CLINICAL SYNOPSIS - NEUROLOGY/ONCOLOGY SERVICE

PATIENT: Harold Thompson DOB: 9/17/48 ID #: SYN017 MEDICAL RECORD #: 584960-B ADMISSION: 4/1/25 DISCHARGE: 4/13/25

PRIMARY DX: Stage IV ALK-positive non-small cell lung cancer with brain metastases ADMISSION REASON: Breakthrough seizure activity and altered mental status

ATTENDING PHYSICIANS: Dr. Marcus Chen (Neuro-oncology), Dr. Priya Sharma (Medical Oncology)

COMPREHENSIVE PATIENT HISTORY

Mr. Thompson is a 76-year-old retired architect with ALK-rearrangement positive NSCLC first diagnosed in September 2020. His initial presentation included progressively worsening headaches over 6 weeks, left-sided visual field disturbances, and one episode of transient expressive aphasia that prompted neurological evaluation. He had no prior history of tobacco use and maintained an active lifestyle until his illness, including regular tennis and cycling. His past medical history was significant only for well-controlled hypertension and hyperlipidemia.

Initial brain MRI revealed multiple contrast-enhancing lesions, the largest measuring 2.4cm in the right parietal lobe with surrounding vasogenic edema. Two additional lesions were identified in the left frontal lobe (1.1cm) and right cerebellum (0.8cm). Subsequent CT chest revealed a 3.2cm spiculated left upper lobe mass. CT-guided biopsy of the lung lesion confirmed adenocarcinoma with immunohistochemistry positive for TTF-1 and napsin A. Molecular testing identified EML4-ALK fusion via FISH and NGS. PD-L1 testing showed 25% TPS (intermediate expression). Initial PET/CT showed FDG-avid primary lesion (SUV 12.4) without evidence of extracranial metastases, supporting a diagnosis of Stage IV disease based on intracranial metastases.

TREATMENT TIMELINE

- 09/25/2020: Initiated on dexamethasone for symptomatic brain edema
- 10/02/2020: Stereotactic radiosurgery to all three brain lesions (20 Gy to right parietal, 18 Gy to left frontal, 18 Gy to cerebellar lesion)
- 10/05/2020: Started alectinib 600mg BID
- 11/15/2020: Follow-up MRI showing significant decrease in size and enhancement of all treated lesions; dexamethasone tapered and discontinued
- 01/10/2021: Near-complete resolution of brain metastases and 60% reduction in primary lung lesion
- 04/2021 - 12/2022: Maintained excellent disease control with stable imaging every 3 months
- 01/15/2023: Surveillance MRI revealed new 0.6cm enhancing lesion in left temporal lobe
- 02/05/2023: Disease progression confirmed with enlargement of primary lung lesion to 2.0cm (previously 1.3cm) and two new small brain lesions
- 02/12/2023: Switched to lorlatinib 100mg daily

- 03/15/2023: SRS to new brain lesions (18 Gy each)
- 04/2023 - 03/2025: Maintained disease control on lorlatinib with stable primary disease and brain metastases

Patient developed gradual onset of lorlatinib-related adverse effects including hyperlipidemia (requiring high-intensity statin therapy), peripheral edema (managed with compression stockings and intermittent furosemide), and mild cognitive effects (primarily affecting short-term memory and executive function). Despite these side effects, he maintained reasonable quality of life with ECOG performance status 1 and continued independent living with his wife.

CURRENT ADMISSION DETAILS

On March 31, 2025, Mr. Thompson experienced a witnessed generalized tonic-clonic seizure at home while watching television. The event lasted approximately 2 minutes according to his wife, followed by post-ictal confusion lasting approximately 30 minutes. EMS was called, and patient was transported to the Emergency Department. Upon arrival, patient was alert but disoriented to time and place, with no focal neurological deficits. Laboratory studies were unremarkable except for mild hyponatremia (Na 132 mEq/L). Levetiracetam loading dose (1000mg IV) was administered, and the patient was admitted for further evaluation.

HOSPITAL DIAGNOSTIC WORKUP

Neuroimaging: MRI brain with and without contrast (4/1/25) revealed enlargement of previously stable right parietal metastasis now measuring 1.8cm (previously 0.6cm) with surrounding vasogenic edema extending into the corona radiata. Multiple other small brain metastases appeared stable to improved compared to prior imaging. No evidence of hemorrhage or infarction.

MR spectroscopy (4/3/25) of the enlarging right parietal lesion showed spectrum consistent with radiation necrosis rather than true disease progression, characterized by elevated lipid/lactate peak, reduced choline/NAA ratio, and absence of significant choline elevation typically seen with tumor recurrence.

MR perfusion (4/3/25) demonstrated reduced relative cerebral blood volume (rCBV) in the enhancing region compared to normal brain parenchyma, supporting radiation necrosis rather than true progression.

Functional Neuroimaging: FDG-PET brain (4/4/25) showed hypometabolism in the right parietal region corresponding to the enlarging lesion, further supporting radiation necrosis rather than metabolically active tumor.

Body Imaging: CT chest/abdomen/pelvis (4/5/25): Primary left upper lobe mass decreased to 0.9cm (stable from previous 3-month scan). No evidence of extracranial progression. No new pulmonary, hepatic, adrenal, or osseous lesions.

Neurophysiologic Studies: EEG (4/3/25): Mild diffuse slowing, maximum in the right posterior quadrant, without epileptiform activity or seizures during recording. Findings consistent with focal structural abnormality with irritative potential.

Laboratory Studies:

- Complete blood count: WBC 6.8 K/μL, Hgb 13.2 g/dL, Plt 245 K/μL
- Comprehensive metabolic panel: Na 134 mEq/L, K 4.1 mEq/L, Cl 102 mEq/L, CO2 24 mEq/L, BUN 18 mg/dL, Cr 0.9 mg/dL, Glucose 94 mg/dL, Ca 9.2 mg/dL, Mg 1.9 mg/dL, Phos 3.4 mg/dL
- Liver function tests: AST 28 U/L, ALT 32 U/L, Alk Phos 78 U/L, T. Bili 0.6 mg/dL, Albumin 3.9 g/dL
- Lipid panel: Total cholesterol 248 mg/dL, LDL 162 mg/dL, HDL 42 mg/dL, Triglycerides 220 mg/dL (elevated despite statin therapy)
- Lorlatinib level: 650 ng/mL (below expected therapeutic range of 800-1200 ng/mL)
- Thyroid function: TSH 2.8 μIU/mL, Free T4 1.1 ng/dL (normal)
- Vitamin B12, folate, and homocysteine: Within normal limits

MEDICATION RECONCILIATION

During medication reconciliation, it was discovered that patient had been prescribed omeprazole 40mg daily for GERD symptoms by his primary care physician approximately 6 weeks prior to admission. Review of potential drug interactions identified significant interaction between omeprazole and lorlatinib, with proton pump inhibitors known to reduce lorlatinib plasma concentrations by approximately 25-30% due to pH-dependent absorption. This was confirmed by subtherapeutic lorlatinib level.

HOSPITAL COURSE

The patient was initially maintained on levetiracetam 1000mg IV q12h with no recurrence of seizure activity. Given the MRI findings of enlarged right parietal lesion with surrounding edema, dexamethasone was initiated at 4mg IV q6h with significant improvement in mild left-sided weakness (4+/5) that had been noted on detailed neurological examination.

Repeat MRI with spectroscopy and perfusion studies suggested radiation necrosis rather than true disease progression at the right parietal site. Neurosurgery was consulted and determined that surgical intervention was not indicated given the radiographic features consistent with radiation necrosis and the response to corticosteroids.

Radiation Oncology was consulted regarding potential repeat stereotactic radiosurgery (SRS). After reviewing the imaging studies, they recommended against repeat SRS given the findings consistent with radiation necrosis, noting that additional radiation could potentially worsen the necrosis. They suggested conservative management with corticosteroids and anti-seizure medication.

The subtherapeutic lorlatinib level prompted consultation with Clinical Pharmacology, who confirmed the significant drug interaction between omeprazole and lorlatinib. Omeprazole was discontinued and pantoprazole was substituted at appropriate timing interval (at least 6 hours apart from lorlatinib administration) to minimize the interaction. Pantoprazole was chosen as it has less impact on gastric pH compared to omeprazole and can be administered with specific timing to minimize the interaction.

Patient's anti-seizure regimen was optimized by increasing levetiracetam to 1000mg PO BID (from previous 750mg BID) with plans for therapeutic drug monitoring at outpatient follow-up. Neurology recommended against adding a second antiepileptic agent given the absence of recurrent seizures on monotherapy.

Neuropsychological assessment revealed mild impairment in executive function and working memory, which represented a slight decline from baseline. These changes were attributed to a combination of radiation necrosis effects, medication effects (lorlatinib, dexamethasone), and underlying disease. Recommendations included cognitive rehabilitation strategies and consideration of memantine for neuroprotection.

Patient had gradual improvement in mental status throughout hospitalization, returning to his neurological baseline by day 5. He remained seizure-free for the duration of admission. Dexamethasone was gradually tapered to 4mg BID by discharge, with plan for continued outpatient taper.

CONSULTATIONS:

1. Neurosurgery (Dr. Patel): Recommended against surgical intervention given radiographic features consistent with radiation necrosis and response to corticosteroids.
2. Radiation Oncology (Dr. Johnson): Advised against repeat SRS given findings of radiation necrosis, recommending conservative management with corticosteroids.
3. Clinical Pharmacology (Dr. Williams): Confirmed drug interaction between omeprazole and lorlatinib, recommended medication adjustment and specific timing of administration.
4. Neuropsychology (Dr. Rodriguez): Documented mild cognitive impairment, provided recommendations for cognitive rehabilitation and potential neuroprotective strategies.
5. Physical Therapy: Performed fall risk assessment and provided balance training exercises.
6. Social Work: Evaluated home safety and caregiver support, arranged for home health services.

MEDICATIONS AT DISCHARGE:

1. Lorlatinib 100mg PO daily (take on empty stomach)
2. Levetiracetam 1000mg PO BID (increased from 750mg BID)
3. Dexamethasone 4mg PO BID x 3 days, then 2mg BID x 3 days, then 2mg daily x 3 days, then 1mg daily x 3 days, then discontinue
4. Pantoprazole 40mg PO daily (take at least 6 hours after lorlatinib)
5. Atorvastatin 80mg PO daily
6. Amlodipine 5mg PO daily
7. Vitamin D3 1000 IU daily
8. Calcium carbonate 600mg BID
9. Escitalopram 10mg daily
10. Memantine 5mg daily x 7 days, then 5mg BID x 7 days, then 5mg qAM and 10mg qPM x 7 days, then 10mg BID (for neuroprotection)
11. Furosemide 20mg PO PRN lower extremity edema (max 3x/week)
12. Acetaminophen 650mg PO q6h PRN headache or mild pain

DISCHARGE PLAN:

1. Follow-up with Neuro-oncology (Dr. Chen) in 2 weeks (4/27/25)
2. Follow-up with Medical Oncology (Dr. Sharma) in 3 weeks (5/5/25)
3. Repeat MRI brain in 4 weeks to assess response to steroid therapy and confirm stability of radiation necrosis

4. Repeat lorlatinib level in 2 weeks to ensure therapeutic range after medication adjustment
5. Seizure precautions reviewed with patient and family
6. Avoidance of driving until 3 months seizure-free
7. Home safety evaluation scheduled
8. Home health nursing to monitor neurological status and medication compliance
9. Physical therapy for balance and strengthening exercises twice weekly
10. Occupational therapy for cognitive strategies once weekly
11. Caregiver education completed regarding seizure management and steroid taper
12. Steroid taper schedule provided in writing

COGNITIVE AND FUNCTIONAL STATUS AT DISCHARGE:

- Mental Status: Alert and oriented to person, place, and time. MMSE score 26/30 (mild impairment)
- Language: Intact comprehension and expression without dysarthria or aphasia
- Motor: 5/5 strength throughout without focal deficits
- Sensation: Intact to light touch, pinprick, vibration, and proprioception
- Coordination: Mild dysmetria on left finger-to-nose testing
- Gait: Steady with minimal widened base, able to tandem walk with mild difficulty
- Balance: Berg Balance Scale 48/56 (low fall risk)
- Activities of Daily Living: Independent in basic ADLs, mild assistance needed with complex IADLs (medication management, finances)

PROGNOSIS & CLINICAL COURSE:

Mr. Thompson has demonstrated remarkable response and tolerability to ALK-targeted therapies, with initial PFS of 28 months on alectinib and continued disease control on second-line lorlatinib. Current event appears related to radiation necrosis rather than true CNS progression, which carries a more favorable prognosis. Correction of drug interaction should improve pharmacokinetics and CNS penetration of lorlatinib.

Literature review suggests that CNS radiation necrosis occurs in approximately 5-10% of patients who receive SRS for brain metastases, with median time to development around 12-18 months post-radiation. Mr. Thompson's presentation at 53 months post-initial SRS is somewhat delayed but within the reported range. The development of radiation necrosis, while requiring intervention, actually indicates effective local control of the original metastatic lesions rather than true disease progression.

The long-term outlook for ALK-positive NSCLC patients has improved dramatically with sequential ALK inhibitor therapy. Recent literature suggests median overall survival exceeding 5 years from diagnosis with access to multiple generations of ALK inhibitors. Mr. Thompson has already achieved 54 months of survival with good quality of life and maintained functional independence. Assuming continued disease control with lorlatinib (after correction of medication interaction), we anticipate continued survival benefit with preserved neurological function.

Current management challenges include:

1. Optimizing CNS penetration of lorlatinib through appropriate dosing and avoidance of drug interactions

2. Managing radiation necrosis with the shortest effective course of corticosteroids
3. Balancing seizure control against potential cognitive side effects of antiepileptic therapy
4. Monitoring and managing cumulative toxicities of long-term ALK inhibitor therapy
5. Surveillance for emergence of lorlatinib-resistant clones
6. Preserving cognitive function and quality of life

Overall, patient continues to maintain good quality of life with ECOG performance status 1 despite recent setback. Prognosis remains favorable given continued response to targeted therapy and absence of systemic disease progression. Estimated overall survival from initial diagnosis now exceeds 54 months, well above historical norms for ALK-positive NSCLC with brain metastases.

POTENTIAL THERAPEUTIC OPTIONS IF DISEASE PROGRESSION OCCURS:

1. TPX-0131 or other fourth-generation ALK inhibitors under investigation (most appropriate for progression with secondary ALK resistance mutations)
2. Combination strategies with ALK inhibitors plus checkpoint inhibitors
3. Consideration of chemotherapy (pemetrexed-based) if molecular targeted options exhausted
4. Clinical trials of novel agents including antibody-drug conjugates targeting ALK-expressing cells
5. Localized approaches for oligoprogressive disease including stereotactic body radiation therapy

MOLECULAR MONITORING:

We have initiated collection of plasma ctDNA to monitor for emergence of resistance mutations. This will allow early detection of secondary ALK mutations that might guide selection of subsequent therapy.

MULTIDISCIPLINARY RECOMMENDATIONS:

Our Neuro-oncology Tumor Board reviewed this case on April 10, 2025 and provided the following consensus recommendations:

1. Continue lorlatinib with careful attention to drug interactions and therapeutic drug monitoring
2. Complete steroid taper as tolerated with close monitoring for recurrent symptoms
3. Consider prophylactic levetiracetam for at least 6-12 months given seizure event
4. Follow radiation necrosis with serial MRI including perfusion imaging
5. Implement cognitive rehabilitation strategies
6. Consider bevacizumab if radiation necrosis symptoms recur after steroid taper (off-label use)

These recommendations have been integrated into the treatment plan outlined above.

RESEARCH OPPORTUNITIES:

Patient was offered participation in our institutional registry study "Long-term Outcomes and Biomarker Analysis in ALK-positive NSCLC" (IRB #2023-487). He provided consent for

collection of plasma and analysis of circulating tumor DNA for monitoring disease evolution and resistance patterns. These results will be available to guide future therapy if progression occurs.

Dictated by: Marcus Chen, MD, PhD Neuro-oncology Service

Reviewed and approved by: Priya Sharma, MD Medical Oncology Service

cc: Dr. Elizabeth Thompson (Primary Care) Dr. William Johnson (Radiation Oncology) Dr. Anita Patel (Neurosurgery) Dr. Robert Williams (Clinical Pharmacology)