DISCHARGE DIAGNOSIS

1. Status post resection of symptomatic progressive brain metastasis with post-operative cerebral edema
2. ROS1 fusion-positive non-small cell lung cancer with intracranial disease progression during entrectinib therapy

PATIENT IDENTIFIERS Name: Ariane Gray DOB: 02/11/1976 MRN: SYN218 Admission Date: 04/01/2025 Discharge Date: 04/14/2025 Attending: Dr. Maya Lewis (Neuro-Oncology) Consultants: Dr. Nathan Park (Neurosurgery), Dr. Sofia Alvarez (Radiation Oncology)

BRIEF HISTORY OF PRESENT ILLNESS 49-year-old female with history of ROS1-positive NSCLC with brain metastases, on entrectinib since July 2023, presented with 3-day history of progressive headache, nausea, and new-onset left-sided weakness. MRI brain revealed enlargement of a previously stable right parietal metastasis (3.6 cm, previously 1.8 cm) with significant surrounding edema and midline shift. Patient was admitted for neurosurgical intervention and management of mass effect.

DETAILED ONCOLOGIC HISTORY

Initial Diagnosis (June 2023): Patient initially presented with headache and subtle left-sided upper extremity weakness. Brain MRI revealed multiple enhancing lesions (largest 1.8 cm in right parietal lobe). Subsequent CT chest showed a 2.5 cm right upper lobe nodule. Biopsy of the lung lesion confirmed non-small cell lung cancer, adenocarcinoma.

Histopathologic Details - Original Diagnostic Specimen:

CT-guided Biopsy of Right Upper Lobe Nodule (06/10/2023):

- **Gross Description:**
  - Three cores of tan-white tissue measuring 0.7-1.2 cm in length
  - Tissue soft to moderately firm in consistency
- **Microscopic Description:**
  - Well to moderately differentiated adenocarcinoma
  - Predominant acinar growth pattern (70%)
  - Papillary architecture (20%)
  - Lepidic component (10%)
  - Tumor cells demonstrating enlarged nuclei with vesicular chromatin
  - Prominent nucleoli
  - Abundant clear to pale eosinophilic cytoplasm
  - Moderate pleomorphism
  - Mitotic activity: 4 mitoses/10 HPF
  - No necrosis identified
  - Rare intracellular mucin
  - Adjacent lung parenchyma showing reactive pneumocyte hyperplasia
- **Immunohistochemical Profile:**
  - TTF-1: Strongly positive (diffuse)
  - Napsin A: Positive
  - CK7: Positive
  - CK20: Negative
  - p40: Negative
  - Synaptophysin: Negative

    - CD56: Negative
    - ALK (D5F3): Negative
    - ROS1 (D4D6): Positive (diffuse moderate to strong cytoplasmic staining)
    - PD-L1 (22C3): TPS 30%, CPS 45, IC 15%
- **Molecular Testing:**
    - FISH: ROS1 gene rearrangement confirmed (58% of cells positive)
    - Next-Generation Sequencing:
        - CD74-ROS1 fusion (exon 6 of CD74 fused to exon 34 of ROS1)
        - TP53 R249S mutation (allelic frequency 42%)
        - No other actionable alterations
    - TMB: Low (4 mutations/Mb)
    - MSI Status: Stable

Treatment Course Prior to Current Admission:

1. First-Line Therapy:
    - Entrectinib 600 mg PO daily
    - Initiated 07/01/2023
    - Excellent systemic response (primary lung lesion decreased to 0.8 cm)
    - Initial good intracranial response with decrease in size of all lesions
    - Most recent MRI (02/2025) showed stable intracranial disease
    - Recent MRI (03/05/2025) showed isolated progression of right parietal lesion with all other lesions stable
2. Radiation Therapy:
    - Deferred initial SRS/WBRT to assess intracranial response to entrectinib
    - All lesions initially responded to entrectinib monotherapy

HOSPITAL COURSE

Patient underwent right parietal craniotomy with gross total resection of the enlarging brain metastasis on 04/03/2025. Postoperative course was complicated by significant cerebral edema requiring escalation of dexamethasone to 10 mg every 6 hours. Patient developed moderate steroid-induced hyperglycemia requiring insulin management.

Left-sided weakness improved gradually with intensive physical therapy. By discharge, patient had regained full strength in the left lower extremity and 4+/5 strength in the left upper extremity. Headache resolved completely following surgery.

Postoperative MRI on 04/07/2025 showed gross total resection of the right parietal lesion with expected postoperative changes and improving cerebral edema. All other intracranial metastases remained stable.

Multidisciplinary tumor board on 04/10/2025 discussed options for ongoing management. Despite isolated progression of one lesion, systemic disease remains well-controlled on entrectinib. Decision was made to continue entrectinib with close monitoring and consideration of SRS to other stable brain lesions to prevent future progression.

SURGICAL PATHOLOGY

Resection of Right Parietal Brain Metastasis (04/03/2025):

- **Gross Description:**

    - Multiple fragments of tan-gray soft tissue, aggregate measurement 3.5 × 3.2 × 1.8 cm
    - Cut surface showing tan-white homogeneous appearance with focal areas of hemorrhage
    - No obvious necrosis
- **Microscopic Description:**
    - Metastatic adenocarcinoma consistent with lung primary
    - Predominantly solid growth pattern (70%, increased from primary tumor)
    - Acinar architecture (30%, decreased from primary)
    - Loss of papillary and lepidic patterns seen in primary tumor
    - Increased nuclear pleomorphism compared to primary tumor
    - Higher mitotic activity (12 mitoses/10 HPF vs. 4 in primary)
    - Focal areas of necrosis (approximately 15% of tumor volume)
    - Pushing borders against adjacent brain parenchyma
    - Reactive gliosis in surrounding brain tissue
    - Prominent vascularity with focal microvascular proliferation
    - No evidence of hemorrhage or venous invasion
- **Immunohistochemical Profile:**
    - TTF-1: Positive (intensity reduced compared to primary)
    - Napsin A: Weakly positive (reduced from primary)
    - CK7: Positive
    - ROS1 (D4D6): Positive but with heterogeneous staining pattern
        - Approximately 60% of cells showing moderate intensity
        - 40% of cells with weak to absent staining
    - Ki-67: 35% proliferation index (increased from primary)
    - PD-L1 (22C3): TPS 15%, CPS 25, IC 10% (decreased from primary)
    - PTEN: Intact expression
    - p53: Strong diffuse positivity consistent with mutation
- **Molecular Analysis:**
    - Targeted NGS Panel:
        - CD74-ROS1 fusion confirmed
        - TP53 R249S mutation confirmed
        - New ROS1 G2032R resistance mutation detected (allelic frequency 35%)
            - Known solvent front mutation associated with tyrosine kinase inhibitor resistance
        - New MYC amplification (copy number 6)
    - ROS1 Immunohistochemistry Heterogeneity Analysis:
        - Digital quantitative analysis confirmed heterogeneous ROS1 expression
        - Approximately 40% of tumor cells with reduced or absent expression
        - Pattern suggestive of clonal evolution under treatment pressure
- **Final Diagnosis:**
    - Metastatic lung adenocarcinoma with confirmed ROS1 resistance mutation
    - Molecular and morphological evidence of treatment-related adaptive changes
    - Findings consistent with acquired resistance to entrectinib

DIAGNOSTIC STUDIES

MRI Brain with and without contrast (04/07/2025):

- Postoperative changes in right parietal lobe with gross total resection of previously enhancing mass
- Expected postoperative enhancement along resection cavity

- Moderate surrounding edema with less mass effect compared to preoperative imaging
- No midline shift (improved from preoperative imaging)
- Multiple additional small enhancing lesions (largest 0.8 cm in left frontal lobe) unchanged from prior studies
- No hemorrhage or infarct
- No hydrocephalus

CT Chest/Abdomen/Pelvis with contrast (04/08/2025):

- Stable right upper lobe primary lesion (0.8 cm, unchanged)
- No evidence of lymphadenopathy
- No new pulmonary nodules
- No extrathoracic metastases

Laboratory Data (04/13/2025):

- WBC: 10.2×10^9/L
- Hemoglobin: 12.1 g/dL
- Platelets: 245×10^9/L
- Sodium: 138 mmol/L
- Potassium: 4.0 mmol/L
- Chloride: 101 mmol/L
- Bicarbonate: 24 mmol/L
- BUN: 12 mg/dL
- Creatinine: 0.8 mg/dL
- Glucose: 164 mg/dL (elevated due to steroid therapy)
- AST: 28 U/L
- ALT: 32 U/L
- Alkaline phosphatase: 78 U/L
- Total bilirubin: 0.6 mg/dL
- Albumin: 3.8 g/dL

DISCHARGE PLAN

Medications:

1. Entrectinib 600 mg PO daily (continue without interruption)
2. Dexamethasone 4 mg PO q6h with taper schedule:
    - 4 mg PO q6h × 3 days
    - 4 mg PO q8h × 3 days
    - 4 mg PO q12h × 3 days
    - 2 mg PO q12h × 3 days
    - 2 mg PO daily × 3 days, then discontinue
3. Levetiracetam 750 mg PO q12h (seizure prophylaxis)
4. Pantoprazole 40 mg PO daily
5. Insulin glargine 10 units SC qHS (while on dexamethasone)
6. Insulin lispro sliding scale (while on dexamethasone)
7. Acetaminophen 650 mg PO q6h PRN headache
8. Ondansetron 4 mg PO q8h PRN nausea

Follow-up Appointments:

1. Neurosurgery: Dr. Nathan Park in 2 weeks (04/28/2025)
2. Neuro-Oncology: Dr. Maya Lewis in 3 weeks (05/05/2025)
3. Radiation Oncology: Dr. Sofia Alvarez in 4 weeks (05/12/2025) to discuss SRS for remaining lesions
4. Physical Therapy: Outpatient 3x weekly for 4 weeks

Imaging:

1. MRI Brain with and without contrast in 4 weeks to assess postoperative healing and status of other lesions
2. CT Chest/Abdomen/Pelvis in 8 weeks for systemic disease assessment

Additional Recommendations:

1. Based on the identified ROS1 G2032R resistance mutation, consideration for future transition to lorlatinib (if approved for ROS1) or repotrectinib (in clinical trial) if additional lesions develop resistance
2. Enrollment in expanded plasma ctDNA monitoring program to track molecular resistance patterns
3. Consider second-generation ROS1 inhibitor clinical trial referral when systemically indicated

Special Considerations:

1. Continue entrectinib as systemic disease remains well-controlled
2. Focal CNS progression likely represents a compartment-specific resistance mechanism
3. Close monitoring for neurological symptoms given presence of other brain metastases
4. Driving restrictions until follow-up neurosurgical clearance
5. Seizure precautions reviewed with patient and family

CONDITION AT DISCHARGE Patient is alert and oriented x3. Left-sided weakness substantially improved with normal strength in lower extremity and mild residual weakness (4+/5) in upper extremity. Ambulating independently. Surgical site well-healed without signs of infection. Steroid-induced hyperglycemia controlled with insulin regimen. ECOG Performance Status 1 (improved from 2 at admission).

DISCHARGE INSTRUCTIONS The patient has been instructed to:

1. Continue all medications as prescribed
2. Follow steroid taper exactly as directed
3. Monitor blood glucose 4 times daily while on dexamethasone
4. Report any new or worsening neurological symptoms immediately
5. Avoid driving until cleared by neurosurgery
6. Follow activity restrictions (no heavy lifting >10 lbs, no strenuous activity for 6 weeks)
7. Keep incision clean and dry
8. Attend all scheduled follow-up appointments

Maya Lewis, MD, PhD Neuro-Oncology 04/14/2025 16:15

Nathan Park, MD Neurosurgery 04/14/2025 15:30