 1 patient died due to probable aspiration pneumonia and another had sudden death in sleep. In cohort B, of the 13 deaths, 11 patients died due to TBM disease progression. The other 2 died of unrelated causes, 1 due to acute *Escherichia coli* pyelonephritis with bacteremia and another because of enterococcal bacteremia.

Infliximab for CNS-TB in south India (2019-2022)

Table 3. Multivariate Logistic Regression for Predictors of Treatment Outcome at 6 Months

doi: 10.1093/cid/ciad401

				Univariate Analysis		Multivariate Analysis	
Variable	Total (N = 90)	Successful Outcome (n = 38)	Unsuccessful Outcome (n = 52)	RR (95% CI)	*P*	Adjusted RR (95% CI)	*P*
Age (mean ± SD), y	34.48 ± 11.8	33.4 ± 9.4	35.2 ± 13.4	1.0 (.97–1.05)	.491	…	
HIV-positive status, n (%)	7 (7.8)	3 (7.9)	4 (7.9)	1.0 (.41–2.47)	1.000	…	
Microbiologically confirmed TB, n (%)	53 (58.9)	24 (63.2)	29 (55.8)	1.1 (.72–1.98)	.482	…	
Presence of focal neurological deficit, n (%)	76 (84.4)	28 (73.7)	48 (92.3)	.5 (.33–.80)	.020	.2 (.05–.89)	.035
MRC grades 2 and 3, n (%)	80 (88.9)	30 (78.9)	50 (96.2)	.4 (.30–.71)	.016	1.0 (.08–12.92)	.955
MRC grade 1, n (%)	10 (11.1)	8 (21.1)	2 (3.8)				
Baseline mRS 3–5, n (%)	80 (88.9)	30 (78.9)	50 (96.2)	.4 (.30–.71)	.016	.09 (.007–1.12)	.062
Baseline mRS ≤2, n (%)	10 (11.1)	8 (21.1)	2 (3.8)				
Received infliximab, n (%)	30 (33.3)	19 (50)	11 (21.1)	2.0 (1.26–3.17)	.004	6.2 (2.18–17.83)	.001
Did not receive infliximab, n (%)	60 (66.7)	19 (50)	41 (78.8)				

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; MRC, Medical Research Council; mRS, modified Rankin Scale; RR, Relative risk; SD, standard deviation; TB, tuberculosis.

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Infliximab for CNS-TB in south India (2019-2022)

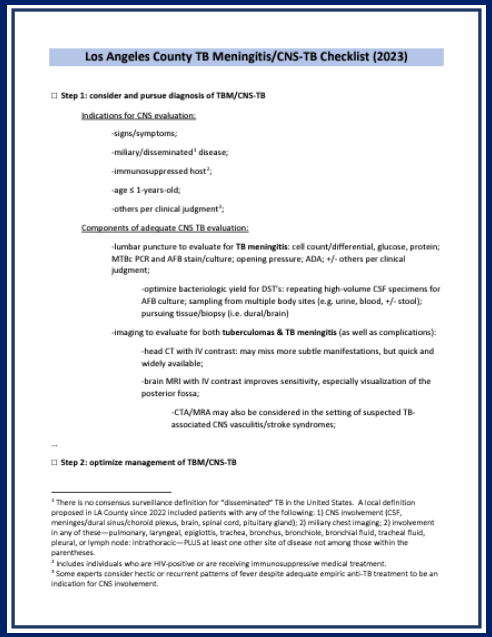
- **Take home:** receipt of 1-3 doses of infliximab (10mg/kg/dose per month) was statistically associated with **successful outcome (disability-free survival) at six months**, but **not** with **death** or **severe disability**
  - Seemed relatively safe, but not designed or powered for safety

- **Major limitations:**
  - Retrospective cohort study prone to biases and confounding
  - Dissimilar rates of tuberculoma and paradoxical response between study groups: **"cohort B serves more as a background to interpret the impact of infliximab…rather than rigorously matched controls"**
  - Single quaternary care center = late intervention (but this should translate to **less** apparent benefit)

doi: 10.1093/cid/ciad401

So…now what?

- **LA County CNS-TB/TBM Checklist (2023):**
  - "glucocorticoids are strongly recommended…"
  - "…consider other emerging strategies [for adjunctive immunomodulation] in consultation with TBCP"
- **And our patient?**
  - Family declined infliximab, but agreed to resumption of prolonged dexamethasone taper
  - Next brain MRI pending in 1 week (3/22/24)



Los Angeles County TB Meningitis/CNS-TB Checklist (2023)

☐ **Step 1: consider and pursue diagnosis of TBM/CNS-TB**

Indications for CNS evaluation:

-signs/symptoms;

-miliary/disseminated[1] disease;

-immunosuppressed host[2];

-age ≤ 1-years-old;

-others per clinical judgment[3];

Components of adequate CNS TB evaluation:

-lumbar puncture to evaluate for **TB meningitis**: cell count/differential, glucose, protein; MTBc PCR and AFB stain/culture; opening pressure; ADA; +/- others per clinical judgment;

-optimize bacteriologic yield for DST's: repeating high-volume CSF specimens for AFB culture; sampling from multiple body sites (e.g. urine, blood, +/- stool); pursuing tissue/biopsy (i.e. dural/brain)

-imaging to evaluate for both **tuberculomas & TB meningitis** (as well as complications):

-head CT with IV contrast: may miss more subtle manifestations, but quick and widely available;

-brain MRI with IV contrast improves sensitivity, especially visualization of the posterior fossa;

-CTA/MRA may also be considered in the setting of suspected TB-associated CNS vasculitis/stroke syndromes;

…

☐ **Step 2: optimize management of TBM/CNS-TB**

[1] There is no consensus surveillance definition for "disseminated" TB in the United States. A local definition proposed in LA County since 2022 included patients with any of the following: 1) CNS involvement (CSF, meninges/dural sinus/choroid plexus, brain, spinal cord, pituitary gland); 2) miliary chest imaging; 2) involvement in any of these—pulmonary, laryngeal, epiglottis, trachea, bronchus, bronchiole, bronchial fluid, tracheal fluid, pleural, or lymph node: intrathoracic—PLUS at least one other site of disease not among those within the parentheses.

[2] Includes individuals who are HIV-positive or are receiving immunosuppressive medical treatment.

[3] Some experts consider hectic or recurrent patterns of fever despite adequate empiric anti-TB treatment to be an indication for CNS involvement.

References

- *Clin Infect Dis* 2017;64(4):501-509.
- *Clin Infect Dis* 2023 Nov 17;77(10):1460-1467.
- *N Engl J Med* 2004;351:1741-51.
- *Stroke* 2021;52(9):3054-3062.
- *Wellcome Open Res* 2021;5:292. doi: 10.12688/wellcomeopenres.16474.2.

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